

HONG KONG PHARMACEUTICAL *JOURNAL*

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News & Short Communications

Open Forum on the Report of the Review Committee on Regulation of Pharmaceutical Products in Hong Kong

Current Dietetic Practice in the Management of Gout

Coaching to Build an Effective and Sustainable Team

Hong Kong Pharmacy Conference 2010: Pharmacist in the New Decade - Building Our Healthy Land

Recent Advances in Antifungal Therapy

Simultaneous Determination of Flavonoids, Phenolic Compounds and Triterpenes in Herb by Capillary Zonal Electrophoresis Can be Enhanced by the Addition of β -Cyclodextrin

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The Morphological Features, Chemical Constituents and Biological Effects of *Fritillaria Hupehensis* Bulbus (湖北贝母)

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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

Concern Widens over the Quality, Safety and Efficacy of Drugs Sold in Hong Kong



Drug safety has long been an important issue ever since the Department of Health (DH) of the Hong Kong Government was established. But the recall of tainted Po

Chai Pills firstly ordered by Singapore's Health Sciences Authority on March 8 has sparked more concern from the public in recent days. During the last few months, news about contaminated or unsafe drugs has indeed dominated a variety of media including newspapers, radio, television etc. If we do a database search of news disclosed by the DH in the previous year, it is not difficult to conclude that most news items are relevant to drug safety. In the News and Communication section of this issue, a few examples which were displayed on the DH website are quoted (page 4 – 6). The concern was due to poor quality, improper use, warnings and handling of drugs or the use of banned ingredients in drugs during manufacturing. Because of a series of problems that occurred during last year, a committee has been setup to give recommendations on how these problems could be eliminated. A list of recommendations prepared by the committee and feedback from some pharmacists can be found in a report written by Cheng & Lam from page 7 to 11.

Generally speaking, drug safety concerns can originate from any of the following situations: (a) poor formulae or manufacturing practices;⁽¹⁾ (b) adverse drug reactions due to a short history of use;^(2,3) (c) drug-drug or drug-food interactions;⁽⁴⁾ (d) medication errors during dispensing⁽⁵⁾ or (e) improper uses of "off-label" medicines.⁽⁶⁾

For instance, excipients are additives used to convert pharmacologically active compounds into pharmaceutical dosage forms suitable for administration to patients. But they can exert undesirable consequences on the bioavailability, bioequivalence, and stability of drugs.

The inclusion or addition of an excipient can't be regarded merely as an "inert" or inactive substance; relatively small variations in the physical properties of an excipient, in fact, can produce significant differences in the behavior of formulated products. Proper use of excipients and possible adverse reactions associated with their use should not be overlooked.⁽⁷⁾ Knowledge of the physical and chemical properties of each excipient is vital for the selection of suitable excipients for the formulation of the many varieties of products used as medicines today. Formulators and manufacturers, therefore, should perform suitable experimental studies and analyses to satisfy themselves and regulatory bodies that a formulation is efficacious and safe to use. An exploratory study reported by Zhang & Cheung in page 28 illustrates how different ingredients in complex materials such as herbal substances could be determined simultaneously with today's advanced technologies and knowledge. Their work exemplifies the feasibility of controlling the quality of medicinal products in daily manufacturing.

Medication error during the stage of dispensing, on the other hand, reflects inadequate training or instruction given to staff involved. If staff receive sufficient training and coaching, an effective and sustainable team can be established. On this aspect, an article written by Ho and Chong tell us of a strategic approach involving pharmacy students working as interns being escorted to become members of an effective and sustainable team in a multi-national drug company (p.14). Their learning and training experiences in this multi-national drug company could be a paradigm for local drug companies and hospitals for training their competent staff.

Physicians and patients always need to know how safe a drug is but much evidence seems to indicate that people might never be able to declare that a drug is truly "safe". Infrequent serious adverse effects, including mortality, might not become evident until the drug has been

used for some time.⁽⁸⁾ Because no drug is absolutely safe, a drug is approved for marketing when regulatory bodies, such as FDA, TGA, DH etc judge that its' known benefits outweigh its' known risks. Therefore, a newly introduced drug may have to face some degree of risk due to the short history of its' use. However, regulatory bodies should play a role in continuously assessing a drug's risks and benefits after a drug is on the market. Both regulatory bodies and health professionals should also closely review and make decisions on reports of adverse drug reactions or safety problems even though the decision making process for post market safety of drugs is complex.

There is no ultimate solution to avoid the risk of using a medicine but we can minimize its' undesirable effect through concerted efforts by implementing regulatory policy, standard operating procedures, adequate trainings, monitoring, regularly reviewing practices and process.

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Cheung Hon-Young
Editor-in-Chief
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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:

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- OTC & Health
- Pharmaceutical Technique & 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.

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

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Medicine Found to Have Exceeded Heavy Metal Limit

Date: January 22, 2010

The Department of Health (DH) urged members of the public not to buy or use a medicine named “Bao Shu Tang Wu Zi Yan Zong Wan”, as it was found to have exceeded the heavy metal limit. The appeal was made in view of the laboratory findings about maximum permitted level of lead in the product being exceeded. The product was

found during DH’s market surveillance exercise. Chronic exposure to lead may lead to anaemia, joint and muscle pain, brain and kidney damage. DH instructed the wholesaler “Hong Kong Wah Sheng Medical Limited” to recall the medicine from the market. The wholesaler has earlier submitted an application for proprietary Chinese medicine

registration to Chinese Medicines Board (CMB) of the Chinese Medicine Council regarding “Bao Shu Tang Wu Zi Yan Zong Wan”. The application will be considered with the recent laboratory finding by the CMB.

Source: <http://www.dh.gov.hk/english/press/2010/100122-3.html>

Advice on Safe Use of Medicines Containing Sibutramine

Date: January 22, 2010

The Department of Health (DH) drew public attention to the safe use of medicines containing sibutramine. The European Medicines Agency, based on results of a recent study, considered the risks of sibutramine to be greater than their benefits and that the agency’s Committee for Medicinal Products for Human Use has recommended suspension of marketing authorisation for medicines containing sibutramine. The Food and Drug Administration (FDA) of the United States, after reviewing the relevant study data, had requested manufacturers to add a new contraindication to the label stating that sibutramine is not to be used in patients with a history of cardiovascular diseases

including history of coronary artery disease, stroke or transient ischemic attack, arrhythmias, congestive heart failure, peripheral arterial disease and uncontrolled hypertension. The FDA will complete its full review and convene a meeting to determine if additional regulatory actions should be taken to ensure safe use of the medicines later.

In Hong Kong, the DH has seriously considered the possible side effects, volume of demand and made an immediate risk assessment of medicines containing sibutramine. There is a total of 40 registered drugs contained sibutramine and are prescription drugs. The existing package inserts carry a

warning that the medicines should not be used in patients with a history of coronary heart disease, congestive heart failure, arrhythmias or stroke. The Registration Committee of the Pharmacy and Poisons Board will review the relevant data in an upcoming meeting in early February to decide if further regulatory actions are required. Sibutramine is a western medicine used as an appetite suppressant. Its side effects included increased blood pressure and heart rate, psychosis and possibly convulsion. People with heart problems should not take it.

Source: <http://www.dh.gov.hk/english/press/2010/100122-4.html>

Public Warned Against Unsafe Cosmetic Cream

Date: January 28, 2010

The Department of Health called on members of the public not to use a facial cream called “UV Whitening” following a case of mercury poisoning reported by the Hospital Authority. A 43-year-old woman who used the product twice daily for two months developed fatigue and lower limb swelling. She was admitted to Kwong Wah Hospital on January 3 and discharged on January 13. Laboratory

result showed that the level of mercury in the cream was 19,412 times the acceptable level. The case has been referred to the Customs and Excise Department for follow-up. Members of the public should stop using the cream immediately and seek advice from their doctors as soon as possible. Mercury poisoning was caused by mercury overdose in the body, causing

damage mainly to the nervous system and kidneys. Symptoms may include tremors, irritability, insomnia, memory deterioration, difficulty with concentration, impaired hearing and vision or change in taste. In most severe cases, renal failure may occur.

Source: <http://www.dh.gov.hk/english/press/2010/100128-2.html>

Expert Group Views on Serious Adverse Events with History of HSI Vaccination

Date: January 28, 2010

At its meeting on 28 Jan 2010, members of the Expert Group on Serious Adverse Events with History of Human Swine Influenza (HSI) vaccination, reached consensus views on reported cases of Guillain-Barre Syndrome (GBS) and intrauterine deaths (IUD) with history of HSI vaccination.

On the GBS compatible case reported on January 6, 2010, the expert group noted that to date, the World Health Organization (WHO) has found no evidence suggesting a causal relationship between GBS and HSI vaccination and that the reported number of GBS cases worldwide has been in line with usual background rates prior to the introduction of such vaccines. It was also noted that recent incidences of GBS after the start of HSI vaccination programme in Hong Kong does not increase over the baseline, which is about 40 to 60 cases per year. "While it is always difficult to completely rule out a rare, idiosyncratic

response to any vaccine or drug for an individual patient, literature review shows that the majority of GBS cases that are temporally associated with vaccination occurred from the second to third week, with a median latency of 13 days," a spokesman said.

On the two reported cases of intrauterine deaths with history of human swine influenza vaccination, it was noted that the Department of Health received the reports on January 20 and January 23, 2010 respectively. Both cases had known risk factors, namely, advanced maternal age and long-term medication in one case and gestational diabetes mellitus in the other. About 150 to 220 cases of IUD occur in Hong Kong every year. A significant proportion, 15 to 70 per cent, of the cases does not have identifiable causes. It was noted that as at January 27, 2010, a total of 1,375 pregnant women have received HSI vaccine.

Currently, the proportion of IUD among vaccinated women have not exceeded the local baseline incidence of IUD, i.e., around 0.15 per cent versus 0.2 to 0.4 per cent. The rate of stillbirths among vaccinated pregnant women is therefore at the low end of usual background levels. More extensive overseas experience and recommendations from the World Health Organization (WHO) on the use of human swine influenza (HSI) vaccine in pregnant women have confirmed the safety profile of HSI vaccine including the lack of any demonstrable association with IUD. There is currently no evidence that HSI vaccines increase the chance of IUD based on both local data and international experience. It is unlikely that the two observed IUD cases were caused by previous HSI vaccination.

Source: <http://www.dh.gov.hk/english/press/2010/100128-4.html>

Recall of LifeScan OneTouch SureStep Blood Glucose Test Strips with Incorrect Readings

Date: February 12, 2010

The Department of Health (DH) was notified by Johnson & Johnson (Hong Kong) Limited that the company had initiated a voluntary recall of blood glucose test strip which may provide low readings. Only one affected lot (lot number 2966727) of LifeScan OneTouch SureStep Test Strips was

supplied to Hong Kong. The affected test strips may provide low test results when the blood glucose level is greater than 22.2 mmol/L. A total of 2,160 boxes of the lot have been imported to Hong Kong. Among them, 2,116 unsold boxes have already been retrieved from the market. Only 44 boxes have

been sold in Hong Kong. The DH has not received any report of adverse events arising from the test strip. The department will closely monitor the recall.

Source: <http://www.dh.gov.hk/english/press/2010/100212-5.html>

Recall of Pharmaceutical Product with Wrong Label

Date: February 19, 2010

The Department of Health announced that Trenton-Boma Ltd, a licensed wholesaler of pharmaceutical products, had initiated a recall of one batch of PMS-Carvedilol 12.5 mg tablets (registration no. HK-52639). The batch number of the product being recalled is 444937. The product is manufactured in Canada. It is used for the treatment of high blood pressure

and heart failure. It is a prescription-only medicine. A total of 2218 bottles (100 tablets per bottle) of the batch had been supplied to the Hospital Authority, 71 bottles to some private doctors and pharmacies. Based on information available so far, the recall is initiated because, on some of the bottles of the product, the additional label, which the wholesaler has added in order to

comply with the local statutory labelling requirements, states incorrectly that each tablet contains 6.25 mg carvedilol and shows an incorrect registration number. The wholesaler has initiated a recall exercise at retail level. The DH will closely monitor the recall exercise.

Source: <http://www.dh.gov.hk/english/press/2010/100219-2.html>

Advice on New Safety Controls for Asthma Medicines

Date: February 19, 2010

The Department of Health (DH) drew public attention to the safe use of long-acting beta agonists (LABAs), medications used to treat asthma. The warning came after U.S. Food and Drug Administration (FDA)'s announcement that LABAs should never be used alone in treating asthma in children or adults and that manufacturers will be required to include this warning in the product labels or package inserts of

these drugs and take steps to reduce the overall use of these medications. The new requirements are based on FDA's analysis of clinical trials showing the use of LABAs is associated with an increased risk of severe worsening of asthma symptoms, leading to hospitalisation and even death in some asthma patients. In Hong Kong, there are 16 products containing LABAs currently registered in Hong Kong. These

LABAs are salmeterol and formoterol. The Registration Committee of the Pharmacy and Poisons Board will review the relevant information in an upcoming meeting. Asthma patients using these medicines should consult medical professionals for appropriate advice and treatment. Their doctors should be informed about any problems encountered after treatment.

Source: <http://www.dh.gov.hk/english/press/2010/100219-3.html>

Recall of Pharmaceutical Products

Date: March 15, 2010

Neochem Pharmaceutical Laboratories, a licensed drug manufacturer, is recalling two products Neo-Celemine Syrup (Registration Number HK-24685) and Betamine Syrup (Registration Number HK-24681), which were found to contain lower than registered content in one of their active ingredients, betamethasone. The batch number of both products being recalled bore the same batch number 092048. According to the labels of Neo-Celemine Syrup and Betamine Syrup, each 5ml of the products should

contain 0.25mg betamethasone. Today, testing of samples collected during the Department of Health's (DH) inspection of the manufacturer showed that the concerned products only contained 3mcg (microgram) betamethasone per 5ml. Neo-Celemine Syrup and Betamine Syrup are used for the treatment of difficult cases of respiratory, eye, and skin allergies. They are both prescription medicines.

Deviations from the registered content of active ingredients of a pharmaceutical

product would affect treatment effectiveness. Based on information in hand, a total of 124 bottles (3.6 litres per bottle) of the affected Neo-Celemine Syrup and 150 bottles (3.6 litres per bottle) of the affected Betamine Syrup had been supplied to private doctors and some pharmacies. The manufacturer has initiated a recall at retail level. The DH will closely monitor the recall.

Source: <http://www.dh.gov.hk/english/press/2010/100315-2.html>

Warning Against Avelox

Date: March 23, 2010

The Department of Health (DH) drew attention to a warning issued by Health Canada to healthcare professionals following their safety review on Avelox (moxifloxacin), which concluded that Avelox may be associated with the rare but potentially life threatening risk of liver injury. Symptoms of liver problems include

abdominal pain, loss of appetite, yellowing of the skin and eyes, severe itching, dark urine, and pale-coloured stools. Avelox is a registered prescription drug in Hong Kong, available in tablets and injections. It is an antibacterial agent used to treat a broad range of bacterial infections, including respiratory infections. Patients are advised

to seek advice from their attending doctors if they develop signs and symptoms of liver problems. DH would liaise with Health Canada for details and the Registration Committee of the Pharmacy and Poisons Board will follow up the issue.

Source : <http://www.dh.gov.hk/english/press/2010/100323-3.html>

Recall of Po Chai Pills

Date: March 24, 2010

The Department of Health (DH) directed licensed manufacturer in proprietary Chinese medicines Li Chung Shing Tong (Holdings) Ltd. HK to recall Po Chai Pills Capsule Form and Po Chai Pills Bottle Form from local retail outlets and consumers as its capsule form was found in Singapore to contain phenolphthalein and sibutramine, which can cause very serious side effects.

The finding came to light when the DH learnt that the Health Sciences Authority of Singapore, announced a recall of Po

Chai Pills Capsule Form. In Hong Kong, Po Chai Pills Bottle Form is registered as proprietary Chinese medicine and sold locally while Po Chai Pills Capsule Form is applying for registration as a proprietary Chinese medicine. Phenolphthalein was once used for treating constipation but had been banned in 2001 for its cancer causing effect. Sibutramine is a western medicine used as an appetite suppressant. Its side effects include increased blood pressure and heart rate, psychosis and possibly convulsion. Products containing

sibutramine are western pharmaceutical products and must be registered as such before it can be sold in Hong Kong. It can only be sold on a doctor's prescription and dispensed under the supervision of a pharmacist. The sale of unregistered pharmaceutical products was an offence under the Pharmacy and Poisons Ordinance. The maximum penalty is a fine of \$100,000 and two years' imprisonment.

Source: <http://www.dh.gov.hk/english/press/2010/100324.html>

Open Forum on the Report of the Review Committee on Regulation of Pharmaceutical Products in Hong Kong

CHENG, Mary Catherine; LAM, PY Daisy

BACKGROUND

In early 2009, a series of drug incidents in Hong Kong had caused public concerns on drug safety. A Review Committee on the Regulation of Pharmaceutical Products chaired by the Permanent Secretary for Health with members from the pharmaceutical sector, medical profession, academia, patient groups and consumer representative was set up on 24 March 2009. The Review Committee (RC) evaluated the existing system for the control on pharmaceutical products and discussed in depth to come up with long term measures to protect public health and to ensure public safety. The report of the Review Committee on Regulation of Pharmaceutical Products in Hong Kong was issued in early January 2010 with a total of 75 recommendations to be implemented in phases. The full report can be obtained at: http://www.fhb.gov.hk/en/press_and_publications/otherinfo/100105_pharm_review/index.html. The 75 recommendations are listed in Annex 1.

OPEN FORUM

The Pharmaceutical Society of Hong Kong organized two open forums for pharmacists to voice their opinions on the recommendations. The first open forum was held on 30th January 2010 at Ruttonjee Hospital and was attended by 65 pharmacists (community-28, industry-6, Hospital Authority(HA)-3, trade-1, others without indication of sector-24). The second open forum was held on 6 February 2010 at the Club House of the Pharmaceutical Society of Hong Kong and was attended by 33 pharmacists (community-10, Department of Health(DH)/HA-4, industry-3, trade-1, others without indication of sector-15). The Pharmacy & Poisons Board members and the General Council members of the Pharmaceutical Society of Hong Kong were present to listen to the views of pharmacists.

SUMMARY OF COMMENTS

The organizers used a projector to take the audience through the recommendations. Pharmacists were invited to give their opinions freely on the different recommendations. The following is a summary of the comments raised during the forums.

Regulation of Drug Manufacturers (Recommendations 1-12)

1. Qualification of the Authorized Person

There were divided opinions on this recommendation.

Against:

The Authorized Person (AP) of a local manufacturer should be a registered pharmacist with relevant experience. A pharmacist acting as AP is bound by both the responsibilities of AP as laid down under GMP and the disciplinary mechanism of the Pharmacy and Poisons Board against his professional status. Such a "double gate-keeping mechanism" is desirable for the protection of public health". To relax AP to non-pharmacists may adversely affect public safety as pharmacist is always the best person to deal with drugs.

Pro:

The AP need not be a pharmacist as it may not be easy to employ a pharmacist as AP and it is not a requirement by the Pharmaceutical Inspection Cooperation Scheme (PIC/S) to hire a pharmacist as AP. The AP should be a person with relevant knowledge and experience depending on the product characteristics and manufacturing needs of the individual manufacturer. It is agreed that there should be a set of strict selection criteria/requirements for AP. With the established licensing or listing scheme, AP need not be a pharmacist.

2. Upgrade of Hong Kong Good Manufacturing Practice (GMP) Standard by phases to PIC/S Standard

All pharmacists agreed to the above recommendation. DH has to take lead in the implementation of PIC/S by training of its inspectors to PIC/S standard and to

assist local manufacturers in progressing towards the PIC/S standards. Some pharmacists suggested that registered drugs produced in accordance to manufacturers with WHO 1995, WHO 1997 or PIC/S GMP standards should be differentiated in the labels. Proper labeling of GMP standard on drug package is a possible method to aid public's choice. Local manufacturers can do so on a voluntary basis. The DH website should enable the search of registered drugs in HK and also the GMP standard information of both the local or overseas drug manufacturers producing those drugs.

3. Microbial Monitoring in finished products

A pharmacist remarked that microbial testing will be required in the quality control of finished products produced by local manufacturers but not required in the imported drugs. Microbial monitoring in local drug manufacturer is unfair and unnecessary.

Pre-Market Control of Drugs (Recommendations 13-17)

1. To Require Bioavailability and Bioequivalence (BABE) Studies for Drug Registration

It was suggested that a list of approved institutions/companies to conduct BABE studies should be made available by DH. The report did not address the need to re-do BABE studies of overseas generic products.

2. To Change the Term "Poison 毒藥" on Drug Label

A pharmacist suggested that some of the non-poisons which possess the risk of misuse/poisoning (e.g. Paracetamol) should be reclassified as poison, rather than enhancing the control of non-poisons. It was explained by a Pharmacy and Poisons Board (P&PB) member that some of the drugs are classified as non-poisons so that they are easily accessible by the public. Terms like "POM" or "Prescription

Drugs" on packaging are self-explanatory. This will facilitate pharmacists or other pharmacy staff to explain the need of a prescription. A pharmacist suggested that health food products, which are neither poisons nor non-poisons, should be regulated. It was explained by a member of the RC that according to the Chairperson of the RC, health food is out of the scope of the RC discussion.

3. To Delete the Phrase "to be marketed for use within Hong Kong" on the Certificate of Registration of Pharmaceutical Products

A pharmacist opined that deleting the line "to be marketed for use within Hong Kong" might be an act to avoid responsibility of patent infringement. Another pharmacist remarked that it was not acceptable to place the responsibility of checking patent linkage to drug users. Some pharmacists agreed that measures to deal with patent infringement were commercial issues and should not be done by the Government. Possible and convenient ways to check the patent status of a drug were however demanded by local manufacturers. It was suggested that DH could request drug manufacturers to declare the patent when submitting the application for registration. A P&PB member said that the patent issue was addressed by P&PB a few years ago but was found to be too complicated to be handled by DH.

Regulations of Importers/Exporters and Wholesalers (Recommendations 18-28)

No comments were received on the above.

Regulations of Retailers (Recommendations 29-39)

1. Presence of a Registered Pharmacist whenever an Authorized Sellers of Poisons (ASP) is open (3/3)

Against:

Many of the community pharmacists were against this recommendation. They opined that the requirement for pharmacists to be present during the opening hours of business of the ASP is not practical and not reasonable under the current situation. It is doubtful that 3/3 requirement can help enhance drug safety. Implementing 3/3 in an environment where pharmacists have limited control of ethical and legal drug sales increases the risk of pharmacists' violation of law. Pharmacists at ASPs

may risk losing their jobs when they actively influence the decision of the employers. This recommendation could only be implemented when there is Separation of Prescribing and Dispensing (SPD). Hospital Authority should send more prescriptions out to be dispensed in the community pharmacies. If there are sufficient prescriptions/sales, the pharmacists or owners of the pharmacies will no longer need to take the risk of illegal sales. There should be measures to increase the viability of ASPs before the implementation of 3/3. De-regulation of selected P1S1S3 to P1 or P1S1 may help to increase ASP's viability and business. Recommendation no. 30 should be suspended/delay until the best condition for implementation is available.

Pro:

There were pharmacists who supported the recommendation and said that recommendation no. 30 is only a principal; the legal issue can be addressed in the later stages. All recommendations from the RC report will have a cost impact in all Pharmacy sectors, including community, hospitals or industry. The increased cost for additional pharmacist manpower by ASP owner is not an argument. The 3/3 requirement can be regarded as an investment for future SPD. Pharmacists are not only required to dispense prescriptions, they should be available in the pharmacies to provide health education and consultation. SPD and business growth will come after the upgrade of pharmacist profession status. Pharmacists should take time to bargain for resources and supports from Government to aid the implementation of 3/3.

2. Tightening Licensing Conditions for Listed Sellers of Poisons (LSP)

A pharmacist opined that LSPs should be replaced by ASPs as pharmacists are essential in enhancing drug safety. Non-poisons should be sold in restricted quantity at LSPs to avoid misuse. For example, Paracetamol tablets sold in supermarkets could be 4 tablets per pack.

3. All Part 1 Poisons to be Stored in Locked Receptacle

There were different opinions expressed.

Against:

A pharmacist opined that due to the fact that pharmacist is not the sole key holder of poisons, ASP owners should be made officially another poison key holder. All drugs (poisons and non-poisons) should not be locked.

Pro:

Another pharmacist suggested that it is the pharmacist's authority to be the sole key holder of poisons and this authority should not be removed. Pharmacists should overcome, not avoid, the existing difficulties when we fight for the change and improvement in our profession.

4. To Require Retailers and Doctors to have Written Records for Drug Orders

There were different opinions expressed.

Against:

Pharmacists are capable and have the right to give clear verbal drug orders. Written drug order is also not required in overseas countries. It is too troublesome and impractical to keep written drug orders and sale invoices for as long as the expiry dates of the drugs for DH's inspection. Written drug order cannot eliminate the malpractice of drug transaction without official records.

Pro:

The purpose to require written records for all drug orders is to ensure traceability of any single drug item at drug recalls, so keeping written drug orders is a measure to enhance drug safety. Requiring written drug orders may reduce doctor's interest in drug dispensing. This may ultimately facilitate SPD. The increase workload of ASPs and wholesalers will gradually be eased with the help of electronic ordering. Although written order may not eliminate the malpractice of drug transaction without official records altogether, it will still lead to positive impacts in controlling the existing malpractice.

Regulation of Drug Procurement (Recommendations 40-53)

Pharmacists and Senior Pharmacists manpower should be added in HA instead of only in DH to cater for the increased workload in HA after the procurement recommendations. It is unreasonable to have different standards for HA, private hospitals and general practitioners in drug procurement. Quality control should be done by DH and not HA. Counterfeit drugs should be made differentiable by pharmacists/pharmacies in the drug procurement process. It would be useful for DH to establish a database with characteristics of genuine drugs. The requirement to keep samples of each batch of drugs that are still within the expiry date is costly and impractical.

Pharmacovigilance (Recommendations 54-66), Risk Communications (Recommendations 67-72), Penalty System (Recommendations 73-74)

No comments were received on the above.

Manpower Requirements (Recommendation 75)

The "Centre for Drug Safety" should not be under the Department of Health. It should be a separate organization having the authority to monitor the services provided by DH. There should be open recruitment for capable and suitable persons to fill the key positions.

CONCLUSION

Based on the feedback in the open forums, the majority of the recommendations are supported by pharmacists. The most controversial is recommendation no. 30 in which the presence of a registered pharmacist is required whenever an ASP is open. Most community pharmacists have expressed that unless there is the Separation of Prescribing and Dispensing and/or more prescriptions from the HA to be filled in the community pharmacies, the 3/3 requirement should not be implemented. It is rather ironic to see so many good recommendations in the report while the road map leading to the Separation of Prescribing and Dispensing has not been mentioned in the report. Is the task so daunting that it is out of the scope of discussion by the Review Committee? Did the RC members truly believe that the illegal sales in the community pharmacies could be wiped out with the 3/3 requirement and increased inspections and prosecutions? All in all, the Review Committee has put forth a lot of good recommendations, which if implemented in a timely manner, will have a profound and positive impact on the way our local pharmacy profession to move forward. There is an enormous challenge as well as massive opportunities in the years ahead. It is necessary for all pharmacists to join hands to bring the pharmacy profession to a higher horizon. We should be determined to practice to our highest standards and encourage the trade to perform responsibly.

Authors' background

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ANNEX 1

Summary of the 75 Recommendations by the Review Committee

Recommendations which can be implemented with existing resources are marked with an "*" while recommendations which will be implemented when new resources are available are marked with a "#".

Regulation of Drug Manufacturers

Recommendation 1# – to upgrade Hong Kong's current GMP licensing standards by a phased approach to PIC/S standards over a period of four years.

Recommendation 2# – to require imported drugs to comply with the same standards once local drugs attained the PIC/S standards.

Recommendation 3# – to strengthen the control of the use of Active Pharmaceutical Ingredients (APIs) and contract laboratories by local manufacturers.

Recommendation 4* – to strengthen the experience requirement for existing APs from at least one year of relevant working experience to at least three years; and for the heads of production and quality control from at least one year to at least two years for pharmacy degree holders and from at least two years to at least three years for holders of higher diploma in pharmacy-related subjects.

Recommendation 5# – to draw up a set of qualification requirements of Authorized Persons (APs), to establish a licensing or listing scheme and to liaise with the universities for offering a structured training programme for APs.

Recommendation 6# – to empower the Pharmacy and Poisons Board to maintain an AP register and remove any AP from the register should he be found incompetent to perform the AP role.

Recommendation 7* – to increase the number of inspections to local manufacturers. While most of the inspections to manufacturing premises should remain announced, some unannounced inspections should be introduced. Further, one of the two inspectors in the inspection team should be retained for subsequent inspections to facilitate effective follow-up on irregularities identified.

Recommendation 8# – to set up a multi-disciplinary GMP inspection team with professionals of other related disciplines

like biochemists, chemists, engineers, microbiologists, etc. for effective auditing of manufacturers with diversified production environment.

Recommendation 9# – to develop structured, practical and continuous training programmes for all levels of players in the GMP system including DH inspectors, APs, production and quality control heads, and other workers.

Recommendation 10* – to state in the licensing conditions that local manufacturers should either (a) appoint the AP as a board member; or (b) invite the AP to attend board meetings and allow the AP to speak and have his remarks put on record where safety, efficacy and quality issues of products are concerned. This recommendation should be put on trial for two years and then reviewed.

Recommendation 11# – to introduce a code of practice to govern the conducts of the manufacturers and the APs.

Recommendation 12* – to require all local manufacturers to adopt the enhanced microbiological monitoring model covering raw materials, granules, finished products and stability studies.

Pre-market Control of Drugs

Recommendation 13# – to require BABE studies as registration requirement for pharmaceutical products to enhance quality of generic drugs. The implementation should be by phases starting in April 2010. It will begin with antiepileptic drugs, which have a narrow therapeutic index where a comparatively small difference in the absorption of the drug by the human body may lead to undesirable consequences.

Recommendation 14* – to replace the term "Poison 毒藥", as required to be labelled on pharmaceutical products classified as poisons, with other terms to alleviate the unnecessary concern of consumers that the products might be harmful and unsuitable for use or consumption.

Recommendation 15* – to delete the phrase "to be marketed for use within Hong Kong" on the certificate of registration of pharmaceutical products.

Recommendation 16* – to extend the validity of clinical trial certificate from not more than two years to not more than five years.

Recommendation 17# – to shorten the time-frame for processing applications for

registration of pharmaceutical products, change of particulars of registered products and clinical trials by 40% - 50%.

Regulation of Importers/Exporters and Wholesalers

Recommendation 18# – to require all wholesalers of non-poisons to be subject to inspection and licensing control.

Recommendation 19# – to require all wholesalers to keep transactions records of all pharmaceutical products, including Part II poisons and non-poisons in the same manner as for Part I poisons, and to require wholesalers to keep samples of each batch of drugs handled to facilitate investigation when needed.

Recommendation 20* – to require both primary and secondary packaging be carried out by a licensed manufacturer.

Recommendation 21* – to introduce a code of practice for importers/exporters and wholesalers detailing their roles and responsibilities, including the requirement of batch release certificate, the reporting of adverse drug reactions, proper storage and transportation of drugs, etc.

Recommendation 22# – to strengthen the monitoring of importers/exporters and wholesalers by means of more frequent and more detailed inspections, especially after the introduction of a code of practice.

Recommendation 23# – to set up a dedicated team of pharmacist inspectors to advise C&ED staff on pharmaceutical imports at various ports of entry.

Recommendation 24# – to set up a record and tracking system by requiring EL applicants to produce the ILs of the imported drugs to be re-exported.

Recommendation 25# – to prescribe in the licensing conditions for ILs for the products for re-export that the importer should not sell unregistered imported drugs in Hong Kong and must re-export the products within a specified period of time, say one year.

Recommendation 26# – to conduct a joint review with C&ED to determine a new weekly quota for post-shipment consignment checks of licences which should be a statistically significant sample size of the ILs and ELs population.

Recommendation 27# – to require exporters who chose to export products by mail to clear their products at designated post offices. DH should

include the requirement in the ELs and discuss with C&ED for the introduction of a daily quota on outgoing mail parcels of drugs for verification of content and endorsement by C&ED.

Recommendation 28# – to develop an electronic record system among DH, C&ED and TID to facilitate the tracking of imported and exported drugs.

Regulation of Retailers

Recommendation 29# – to require all retailers of non-poisons to be subject to licensing and inspection control.

Recommendation 30# – in the longer term after taking into account the market operating conditions and the availability of sufficient pharmacists, to require the presence of a registered pharmacist whenever an ASP is open for business. Heightened enforcement actions should be taken against those non-pharmacists who violate and interrupt the pharmacists' performance of their duties at ASPs.

Recommendation 31* – to require all Part I Poisons be stored in locked receptacle in the premises of an ASP and that only the pharmacist should hold the key to the locked receptacle.

Recommendation 32* – to add a provision in the Pharmacy and Poisons Ordinance for the issuance and revision of the code of practice for ASPs in order to give a legal status to the code to enhance monitoring on the operation of ASPs; and to introduce a code of practice for LSPs which should enjoy the same legal status as the code for ASPs.

Recommendation 33* – to give the Pharmacy and Poisons Board the authority to revoke the licence of an ASP at any time after the ASP has been convicted of serious drug offence.

Recommendation 34* – to tighten the licensing conditions for the refusal or renewal of ASP or LSP applications. DH should evaluate what type of drug offences should be included based on their public health impact.

Recommendation 35# – to strengthen the monitoring of ASPs and LSPs by means of more frequent and more detailed inspections.

Recommendation 36* – to require ASPs and LSPs to purchase drugs from licensed traders only.

Recommendation 37* – to require that all orders for drugs to have written records.

Recommendation 38* – to require ASPs

to sell pharmaceutical products in their original packing, save in the case of a doctor prescription drug which is required by law to be dispensed in exact quantity in accordance with the prescription and in the case of pharmacist dispensing drugs to patients according to their need with proper labelling.

Recommendation 39* – to require ASPs and LSPs to keep all the supporting documents including drug orders and sales invoices related to every purchase of all pharmaceutical products, and the documents should be kept as long as the expiry date of the pharmaceutical product concerned for DH's inspection if necessary.

Regulation of Drug Procurement

Recommendation 40# – both DH and HA to conduct post-delivery surveillance including microbiological and chemical testing to ensure drug quality.

Recommendation 41* – both DH and HA to require the suppliers to provide additional information, such as pack size and registration number, etc. in the delivery documents to enable more effective physical checking and verification if drugs received are legally conforming.

Recommendation 42# – both DH and HA to provide additional training to staff and monitor the workflow in the repacking activities in drug dispensing to minimize errors.

Recommendation 43* – to impose a new requirement on suppliers to keep samples of each batch of drugs that are still within the expiration period to facilitate investigation when needed.

Recommendation 44# – to upgrade DH's central inventory monitoring computer system to enhance the traceability of drugs.

Recommendation 45# – DH to enrich the database of registered pharmaceutical products so as to provide more detailed information to the public on registration details of products, e.g. pack-size, labelling, legal classification, etc.

Recommendation 46* – HA to require suppliers to provide evidence that their products are either registered or are exempted from registration under the law.

Recommendation 47* – HA to require suppliers to provide microbiological test results for high risk drug items and batch release certificates on all drugs supplied to HA to ensure safety and quality.

Recommendation 48* – HA to use

multiple sources for supply of high risk products with high usage volume.

Recommendation 49# – HA to establish a Drug Quality Assurance Office to enhance quality monitoring of products, performance management of manufacturers and suppliers and quality incident management as well as to monitor the implementation of all improvement initiatives.

Recommendation 50# – HA to enhance the current electronic system, such as exploring the use of RFID, bar coding, wireless data transmission, etc. to enable product traceability and effective stores management.

Recommendation 51* – HA to require suppliers to provide drugs in suitable pack sizes as far as possible to reduce the need for repacking.

Recommendation 52* – DH to issue a set of guiding principles on drug

procurement for the private medical sector and encourage private hospitals, MCOs and private medical practitioners in solo or joint practices to follow this set of guiding principles as far as

practicable. Recommendation 53* – DH to encourage private hospitals to develop an automated inventory management system and bar-coding system for pharmaceutical products.

Pharmacovigilance

Recommendation 54* – to establish a pharmacovigilance advisory body to review DH assessments of the ADR reports received, advise DH on action on specific cases, serve as an editorial advisory board of the pharmacovigilance bulletin and assist DH in the promotion of pharmacovigilance activities.

Recommendation 55# – DH to set up a dedicated team to promote pharmacovigilance work among professionals, education institutions and the industry; handle ADR reports received; disseminate information; and support the pharmacovigilance advisory body.

Recommendation 56* – DH to publish a regular pharmacovigilance bulletin for distribution to all doctors, dentists and pharmacists, and a user-friendly version of the bulletin for reference of the general public.

Recommendation 57# – DH to include an ADR report form in mails to doctors and pharmacists, enhance DH website such that doctors and pharmacists could

subscribe and receive emails from DH on ADR as soon as they become known, encourage the use of electronic reporting of ADRs, and develop additional electronic interface for dentists and pharmacists to facilitate ADR reporting.

Recommendation 58# – DH to publish guidelines for the drug industry on their responsibilities to report ADRs, to educate and encourage them to report ADRs and to develop a culture of awareness of pharmacovigilance.

Recommendation 59* – to require the drug industry to report any actions taken by overseas drug regulatory authorities on any drugs as a consequence of safety issues and require manufacturers to inform DH if they have committed to the request of European Union or United States to develop an EU Risk Management Plans (RMP) or US Risk Evaluation and Mitigation Strategies (REM) as a condition for approving a new drug.

Recommendation 60* – DH to review ADR reports within three working days.

Recommendation 61* – DH to establish liaison with overseas health authorities for exchange of ADR information as well as providing training on pharmacovigilance to staff.

Recommendation 62# – DH to review the progress and effectiveness of the development and implementation of the improved pharmacovigilance measures in two years' time.

Recommendation 63# – DH to continue the heightened surveillance against high risk products sold in the market and set up a dedicated team of pharmacists to handle increased sampling of high risk products.

Recommendation 64* – to adopt a risk-based approach in drug recall and public communication. Specifically DH should revise the recall guidelines to include the different stages of recall procedures, the classification of the recall, the level of the recall, the strategy of the recall including the dissemination of information to the public, the responsibilities of the trade including refund, and the monitoring of all follow up actions, including the effectiveness of the recall.

Recommendation 65* – DH to inform the Consumer Council on every drug recall incident at consumer level to widen the dissemination network of the drug recall message.

Recommendation 66* – DH to add a refund mechanism in the recall guidelines

requiring manufacturers and wholesalers to provide refund details to consumers at retail level in the event of drug recall.

Risk Communication

Recommendation 67# – to set up a dedicated, multi-disciplinary team to oversee education and training. The team should collaborate with and coordinate efforts of the academia, Consumer Council and relevant professional bodies in the provision of education and training programmes on drug safety.

Recommendation 68# – to continue organizing seminars with additional focus on quality control for the management at different levels of the drug supply chain as well as front-line staff.

Recommendation 69# – to enhance the content of “Compendium of Pharmaceutical Products” on DH website to provide more information about each registered drug.

Recommendation 70# – to set up a designated website on drug safety to provide a better platform for information dissemination and exchange.

Recommendation 71* – to establish a working group to work out the prototype of the enhanced website and its contents.

Recommendation 72# – to require that more information on drugs and patient oriented advice be provided along with drugs dispensed to patients at hospitals or clinics.

Penalty System

Recommendation 73* – to include more aggravating factors in the facts of the case submitted to the Court to reflect the seriousness of the offence concerned for the Court to impose an appropriate sentence.

Recommendation 74* – to amend the Pharmacy and Poisons Ordinance to include provision for the Court to order the convicted person to pay the analytical costs incurred by the Government to increase the deterrent effect.

Manpower Requirements

Recommendation 75# – to expand DH's Pharmaceutical Service into a dedicated office on drugs to strengthen DH's regulatory role in enhancing drug safety. In the long run, consideration will be given to expanding the office to be a “Centre for Drug Safety”.

Current Dietetic Practice in the Management of Gout

CHAN, Yuk Yi Joanne

ABSTRACT

Gout is one of the most common forms of arthritis that occurs amongst men globally, affecting synovial fluid of joints, manifests in series of inflammatory response and intensive pain. The therapeutic goal in the dietetic management is the lowering of serum uric acid to prevent crystal formation and deposition in the affected joints. Conventional intervention involves the use of urate lowering drugs in conjunction with various dietetic strategies to prevent exacerbation, including weight lost and dietary modifications with an aim to reduce the uricosuric effect of dietary proteins, increase fluid intake and weight control.

Keywords: Gout; Arthritis; Nutrition; Purines; Uric acid; Dietetic management

INTRODUCTION

Gout is one of the most common forms of arthritis that occurs amongst men globally. It can be caused by different factors such as disease, drugs: including diuretics and diet leading to the build up of insoluble uric acid formed as an end product during purine metabolism of which under normal circumstances is excreted in the urine as monosodium urate (MSU). Elevated amounts in blood reaching saturated point of 6.8 mg/dL may lead to the formation and deposition of urate crystals. Most commonly affected areas are within synovial fluid of joints such as great toe, foot, ankle, knee, wrist, finger, elbow triggering a series of inflammatory response involving the production of Interleukin 1, characterized by the swelling of the joints and can be intensely painful of which usually resolves within 7 to 10 days. Uric acid crystals possibly can also be deposited under the skin around hands, elbows and ears.

The therapeutic goal of lowering serum uric acid (SUA) in individuals is to prevent crystal formation and deposition in joints by achieving a SUA level of ≤ 6 mg dL⁻¹,⁽¹⁾ this is often achieved by prevention treatments such as the use of urate lowering drug and or in conjunction with dietary recommendations by dietitians.

GOUT AND NUTRITION

Foods highest in purines (150-1,000 mg/100 g)	Anchovies, sardines. Mackerel, kidney, brain, liver, heart, meat extract, scallops, mussels, goose, fish roe, yeast extract
Foods high in purines (50-150 mg/100 g)	Other shellfish- crab, shrimps, eel, beef, veal, pork, lamb, game, chicken, duck, turkey, other fish besides those stated as highest in purines, legumes, beans, lentils, soya, peas, asparagus, cauliflower, mushroom, spinach, wheatgerm and bran
Foods lowest in purines (0-50 mg/100 g)	Milk, nuts, eggs, cheese, pasta, noodles, bread and cereals except wholegrains, cakes and biscuits, chocolates, ice cream

Despite the general population may feel that adhering to dietary advice maybe difficult to follow in comparison to taking medications, 97% of fifty-nine rheumatologist respondents reported that they would consider diet in the management of their patients with gout in a recent research conducted by Shulten et al.⁽²⁾ Nevertheless, in the view of dietetic practice, there is evidence to support that dietary recommendations and adherence of specific food commodities will aid the lowering of SUA levels.

A recent research by Bowering et al, have shown that increases the intake of dietary protein increases the uric acid turnover rate without altering the urate pool size.⁽³⁾ Whereas consuming increased intake of purine rich foods such as meat and seafood and alcohol increasing the risk of gout, despite the consumption of purine rich vegetables have no associated with elevated uric acid levels. Choi et al, have shown intake of dairy have shown the ability to have serum uric acid lowering effect whether it is because dairy is low in purine as it replaces other meat intake thus not affecting the urate pool or by its uricosuric effect due to milk proteins (casein and lactalbumin).⁽⁴⁾

However, little is known regarding the precise quantity of foods as the quantity varies whether it is cooked, the way of processing, bioavailability of the food.

DIETETIC PRACTICE IN PREVENTION OF RECURRENT GOUT

Lose weight with light physical activity

Carefully losing weight to ideal body weight in combination with exercise in adherence to WHO recommendation of less than 2 kg per month have shown to make a moderate contribution to the lowering of serum uric acid levels.

Eat to the recommended protein intake

Despite researches completed by Choi et al⁽⁴⁾ and Bowering et al⁽³⁾ respectively have shown that increasing total protein intake increases uric acid turnover rate with out affecting the serum urate pool. Increasing protein intake may lead to the excessive intake of calories leading to

weight gain, hence the adverse effect on gout management.

Decrease in purine intake

High purine intake is significantly associated with the onset of gout and that the lowering consumption has been the main dietetic practice in terms of the therapeutic goal. The UK gout Society has distinctly listed out foods that are highest, moderate and lowest in purines as a recommendation to those who suffers from gout.

Increase fluid intake 8 to 10 glasses per day

Fluid intake aiming at 8 to 10 glasses per day helps to prevent the formation of urate crystals and the elimination of excess SUA.

Drink 1 to 2 glasses of skimmed milk per day

With evidence of the inverse relationship between increasing dairy intake and SUA shown by Choi et al.⁽⁵⁾ 1 to 2 glasses of skimmed milk per day is recommended to help the prevention of gout.

Vitamin C supplementation

Supplementation of 500 mg per day of vitamin C results in a decrease of SUA due to the enhancement of excretion by the kidneys has shown by a research conducted by Choi et al.⁽⁴⁾ It is common amongst rheumatologist during current practice to recommend vitamin C supplementation in conjunction with their advice.

Author's background

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Coaching to Build an Effective and Sustainable Team

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ABSTRACT

The ability to raise the performance of employees and seek long-term goals for them to work toward is a key strategy for effective managers. Through coaching, a manager can develop staff to take on more responsibility and get the best from the team, allowing the manager to focus on achieving better results for the organization. Four pharmacy students from the Chinese University of Hong Kong discussed about their experience working at a multi-national pharmaceutical corporation, and how coaching helps them to succeed and transition to the workplace.

Keywords: *Coaching; Maximizing potentials; Work performance; Mentor; Learning*

INTRODUCTION

Effective coaching often helps managers to materialize long term business success by increasing employees' work performance, bringing out potentials, and building trusting relationships with employees at work. In fact, the future of any prosperous organizations rest with the balance between increasing capabilities and productivity of its workforce, which can be indirectly improved through developing an individual employee.

Recent years, a lot of companies including pharmacies and hospitals, tend to find ways to cut cost and raise revenues. Companies or organizations that focused on short term cost saving measures, rather than investing and developing a longer-term human development during the financial downturn, are beginning to realize that employees are the core of any sustainable business growth.

Many pharmacists that work in hospitals, community pharmacies, manufacturers or multi-national

companies have to manage and lead a team of colleagues. Coaching ensures that managers can focus on the issues that are important, while engaging colleagues to achieve better performance. This article aims to highlight the long-term benefits of coaching, the steps that would lead to a successful coaching relationship, and ways to conduct coaching effectively. The article ends with a summary of the interview with four students from the Chinese University of Hong Kong who interns at a multi-national pharmaceutical company in Hong Kong.

Achieving more and better together

Coaching can often be seen as a process of bringing out potentials of the person being coached, through elevating an individual's or team's present level of performance to the desired one. Imagine going on a hiking trip with several colleagues. Each one of them has particular skill sets and abilities, and may even carry invaluable tools that would be tremendously helpful to the team. Taking initiatives to coach is a crucial step in establishing relationships and gaining trust from the employees.

Coaching is an effective way for pharmacists and managers to work with his/her staff, enabling them to shoulder some of the workload, while providing room for staff development and growth. The ultimate goal for the team is to advance and achieve more together, but just as important is to develop the staff's capabilities and skills so that they could eventually carry on the task by themselves.

Through coaching, a good manager can focus on more important issues – managing people rather than tasks. Once the potentials of an employee are realized, the manager can begin to delegate and lift off some of the responsibilities to the individual, sparing out time for essential items. This article aims to discuss the tools and steps that

would help any managers to climb the mountain further by engaging his/her team through coaching.

UNDERSTANDING COACHING

Coaching has been recognized as one of the most cost-effective way of improving individual performance. It is often used in the sports world, but increasingly the process is applied to the business world.⁽¹⁾

What is coaching?

Coaching is defined as a set of skills for managing employees' performance to deliver results. It can be used by managers to handle issues at work, interact with employees constructively, and develop staff to reach their fullest potentials.⁽²⁾ Through engaging in a challenging environment, employees learn, grow and develop skills and abilities.

Types of coaching

There are different types of coaching:⁽³⁾ Life coaching aims to help coachee determine and achieve personal goals. Personal coaching takes place through establishing a relationship that is designed to coach based on the coachee's interests, goals and objectives. Business coaching is the practice of providing positive support and feedback while offering advice in order to help an individual or group to recognize ways in which they can improve the effectiveness of their business.

How coaching works?

Offering specific interacting skills and encouraging employee of long-term learning can be part of the coaching process. It can take place over a single coaching session or a series of sessions. A coach will work closely with the coachee to assess performance, discuss problems, define achievable goals, explore new initiatives, and support a coachee's plan of action.

The coaching process

Coaching is a continuous process of improvement whereby new achievements establish the platform for future challenges. For any one coaching process, there is a cycle of six basic stages from establishing goals to completing the plan of action.⁽⁴⁾

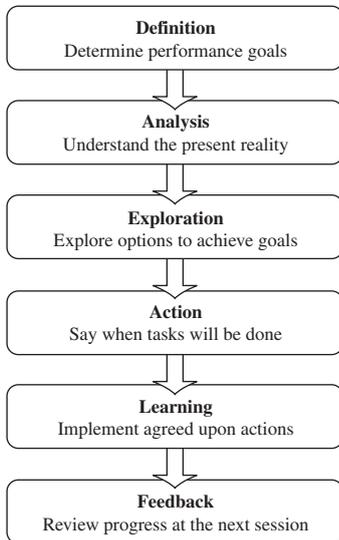


Figure 1. Structural chart of coaching process.

The coaching process can be structured in six-steps (Fig.1). The coach and staff start by discussing and agreeing on the goals of coaching. Next, they discuss the present situations and problems that the coachee is facing. This is followed by investigating and exploring the available options, and identifying and committing to a course of action. Throughout the process, the coach continues to provide support. Each step along the process ensures that performance levels can be raised continuously. In the final step, the coach and coachee reflect on the process and establish plans to build upon the learning.

Effective coaching can occur even when the manager does not have detail information about the individual's work. It is a learning technique that involves observing an individual at work, knowing their personal goals, and providing feedback to enhance performance or correct deficiencies. It is about helping employees to implement the plan of action and learn from their mistakes, avoiding to focus on the tasks to be done but rather, encouraging participation and voicing out ideas, while guiding them to succeed in achieving their objectives.

Why coaching?

Coaching has become the cornerstone

of employee development in many organizations. Its primary emphasis is on maximizing people's potential, improving skills and knowledge by developing employee's self-confidence and creativity. When the team has a positive attitude, they are more willing to take on new challenges and try new approaches.

Harvard Business Review summarizes that "the purpose of coaching is to produce behavioral change and growth in the coachee for the economic benefit of the client. The best way to maximize the likelihood of good results is to qualify all the people involved."⁽⁵⁾

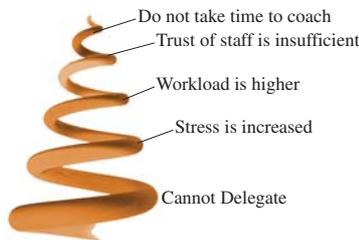
Managers can achieve more for the organization

Through the process of coaching, managers can develop a trustworthy relationship with the employees. Once trust is established, the manager can begin to delegate responsibilities and reduce the time to supervise because the staff is more capable to make their own decisions. As the manager coaches, delegates, and spends less time to supervise, there is more time to manage people and focus on more important issues.

Upward Spiral of Responsibility⁽⁶⁾



Downward Spiral of Development⁽⁷⁾



Employees take up new challenges

Asking questions and giving constructive feedback can be beneficial to help an employee to find his/her direction. Use their successes and mistakes as a learning to help them to build on their strengths and to develop new skills, so that they can take on new challenges. When self-confidence and motivation grow, people take on more challenging

assignments, and are willing to make initiatives to solve problems for the organization.

Employees are engaged

When people have the opportunity to take part in decision making, they have greater commitment to the final decision, and they are more likely to perform their best. Employees will feel most motivated when they're involved in making decisions about their career and development. Coaching is a two-way process that engages people to actively seek for ways to achieve their goals without setting the detail guidelines.

Employees are productive

Through coaching, team member's skills develop, work becomes more efficient, and the productivity of the team increases. Each employee are clear on the objectives and goals of the coach, they acknowledge their responsibilities, and what good performance looks like. With this knowledge, teams can spot and correct mistakes more quickly, and can use their skill to deliver the required quality of work. The result is greater productivity.

Coaching is beneficial to all (Fig. 2)

Coaching is a long-term strategy. But the benefits of managerial coaching can be achieved for both employees and managers. Managers benefit from delegating and empowering employees, freeing up more time to work on important tasks. On the other hand, coaching helps employees to have a clearer career focus, greater commitment and job satisfaction.

COMMON MYTHS AND MISUNDERSTANDING

The benefits for individuals and their organizations can be plentiful if the coaching intervention is applied with the correct principles. It is important, therefore, to dismiss the myths that surround coaching for potential coaches. The following lists the common myths about coaching.⁽⁹⁾

Coaching will not work without any good role models

Coaching depends less on the qualities of a manager than on the behaviors of the manager and the tools he/she choose to use to encourage employee

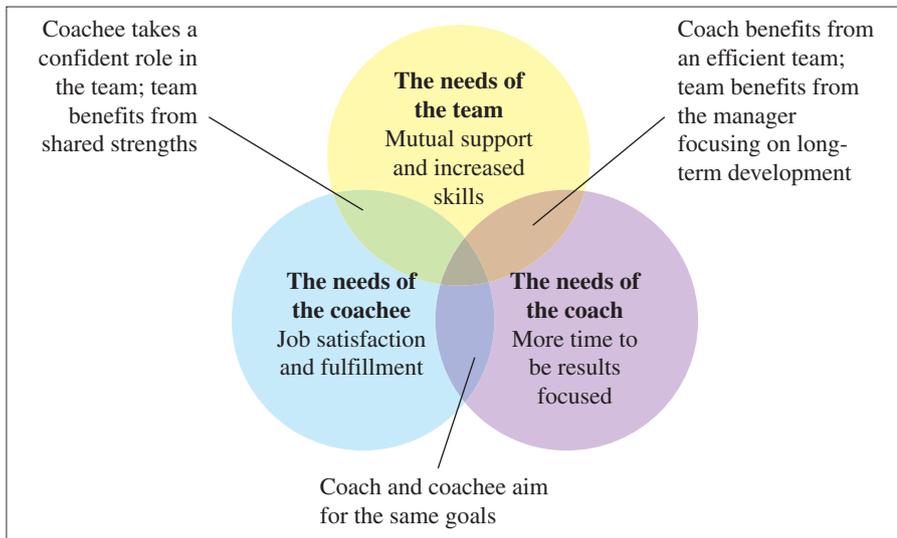


Figure 2. Benefits of coaching (9)

performance. With a positive attitude, anyone can take up the responsibility to provide good coaching and leadership.

Coaching means seeking consensus on every decision you make

Coaching often involves collaboration among managers and employees, but decisions do not always have to be made by consensus as different position has different levels of responsibilities and tasks. As a manager, decisions can be made with no input or discussion from the staff. Moreover, when the responsibility for action rests with the employee, the manager has to trust and give accountability for the staff to make the decision.

Coaching is not necessary for good employees

Even good employees need direction, goals, feedback, training, and challenging work. Coaching is a way to ensure that even the best employees' capabilities and potentials can be maximized.

Employees have to ask for coaching in order to be receptive to it

Coaching does not require invitations from your employees, and it certainly is not based on who the manager think is coachable. Coaching is to offer leadership for the employees. Employees will be receptive when they understand that coaching is to improve their skills and to ensure that quality performance is delivered to meet the needs of the business.

Anyone can be an effective coach even if they lack technical competence in the area

Not all managers can manage any function effectively. When the area of work requires technical competence, it is difficult to coach without a deep understanding of what employees do.

On the other hand, managers at higher levels often have to work across multiple functions, dealing with employees with different responsibilities. Most managers do not have the technical competence for all the areas. Coaching at this level would be important because it allows managers to set direction for the business and coach others to be more effective in managing their employees.

Coaching is about being nice to employees

Coaching focuses on personal influence rather than personality. It is about honestly communicating with employees and actively giving them constructive feedback about their performance. The key is to be assertive rather than nice.

Coaching equals feedback

There are a number of important coaching tools and habits, and giving insightful feedback is only one of the many. Effective questioning is another useful tool that can lead to empowerment for the coachees. Establishing a good relationship is another essential skill.

Coaching is time-consuming

The most effective use of time for a manager is to help others to be more effective. Coaching thrives on the use of quality time, which means spending time with employees, helping them to perform effectively and independently. With practice, coaching can become a routine part of the manager's work. In fact, small investments of time, delivered at the appropriate moment, can lead to tangible results for the individuals and the organization.

DIFFERENCES BETWEEN COACHING AND MENTORING

A coach and mentor often perform their work using similar skill sets, such as strong interpersonal and communication skills. The differences between mentoring and coaching are summarized in Table 1.(10)

Mentoring focuses specifically on the person, where the mentor provides guidance, direction for individual growth and advices on career while coaching is job-focused and performance oriented. Mentors facilitate mentees to discover their direction, while a coach has a set agenda to reinforce or change skills and behaviors.

Informal mentoring relationships are often initiated and maintained by the mentee while very often in an organization, coaching comes with the job. There is often an implied level of authority of a coach, who can request for compliance and changes. The influence of a mentor, on the other hand, depends on his/her perceived value in the mentoring relationship.

Coaching can result in more team work and enhanced job performance, whereas mentoring can be a learning process for the mentor from the feedback and insights from the mentee. Mentors often give broader life and career guidance, whereas a coach would be responsible for tasks or products based issues at work.

In fact, some argue that coaching

Table 1. Differences between coach and mentor		
	Mentor	Coach
Focus	Individual	Performance
Role	Facilitator with no agenda	Specific agenda
Relationship	Self selecting	Comes with the job
Source of influence	Perceived value	Position
Personal returns	Affirmation / learning	Teamwork / performance
Arena	Life	Task

involves aspects of mentoring. The emphasis of the mentoring in coaching is on employees, enabling them to solve problems, make decisions, and set plans at their own level of responsibility. This form of coaching involves periodically spending time with employees, time in which development takes place for the coaches and coach.

CONDUCTING A COACHING SESSION

Start with a positive topic

Start off the conversation with a lighter topic to put the employee at ease. The topic could be related to a common interest or the achievements of the employee.

Outline the issues

The issues of a coaching session could be work or career-related. Outline the rationale for coaching, and explain the problems if the issue is work performance-related. Make sure that the employee acknowledges that the problem exists, and if necessary, explain the consequences if the problem continues.

Work with the employee's agenda

Find out what the employee hopes to achieve for the session, and establish a clear basis. Engage the coachee so that the coaching is collaborative.

Shape the coaching session

Coaching is an organized way of generating ideas that raise individual performance. The steps of the coaching session could be divided into the GROW steps:⁽¹¹⁾ define the goals, explore present reality, discuss options, and agree on when an action will take place.

Setting goals

Goal setting provides a structure for the coaching session and gives an overview of the resulting action. It sets a direction for the meeting, and ensures that the coachee is progressing toward the goal. The coaching goal is mutually established between the manager and employee. It should be realistic in terms of time frame, and achievable on the employee's level of experience.

Checking reality

It is important for a manager to listen to a coachee's concerns, observe and assess performance. After assessing the present skills level, look for potential ways for the employee to move forward to the desired level.

Discovering options

Through coaching, a manager can learn more about the employee's strengths and skills. The key is to determine how this particular skill can be utilized positively in the job responsibilities. Determine the options available, and align the strengths to the goals agreed upon.

Deciding when

Once goals have been defined, reality checked, and options established, it is up to the coachee to select the most suitable option and consider how it might be put into practice. Ensure that the session ends with a commitment to a specific action within a given time. Schedule the next coaching session so that the employee can report back on results.

TECHNIQUES IN COACHING

There are various coaching tools that are used in business coaching. Coaching technique refers to the art of using such a tool in a way to develop and bring out the potentials of a coachee. Appropriate techniques can be applied through sharing (offering insights and observations), mutual understandings, and challenging (encouraging employees to think for themselves). These sets of tools stimulate thinking and help to provide guidance for employees.

Sharing

A manager can strategically share and pass on his/her thoughts, insights, and wisdom to the employees. Through sharing of experiences and knowledge, employees can learn from the manager's successes and mistakes. Sharing through storytelling is often encouraging and compelling. This type of sharing can include insight on technical matters as well as ways to interact with others, make decisions, or adapt to a corporate culture or work environment.

Other types of sharing involve sharing observations of the employee's behavior and work efforts, in the areas important and helpful to the individual's development. Sharing observations invites employees to reflect and provide the opportunity to learn from past performance.

Sharing might involve providing the direction of where a manager sees the group heading towards in the next few months, highlighting what good results look like on an important project, or sharing how an employee's role evolve if that person works to develop his or her skills and abilities. Sharing in this way provides a sense of direction and a focus on the future. It works to give employees a greater perspective and understanding of their role and performance within the unit or team.

Mutual understandings

The key technique in coaching is to establish an open relationship. When offering feedback to the employee, a manager should try to avoid imposing an opinion, but to offer honest feedback, and be prepared to clarify and expand. Be ready to ask for the coachee's perspectives, and how he or she thinks about the feedback. On the other hand, it is important to remain open to the feedback being offered. Listen attentively, evaluate and assess the validity of the feedback, and also the consequences of acting on it. Be prepared to ask questions to clarify the points being made.

Challenging

The other set of techniques is to challenge coachees to think for themselves. Managers can offer far more help when asking the right questions. Moreover, a manager can guide and support an employee to come up with a plan of action. This is a collaborative effort that involves the manager giving direction, providing information and other resources, giving feedback and establishing the next steps.

Through coaching, a manager can also ask an employee for decisions and recommendations. This begins when the team analyzes possible options, the advantages and disadvantages, and the associated benefits and obstacles. A manager can empower the employee to make decisions that he/she thinks will work best.

Giving challenging assignments is an opportunity for employees to learn and gain valuable experience. The idea is to stretch and challenged the employees. A manager can provide support in terms of giving frequent constructive feedback and encouragement. Most importantly, the process is to challenge the staff to think and do for themselves and allow them to experience success from it.

THE KOLB LEARNING MODEL

Different people work and learn differently, and they might prefer a particular learning style. The Kolb Learning cycle can be used to understand individual learning styles, and to promote and maximize opportunities for learning in work situations.⁽¹²⁾ Kolb's cycle comprises four different stages of learning from experience, and all stages must be followed in sequence for successful learning to take place (Fig. 3). The cycle suggests that learning can only take place when the experience is followed by reflection, concept formulation, and application to new situations.

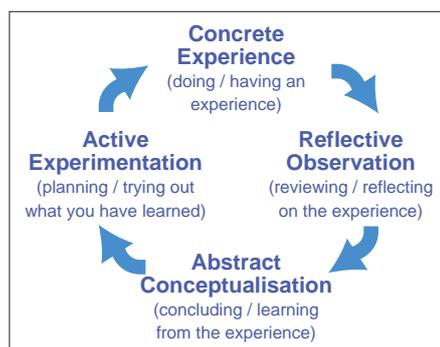


Figure 3. The Kolb learning cycle ⁽¹³⁾

Learning cycle

Concrete Experience: The Kolb learning cycle begins with the person exposed to events in life that could have a positive, negative, emotional or behavioral impact.

Reflection or observation: After the experiences and events, reflection takes place where an individual goes through a thoughtful evaluation of the event and draw out learning.

Abstract conceptualization: After gathering all the information, a person can begin to build the structures that would help to define and conceptualize the world. Theories or rules are defined, and expectations are formed.

Active experimentation: After establishing the explanations about the world, the

concept must be tested. This stage allows the person to verify predictions against reality and experiences. The resulting experience is then fed back into the system, and the cycle begins again.

Learning Styles

The aim of the coach is to create the optimal environment in which an individual can perform and learn effectively. Four different types of learning styles have been identified, in association with the Kolb Learning Cycle. They are the activist, reflectors, theorists and pragmatists.

Activists: Activists are comfortable functioning in the experience stage of the learning cycle. They enjoy getting involved in new experiences, seeking out opportunities, and taking on problems and challenges. Activists learn best when they can actively engage in tasks, be involved in challenging activities, and they excel in situations where they have the opportunities to lead.

Reflectors: Reflectors like to take the time to think through various angles before taking actions. They are often cautious in jumping into conclusions, they prefer to listen and watch. This group of people learn best when they have access to all of the information, and when decisions and actions are not rushed.

Theorists: Theorists tend to integrate and synthesize information about the world into rational explanations or structures. They are interested in principles, assumptions, objectivity and logic. The best learning environment for them is when logical systems or models can be applied, when relationships between facts and ideas can be explored, and when the issue is objective and is based on rational principles.

Pragmatists: Pragmatists value new ideas, and they are practical with the application of the ideas. They enjoy getting on with realistic activities and problem-solving, trying things out, and dealing with practical issues. They learn best when they can see a link between their work and real-world applications.

Understanding and knowing the different learning styles can help a manager to enhance employees' work performance. A manager can facilitate the environment and create work that would best suit the needs and capabilities of the employees,

leading to better performance and job satisfaction.

THE JOHARI WINDOW

Understanding personal development, improving communications, interpersonal relationships, group dynamics, team development and inter-group relationships are key processes of coaching. The Johari Window is a communication model that is used to describe the process of human interaction and to improve understanding between individuals within a team. Two key ideas behind the model is that 1). Individuals can build trust between themselves by disclosing information about themselves, and 2). Individuals can learn about themselves and come to terms with personal issues with the help of feedback from others. The model is used to help people build more trusting relationships with one another, solve issues and work more effectively as a team. It puts emphasis on behavior, empathy, cooperation, inter-group development and interpersonal development.⁽¹⁴⁾

The Johari Window model consists of a foursquare grid as illustrated in Fig. 4.⁽¹⁵⁾

The Johari model divides personal awareness into four types, represented as the four quadrants: open, hidden, blind, and unknown. Each of the windows contains and represents personal feelings and motivation about the person, and shows whether the information is known or not known by themselves or other people. The arrows indicate the movement of the awareness as interaction progresses.

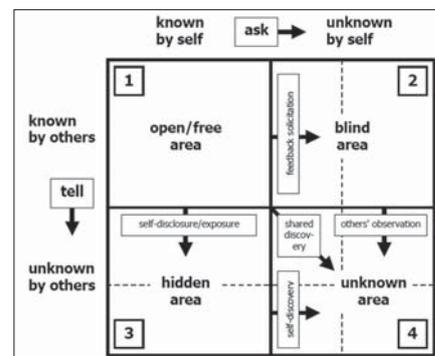


Figure 4. The Johari window of communication

Quadrant 1: Open/Free area

The open/free quadrant represents what is known by the person about him/herself and is also known by others. The aim in any group is to develop this quadrant for every team members, so that good

communications and cooperation occur to become effective and productive.

Quadrant 2: Blind area or blind spot

The blind quadrant represents what is unknown by the person about him/herself but which others know. This can be simple information, or deep issues that are difficult for individuals to face directly, but can be seen by others.

Quadrant 3: Hidden or avoided area

The hidden or avoided quadrant represents what the person knows about him/herself that others do not know. As people get to know and trust each other, it becomes more comfortable to disclose more intimate details about oneself. This process is called self-disclosure.

Quadrant 4: Unknown Area

The unknown quadrant represents what is unknown by the person about him/herself and is also unknown by others. Being placed in new situations often reveals new information not previously known to self or others. Thus, a novel situation can trigger new awareness and personal growth.

Enlarging the open quadrant

The process of enlarging the open quadrant vertically is called self-disclosure, a give and take process between the person and the people he/she interacts with. As information is shared, the boundary with the hidden quadrant moves downwards. And as other people reciprocate, trust tends to build between them.

The process of enlarging the open quadrant horizontally is feedback solicitation. Here the individual learns things about him- or her-self that others can see, but he or she can't. If anyone is interested in learning more about this individual, they reciprocate by disclosing information in their hidden quadrant. As the levels of confidence and self-esteem rises, it is easier to invite others to comment on an individual's blind spots. Active and empathic listening skills are useful.

Working in the open quadrant with others usually allows for enhanced individual and team effectiveness and productivity. The area ensures that there is good communications and cooperation among the team, and members are

free from confusion, conflict and misunderstanding. By encouraging healthy self-disclosure and sensitive feedback, a manager can build a stronger and more effective team.

COACHING PHARMACY STUDENTS FROM THE CUHK

Four students from the Chinese University of Hong Kong Pharmacy School discussed about their experience interning at a multinational pharmaceutical company, Pfizer, in Hong Kong. Third year pharmacy students Anne, Tom, Ada and Vincent, all expressed the importance of the role of a good manager play in helping them to set and define their goals at work. Navigating in a new working environment can be made less intimidating with the coaching process and guidance of a manager.

Tom expressed that he felt motivated when his manager regularly checked on his work progress, offered him advice and honest feedback, and asked detailed questions about the project. He found working closely with the manager to explore the different options to his project as one valuable element of the coaching relationship. On the other hand, strong motivation to do well and job satisfaction came from feeling empowered in a project, said Ada. Anne highlighted that being able to participate and engage in goal-setting for her project was most helpful. Vincent observed that there are two kinds of managers. There are managers who oversee the strategic functions of a business or team, but he found that managers who work closely with employee contributed the most to his performance. The latter type of managers understands an employees' work and is capable of answering questions that may arise.

All four students concluded that a manager who coaches helps them to better understand their strengths and weaknesses, the areas to progress, ways to improve and how to resolve issues that might arise at work. They stressed that understanding the direction and goals are just as important as exploring the different options to achieve the goals.

CONCLUSION

Coaching is a way to lead people to an improved state, and the process requires

building a trusting relationship between the manager and staff. Hiking is a long journey like coaching, which requires the manager to lead the team in the right direction, while delegating responsibilities and empowering the team to decide how to get to the destination and what to do when problem arises. An effective manager can create an environment that is inductive to a staff's learning style and motivate the team to communicate openly to each other. Better performance and results can be achieved when coaching strategies are applied appropriately.

Author's background

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Hong Kong Pharmacy Conference 2010: Pharmacist in the New Decade - Building Our Healthy Land

HUNG, Gloria

Pfizer Corporations Hong Kong Limited

After a painstaking 12-month preparation, the curtain of the 2-day Hong Kong Pharmacy Conference 2010 was finally lowered on 24th January 2010. The theme this year is Pharmacist in the New Decade - Building Our Healthy Land. This is by far the largest Pharmacy event in Hong Kong, attended by over 500 people each day. Apart from the invited overseas speakers and local delegates, we attracted pharmacists from other Asia countries and regions like mainland China, Macau, India, Thailand and Malaysia. The organizing committee is very glad to receive your feedback via evaluation forms and other means.

On the opening day, 23rd January 2010, we were honoured to have Dr. York Chow, the Secretary for Food and Health, Dr. PY Leung, Director (Quality & Safety), Hospital Authority, Professor Vincent Lee of the School of Pharmacy, the Chinese University of Hong Kong, and the Presidents of the three pharmacist societies/association together with Ms. Linda Woo, the Chairlady of the Pharmacy Conference 2010 officiated the opening ceremony while Dr. PY Lam, the Director of Health delivered the opening remarks. Dr. NT Cheung was the first to give us a theme speech on the very important and relevant electronic health record (eHR). Mr. Zhao Zhigang from the Beijing Tiantan Hospital then brought us up-to-date on the current development of pharmaceutical care services in public hospitals in China. He provided excellent reference and insights to the clinical pharmacists in Hong Kong regarding service development. Then Professor Yuen Kwok Yung presented the scientific background and investigation regarding the outbreak of intestinal Zygomycosis due to contaminated allopurinol tablets. With his logical introduction, fascinating pictures and lively presentation style, we learnt a hard topic in an interesting way.

The Conference Dinner was fantastic.

We are amazed every time when we watch our pharmacists, pharmacy interns and students perform in the Pharmacy Conference dinner show. This time they linked a dance performance to a detective story on counterfeit! While many of them were working hard for their pharmacy course and internship, they organized themselves to create and practise for the show. The multitasking skill learnt is indispensable for their life after graduation and registration! Moreover, the games and lucky draw sessions were so enjoyable that some of us could not help putting our delicious food aside.

The second day (24th January 2010) was indeed a busy day. When organizing the programme, we did worry if three concurrent blocks of 8-hour lectures and talks on a Sunday would hold our participants' attention. However, the content of the programme were so extraordinarily good that we simply could not turn away any proposed session. It was divided into three blocks elaborating the themes introduced on the opening day, namely Medication Reconciliation & Informatics, Quality Assurance and Integrative Medicine. We had pharmacist experts and clinicians sharing their knowledge and experience in medication reconciliation, oncology and integrative medicines. All were well attended and some very positive comments have been received from the participants.

There were discussions on the recommendations by the Review Committee on Regulation of Pharmaceutical Products in Hong Kong released in January 2010. The Pharmacy Conference provided an excellent face-to-face platform for over 400 pharmacists to exchange idea with Dr. Gloria Tam, Deputy Director of Health and the rest of the panellists consisting of various members from the Review Committee. Pharmacists from the academia,

community, hospital and industry sectors enthusiastically expressed their thoughts on the issues that they cared about. It was also a golden opportunity for many delegates to meet at one place for the first time to share their different views on the pharmacy profession after the release of the recommendations. It was a good start for further discussions and consultation in our profession.

New elements were introduced to the Pharmacy Conference 2010 such as student debate, Six Sigma workshop and a variety of exhibitors other than pharmaceutical companies. The first year CUHK pharmacy student debate on "Should Pharmacist be on duty for ALL opening hours of Pharmacy" was well attended and the audience enjoyed the interactive setting. The students in the two camps presented their arguments in a professional manner.

In the organizing committee, our pharmacists range from youngsters working hard for their pharmacy degree to the seniors who have rolled up their sleeves since the first pharmacy conference 22 years ago. Concurrent with the preparation for the Pharmacy Conference, our profession has gone through an eventful year when many of our routine duties were affected by various drug incidents. Without exceptional dedication, we could hardly pull together the Pharmacy Conference 2010. Without your participation and enjoyment, our work would have been worthless. Thank you Organizing Committee! Thank you Conference goers! Let's join our hands to build the healthy land!

Author's background

Miss HUNG Gloria is the Vice Chairperson of the Hong Kong Pharmacy Conference 2010. She is currently working at Pfizer Hong Kong.



Photo 1. A photo taken on Day-1 of the Conference. (From the left)

- Mr. Anthony Chan, Chief Pharmacist, Department of Health
- Professor Vincent Lee, Professor and Director, School of Pharmacy, the Chinese University of Hong Kong
- Ms. Anna Lee, Chief Pharmacist, Hospital Authority
- Dr. PY Leung, Director (Quality & Safety), Hospital Authority
- Dr. York Chow, Secretary for Food and Health
- Ms. Linda Woo, Chairlady of the Hong Kong Pharmacy Conference 2010
- Dr. PY Lam, Director of Health
- Ms. Iris Chang, President, the Practising Pharmacists Association of Hong Kong
- Mr. Benjamin Kwong, President, the Pharmaceutical Society of Hong Kong
- Mr. YW So, President, the Society of Hospital Pharmacists of Hong Kong



Photo 2. A photo taken on the 2nd Day of the Conference. (From the left)

- Mr. Samuel Sui Chor Hui, Vice-Chairman, Executive Committee, HK General Chamber of Pharmacy Ltd.
- Dr. Celine Cheng, the Hong Kong Pharmaceutical Manufacturers' Association
- Ms. Sabrina Chan, the Hong Kong Association of Pharmaceutical Industry
- Ms. Iris Chang, the Practising Pharmacists Association of Hong Kong
- Ms. Tina Yap, the Pharmaceutical Distributors Association
- Mr. William Chui, the Society of Hospital Pharmacists of Hong Kong
- Mr. Benjamin Kwong, the Pharmaceutical Society of Hong Kong

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*The odds of quitting smoking are defined as the number of subjects who succeed within a group vs the number who fail. An odds ratio is the ratio of the odds of an event, such as quitting smoking, occurring in one group to the odds of it occurring in another group. Odds ratios were based on results from the 2 comparative trials described in the enclosed page. Numbers were based on a logistic regression model.

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Detailed prescribing information is available upon request.

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- Achieving maximal erection hardness is a key factor and driving force in achieving greater sexual satisfaction^{2,3,4}
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Recent Advances in Antifungal Therapy

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ABSTRACT

For over 50 years, amphotericin B has been the mainstay of antifungal therapy despite its frequent toxicities. To cope with the rise of the incidence of invasive fungal infections and emergence of resistant-strain fungi, several new antifungal agents were developed in the past decade. Some of these newer drugs can now replace amphotericin B as primary treatment option (e.g. voriconazole for invasive aspergillosis, caspofungin for candidemia in neutropenic patients) while some offer new therapeutic options for difficult-to-treat fungal infections (e.g. posaconazole for zygomycosis). The new drugs are from two antifungal classes: triazole and echinocandin groups. The new mode of action from the echinocandins raises the issue about the possibility of the using combination therapy. Pharmacologic properties from some newer agents, including oral formulation with good bioavailability and improved safety profile, make them suitable for use as prophylaxis or long-term maintenance therapy.

Keywords: Antifungal; Triazole; Echinocandin; Aspergillosis; Candidiasis.

INTRODUCTION

Invasive fungal infections (IFI) have emerged as a leading cause of death in cancer patients, transplant recipients and other highly immune-compromised patients. The most common clinical

pathogens include organisms from *Candida* and *Aspergillus* species.^(1,2) However, the incidence of rare and resistant pathogens is increasing. For example, the incidence of zygomycosis, a fulminant and frequently fatal fungal infection, appears to be increasing in some high-risk populations.⁽³⁾

After a long period following the release of first triazole antifungal agents and lipid amphotericin B formulations in early 1990s, several new antifungal drugs have become available in the past decade. These drugs came at the right time, when the incidence of non-albicans *Candida* species and invasive mold infections was on the rise.⁽⁴⁾ Many of these fungi are less susceptible to, or are resistant to older antifungal agents. The new agents include a new generation of the triazoles (voriconazole, posaconazole) and members of the echinocandin class (caspofungin, micafungin and anidulafungin).

NEW TRIAZOLE ANTIFUNGALS

Antifungals in the azole class inhibit the fungal cytochrome P450 enzyme, 14 α -demethylase, thus interfere with ergosterol synthesis.⁽⁵⁾ As an integral component of the fungal cell membrane, depletion of ergosterol causes the loss of the membrane integrity and results in cell lysis.

Spectrum of activity

Each member of the azole class exhibits a unique spectrum of activity. All of them have good activities

against most *Candida* species.⁽⁶⁾ Voriconazole and posaconazole demonstrate extended antifungal spectrum, including fluconazole-resistant *Candida* strains, such as *C. glabrata* and *C. krusei*,⁽⁷⁾ *Aspergillus* species, *Scedosporium apiospermum*, *Fusarium* species and dimorphic fungi.^(8,9) However, voriconazole has poor in vitro activity against *Zygomycetes*.⁽¹⁰⁾ The introduction of posaconazole has extended the coverage further to include the *Zygomycetes* while maintaining activity against yeasts and molds.⁽¹¹⁾

Clinical uses

The Food and Drug Administration (FDA) approved uses for voriconazole and posaconazole were listed in Table 1 together with the recommended dosage regimen.^(12,13)

Voriconazole has been approved for the treatment of invasive aspergillosis since 2002 and has subsequently replaced amphotericin B for this indication. Currently the Infectious Disease Society of America recommends voriconazole as the first-line treatment of invasive aspergillosis.⁽¹⁴⁾ A randomized, unblinded study of voriconazole versus amphotericin B deoxycholate for initial therapy of invasive aspergillosis showed that voriconazole is more efficacious and safer than conventional amphotericin B (52.8% vs 31.6% successful outcomes).⁽¹⁵⁾ On the other hand, voriconazole is also approved as salvage therapy for fusariosis and scedosporiosis, responses of 45.5% and 30% have been reported respectively in studies.^(16,17)

Table 1. Approved indications for voriconazole and posaconazole with dosages.

	FDA-approved indications	Recommended Dosages
Voriconazole	Invasive aspergillosis	6mg/kg Q12H(1 st day loading dose); followed by 3-4mg/kg Q12H (IV) or 200mg Q12H (oral)
	Candidemia in non-neutropenic patients and in other deep <i>Candida</i> infections	
	Serious fungal infections caused by <i>Scedosporium apiospermum</i> and <i>Fusarium</i> spp. in patients intolerant of or refractory to, other therapy	
	Esophageal candidiasis	
Posaconazole	Prophylaxis of Invasive <i>Candida</i> and <i>Aspergillus</i> infections	200mg TDS
	Oropharyngeal Candidiasis	100mg BD(1 st day loading dose), then 100mg daily
	Refractory Oropharyngeal Candidiasis	400mg BD

Posaconazole is licensed for the prophylaxis of invasive fungal infections in severely immune-compromised patients, such as hematopoietic stem cell transplantation (HSCT) or hematological malignancies with prolonged neutropenia. A randomized, multicenter study of 602 patients with neutropenic fever by Cornely et al compared posaconazole with the standard antifungal prophylaxis, either fluconazole or itraconazole.⁽¹⁸⁾ The number of proven or possible IFIs identified was significantly less in the posaconazole group compared with the comparator group (2% vs 8%). Invasive aspergillosis was diagnosed in significantly fewer patients treated with posaconazole versus fluconazole or itraconazole, with 1% versus 7%, respectively. Ulmann et al. randomized 600 allogeneic HSCT patients with graft-versus-host disease to receive 16 weeks of antifungal prophylaxis with either posaconazole or fluconazole.⁽¹⁹⁾ Posaconazole-treated patients had a lower frequency of breakthrough IFIs during treatment (2.4% vs 7.6%) and a lower frequency of Aspergillus infections (1% vs 5.9%) than those who received fluconazole. Posaconazole also appears to be effective in the treatment of zygomycosis.⁽²⁰⁾ Several case reports showed that posaconazole is potentially useful in the treatment of patients with zygomycosis.⁽²¹⁾ In an open-label, multicentre study that evaluated the clinical responses to posaconazole in patients with zygomycosis intolerant of, or with disease refractory to standard therapies (amphotericin B alone or combined with other azoles), the response rate was 70% (16 of 23 patients).⁽²²⁾

Pharmacokinetics

Voriconazole and posaconazole possess different pharmacokinetic profiles. The details of the pharmacokinetic parameters of the newer antifungal agents are listed in Table 2.⁽²³⁾

Voriconazole is available both in oral and intravenous formulations and has excellent bioavailability

(90%). Fatty food has been found to reduce the bioavailability by 80%.⁽²⁴⁾ It is metabolized in the liver and its excretion is not affected by renal failure. However, the presence of sulfobutyl ether β -cyclodextrin sodium in the IV preparation has caused concerns about vehicle accumulation in renal insufficiency and dosage adjustment is therefore needed. In patients with creatinine clearance less than 50ml/min, IV form is best avoided.⁽²⁵⁾ It is mainly eliminated via hepatic metabolism (CYP2C19). Thus in patients with mild to moderate hepatic insufficiency, standard loading doses should be given, but the maintenance dose reduced by 50%. As CYP2C19 is the major metabolic pathway for voriconazole, inter-patient serum concentration differences have been resulted due to genetic polymorphisms.⁽²⁵⁾ The unpredictability of patient enzyme activity has generated needs to determine the serum voriconazole level routinely.

Posaconazole is lipophilic and has a high molecular weight thus is insoluble in water. It is formulated as a suspension with no currently available intravenous formulation.⁽¹³⁾ Absorption is enhanced by food, with a 400% increase in bioavailability when the drug is administered with a high-fat meal.⁽²⁶⁾ It is therefore recommended that posaconazole be administered with a high-fat meal or a nutritional supplement.⁽²⁷⁾ Posaconazole absorption is proportional to a daily dose of 800 mg, after which absorption is saturated. Steady state is typically achieved after 7 to 10 days of therapy, which affect the use of posaconazole as primary therapy for IFIs.⁽²⁸⁾ The median time to the peak posaconazole level is three to five hours, with optimal dosing achieved when it is administered in divided doses (two to four times daily).⁽²⁹⁾ It is metabolized in liver through glucuronidation and most of the drug is excreted unchanged in faeces. Dosage adjustment for hepatic or renal insufficiency is not necessary given the minimal glucuronidation and renal clearance.⁽¹³⁾

Adverse effects

Voriconazole has a few side effects reported, the most common of which are visual disturbances and mild elevation of liver transaminases, rash and gastrointestinal symptoms.⁽³⁰⁾ Visual symptoms are common (14-44%) and they include photophobia and blurred vision. Discontinuation is rarely necessary as these effects are reversible.⁽³⁰⁾

Whereas for posaconazole, the side effects reported are minimal and well-tolerated, including gastrointestinal disturbances and headache.⁽²⁸⁾ Elevated liver enzymes has also been observed.⁽¹²⁾

Drug interactions

The potential for drug interactions with voriconazole is high because it is metabolized by CYP450 enzymes.⁽¹²⁾ Among the potential interactions, there are some of clinical importance which should be caution about. Enzyme inducers, such as rifampin, carbamazepine and long-acting barbiturates, decrease voriconazole level and the combined use should be avoided. Rifabutin and voriconazole co-administration not only decreases voriconazole level but also increases rifabutin concentration to toxic levels thus concomitant use is contraindicated. Voriconazole also interferes with the metabolism of several CYP3A4 and CYP2C9 substrates, and co-administration can lead to toxic levels of those other drugs. Sirolimus, ergot alkaloids, terfenidine and quinidine are contraindicated when voriconazole is used. The drug levels of cyclosporin, tacrolimus and warfarin are increased with concomitant use of voriconazole and thus dosage adjustments are needed and markers for the drug's activity should be monitored (e.g. prothrombin time).

Although not metabolized through CYP450 enzymes, posaconazole inhibits CYP3A4 and causes some drug interactions with its substrates. Yet the interaction profile is improved compared to voriconazole. Dose of cyclosporin or tacrolimus should be reduced when co-administered with posaconazole and drug level closely monitored. Co-administration of posaconazole with the CYP3A4 substrates terfenadine, astemizole, cisapride, and quinidine, which have the potential to cause QTc prolongation, is contraindicated. Because it is a substrate of p-glycoprotein,

Table 2. Pharmacokinetic properties of newer antifungals. (Adopted and amended from George P et al. *Recent advances in antifungal chemotherapy.*)

Drug	Protein binding (%)	Half-life (hr)	Volume of distribution (L)	Bioavailability (%)	Dose adjustment in renal failure	Dose adjustment in hepatic failure
Voriconazole	58	6	2-4.6	90	Yes	Yes
Posaconazole	99	25-31	343-1341	8-47	No	Yes
Caspofungin	96.5	10	9.5	-	No	Yes
Micafungin	99	13	14	-	No	No
Anidulafungin	84	25-42	30-50	-	No	No

co-administration of inducers of this enzyme, such as rifabutin and phenytoin, results in significantly reduced exposure to posaconazole.⁽¹³⁾

THE ECHINOCANDINS

Echinocandins is a group of large, semi-synthetic, cyclic polypeptides.⁽³¹⁾ Caspofungin, introduced in 2002, was the first echinocandins approved by FDA, followed by micafungin in 2005 and anidulafungin in 2006. The principle mechanism of action is the non-competitive inhibition of β -(1,3)-D-glucan synthase, an essential component of the cell wall of many fungi that is not present in mammalian cells.⁽³²⁾ The blockage of this enzyme results in inability of the fungal cell to synthesize β -(1,3)-D-glucan, leading to osmotic instability and eventually, cell death.⁽³³⁾

Spectrum of activity

The echinocandins are active in vitro against most *Candida* species and *Aspergillus* species. All three agents show good activities for most isolates of *Candida*, including those that are either amphotericin B-resistant or fluconazole-resistant, such as *C. glabrata* and *C. krusei*.⁽³⁴⁾ For *Aspergillus* species, the echinocandins appear to be fungistatic rather than fungicidal, through inducing morphological changes at apical tips of the growing hyphae.⁽³⁵⁾ Other fungi, such as the dimorphic fungi, the *Zygomycetes*, *Cryptococcus neoformans* and *Trichosporin* species are poorly inhibited by the echinocandins in vitro due to the lack of significant β -(1,3)-D-glucan in their cell walls.^(34,35)

Clinical uses

The licensed indications approved by FDA with the corresponding dosages for the three agents are listed in Table

3.⁽³⁶⁻³⁸⁾ Caspofungin, being the first licensed drug, has the most clinical experience for its usage. It plays an important role in the empiric therapy for fever of unknown origin. In a multicenter, randomized comparative trial, caspofungin was compared with liposomal amphotericin B in 1095 patients with neutropenic fever and was found to have similar overall favorable response (33.9% vs 33.7%) and less toxic.⁽³⁹⁾ A randomized study comparing caspofungin with amphotericin B in the treatment of invasive Candidemia showed that caspofungin was equally effective (73.4% vs 61.7%) and better tolerated than amphotericin B (2002).⁽⁴⁰⁾ It is also licensed as salvage therapy for invasive aspergillosis refractory to first-line agents.

Micafungin is licensed for the prophylaxis of Candidiasis in patients undergoing stem cell transplantation. In a randomized, double-blind study; micafungin was compared to fluconazole in 882 patients undergoing stem cell transplant. Successful prophylaxis was documented in 80.7% of recipients who received micafungin, and in 73.7% of recipients who received fluconazole, showing superior efficacy for micafungin. The efficacy of micafungin against infections caused by fungi other than *Candida* has not been established.⁽⁴¹⁾

The efficacy of anidulafungin was evaluated in a Phase 3, randomized, double-blind study of patients with candidemia and/or other forms of invasive candidiasis. A total of 245 Patients were randomized to receive IV anidulafungin or IV fluconazole for at least 10 days of treatment. Global response rate was 75.6% vs 60.2% at the end of therapy, showing that anidulafungin is similar in efficacy to fluconazole.⁽⁴²⁾

Pharmacokinetics

Echinocandins are only available as intravenous preparations due to their large molecular structure and poor oral availability.⁽³³⁾ Pharmacokinetics properties of the echinocandins are shown in Table 2. Owing to their long half-lives, they can be administered once daily. Their vitreal and CSF penetration is negligible therefore should not be used in CNS and intraocular infections.

Renal or hepatic dosage adjustments are not necessary for these agents. One exception is the use of caspofungin in moderate hepatic insufficient patients as it is metabolized hepatically. 35 mg daily is recommended after a 70mg-loading dose.⁽³⁶⁾

Adverse effects

In general, echinocandins are well-tolerated and side effects are infrequent. This is mainly to due to more fungal-cell-specific action.⁽³¹⁾ A point to notice is that all three agents have been associated with increase in hepatic transaminases. Hepatitis is otherwise rare. Patients whose hepatic functions deteriorate during therapy should be evaluated for the risk and benefits of catering therapy. Other mild side effects include gastrointestinal disturbances, headache and fever. An infusion-related reaction has been described if rapid administration is given, with tachycardia, hypotension or thrombophlebitis.⁽³⁶⁻³⁸⁾

Drug interactions

Unlike the azoles, the echinocandins are not metabolized via CYP450 enzymes, so there are minimal drug-drug interactions reported. Among the three drugs, caspofungin is shown to have more interactions.⁽³⁶⁾ The use with cyclosporin leads to increase in hepatic transaminase concentration. Concomitant use of caspofungin with cyclosporin should be limited to patients for whom the

Table 3. Approved indications for echinocandins with dosages.

	FDA-approved indications	Recommended Dosages
Caspofungin	Empirical therapy for presumed fungal infections in febrile, neutropenic patients. Candidemia and the following <i>Candida</i> infections: intra-abdominal abscesses, peritonitis and pleural space infections.	70mg daily(1 st day loading dose), then 50mg daily
	Invasive aspergillosis refractory to or intolerant of other therapies Esophageal candidiasis	50mg daily
Micafungin	Candidemia, Acute Disseminated Candidiasis, <i>Candida</i> Peritonitis and Abscesses	100mg daily
	Esophageal Candidiasis Prophylaxis of <i>Candida</i> Infections in Patients Undergoing Hematopoietic Stem Cell Transplantation	150mg daily 50mg daily
Anidulafungin	Candidemia and other forms of <i>Candida</i> infections (intra-abdominal abscess, and peritonitis)	200mg daily(1 st day loading dose), then 100mg daily
	Esophageal Candidiasis	100mg daily(1 st day loading dose), then 50mg daily

potential benefit outweighs the potential risk. Caspofungin may also reduce the level of tacrolimus level thus the blood tacrolimus levels should be monitored so that the dosage can be titrated accordingly. Simultaneous administration with carbamazepine, phenytoin, phenobarbital or dexamethasone can reduce the efficacy of caspofungin.

Micafungin has fewer drug interactions when compared to caspofungin. Study suggested that micafungin is a mild inhibitor of cyclosporin metabolism and thus cyclosporin levels should be monitored.⁽⁴³⁾ In other study, serum concentrations of sirolimus and nifedipine was shown to increase by 21% and 18%, respectively.⁽³⁷⁾ The levels of these two drugs need to be monitored when co-administered with micafungin.

Unlike the other two echinocandins, anidulafungin slowly degrades by undergoing biotransformation in human plasma rather than being metabolized. It is neither a substrate nor an inhibitor of the cytochrome P450 enzyme system or of P-glycoprotein. These facts limit anidulafungin's drug-drug interaction profile.⁽⁴⁴⁾

CONCLUSION

The introduction of the new antifungal agents with extended spectrum and better pharmacological profile offers clinician new therapeutic options for invasive fungal infections. In addition, the different targets of activity offer the possibility of antifungal combinations. Despite the recent advances, invasive fungal infection remains one of the most challenging clinical problems, due to the emergence of resistant strains of fungi, longer life expectancy of immune-compromised patients and introduction of more potent immunosuppressive treatments. More clinical trials should be expected for the newer antifungal agents to evaluate their uses in advanced fungal infections and combination therapy should be investigated to cope with the upcoming difficult-to-treat invasive fungal infections.

Author's background

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Simultaneous Determination of Flavonoids, Phenolic Compounds and Triterpenes in Herb by Capillary Zonal Electrophoresis Can be Enhanced by the Addition of β -Cyclodextrin

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ABSTRACT

A cyclodextrin-modified capillary zonal electrophoresis (CD-CZE) method was established for the separation and determination of three isomeric compounds (ursolic acid, oleanolic acid and betulinic acid), caffeic acid, p-coumaric acid, rosmarinic acid, rutin and quercetin. These eight components, representing some common flavonoids, phenolic compounds and triterpenes in herb, were well separated from each other within 20 min with a borax running buffer (40 mM of borax, pH 9.4) containing 2 mM β -cyclodextrin and 4% methanol (V/V) at the voltage of 25 kV, temperature of 25°C and detection wavelength of 210 nm. The relative standard deviation (RSD) of migration time ranged from 0.25 to 0.74% while those of the peak area ratios ranged from 2.17 to 4.59% for six determinations of the analytes at concentration of 25 μ g mL⁻¹. The correlation coefficients of the calibration curves of analytes were all >0.998, and the recoveries were from 96.8 to 103.6%. The method was successfully applied to determine these bioactive components in the extracts of *Prunella vulgaris* L. and its beverage drink products. Our results reveal that in all beverage drinks analyzed, only the isomeric compounds and rosmarinic acid were found.

Keywords: capillary electrophoresis; cyclodextrin; flavonoids; phenolic compounds; triterpenes; *Prunella vulgaris* L.; Herbal drinks

INTRODUCTION

Capillary electrophoresis (CE), a separation techniques developed in the early 1980s, has attracted more and more attention in phytochemical analysis.⁽¹⁻⁴⁾ Compared to the common HPLC, CE has many advantages including high separation performance, short analytical time, litter reagent consumption, easy operation and environmental friendly. The separation principle of CE is based on the differences in molecular weight and charge ratio of analytes. But analytes with the same ratio (e.g. isomers) can't be separated just by capillary zone electrophoresis. The addition of running buffer modifier is a simple and effective way to solve this problem. Many buffer additives including sodium dodecylsulphate (SDS), protein, crown ethers, cyclodextrins (CDs) etc have been widely explored.⁽⁵⁾ CDs are cyclic oligosaccharide composed of several α (1-4) linked glucopyranose units with hydrophilic cavity, which can form inclusion complexes with various molecules with chiral recognition ability. With this unique propriety, CDs have been widely applied in separation science such as TLC, GC, HPLC, CE etc.⁽⁶⁾ In CE, complexation between the analyte and CD can change its electrophoretic mobility ($\mu \neq \mu_0$). Thus, experimentally measured mobility (μ_a) of the analyte is the weighted average mobilities of the analyte in free (μ_f) and complexed (μ_c) states. The separation of isomers by CDs may base on two reasons: 1) isomers of different formation constants with CD lead to different degrees of complexation; 2) alternatively, both isomers may have the same formation constants, but the mobilities of the isomers complexes were different. Both reasons result in isomer

separation in CE, but it is more common for the first case or a combination of both.⁽⁷⁾ Besides, organic solvent has also been widely used in CE to improve its separation performances and selectivity. The fundament and application of organic solvent in CE has been extensively reviewed by Huie.⁽⁸⁾

Prunella vulgaris L. (Labiatae), also known as the "self-heal", is a perennial plant commonly found in China and Europe. It has long been used as a folk medicine for alleviating sore throat, reducing fever in traditional European and Chinese medicine. It was also used as a material to manufacture functional beverage. The modern pharmacological studies reveal that the methanol or water extract of this herb have many effect including systemic anaphylaxis inhibition;⁽⁹⁾ Antihyperglycemic activity;⁽¹⁰⁾ UVA radiation photoprotection;⁽¹¹⁾ Immune modulation;⁽¹²⁾ antioxidative, anti-viral and anti-bacterial effects.⁽¹³⁾ Based on these pharmacological effects, many bioactive compounds in *Prunella vulgaris* L. have been isolated and reported. These include triterpenes, e.g., oleanolic acid, betulinic acid, ursolic acid (three structure isomers);⁽¹⁴⁾ phenolic acid, e.g. rosmarinic acid, p-coumaric acid, caffeic acid;⁽¹⁵⁾ flavonoid, e.g., quercetin and rutin.⁽¹⁶⁾

To further explore the biological effects and potential application of *Prunella vulgaris* L., quality control of it is very important. Ursolic acid is the dominant compound in *Prunella vulgaris* L. with many bioactivities including hepatoprotection, anti-tumor, acute myeloid leukemia etc.⁽¹⁷⁾ The Chinese

Pharmacopoeia 2005 used it as the only reference for the quality control of *Prunella vulgaris L.*⁽¹⁸⁾ Zhang et al using a HPLC method, however, reported the content of caffeic acid and rosmarinic acid in the different parts of *Prunella vulgaris L.* was different.⁽¹⁹⁾ Presence of rosmarinic acid has also been confirmed by Wang et al with a HPLC method.⁽²⁰⁾ Because the bioactivity and widely contain of oleanolic acid, betulinic acid and ursolic acid in many plants, the separation and determination of these three isomers attract many attentions. Although quantitative analysis of ursolic acid and oleanolic acid by HPLC,⁽²¹⁾ GC,⁽²²⁾ CE⁽²³⁻²⁵⁾ method has been reported, a simultaneous analysis of triterpenes, flavonoids and phenolic compounds in *Prunella vulgaris L.* is still missing for speedy quality control of the herbal extract. In this study, a simple and rapid method based on modification of the capillary zone electrophoresis for simultaneous determination of ursolic acid, oleanolic acid, betulinic acid, caffeic acid, p-courmaric acid, rosmarinic acid, rutin and quercetin was developed. The effects of buffer pH, borax, methanol and β -cyclodextrin (β -CD) concentration on the separation and determination of these eight bioactive compounds were investigated and the method was successfully developed.

EXPERIMENTAL

Chemicals and materials

Ursolic acid, oleanolic acid, betulinic acid (>98%) were obtained from International Lab (USA). Caffeic acid, p-courmaric acid, rosmarinic acid, rutin and quercetin (>98%) were purchased from Sigma Chemical Co.(St. Louis, MO, USA). The structure of these compounds is shown in Fig.1. Borax and β -CD were purchased from Sigma. Methanol was HPLC grade (Bangkok, Thailand). Throughout the study Milli-Q deionised water was used. It was prepared by a Milli-Q water system (Millipore, MA, USA). All other chemicals were of analytical grade. Samples of *Prunella vulgaris L.* and beverage drink of the herb were bought from local market.

The standard stock solution of ursolic acid, oleanolic acid, betulinic acid, caffeic acid, p-courmaric acid, rosmarinic acid, rutin and quercetin was prepared at a

concentration of 1.0 mg mL⁻¹ in methanol and stored at -20°C until use. Less concentrated mixed standard solutions at lower concentration were prepared weekly by diluting the stock solutions with methanol.

Apparatus

All experiments were carried out on a P/ACE MDQ Electrophoresis system equipped with a photo diode array (PDA) detector (Beckman Instruments, Fullerton, CA, USA) equipped with a 60.2 cm (50 cm from the inlet to detector)×50 μ m I.D. fused-silica capillary tube (Beckman Instruments). pH of solutions was measured by a HI 8424 Microcomputer pH meter (Hanna instruments Pty Ltd, Portugal) and samples were sonicated in a Transsonic TS 540 tank (Lab-Line Instruments, INC, Germany).

Electrophoretic procedure

The capillary tube was conditioned prior to its daily use by flushing with 0.1 M NaOH for 5 min, followed by water for another 5 min and finally with the buffer for 5 min. The running buffer was 40 mM borax (without pH modify, pH=9.4) 2 mM β -cyclodextrin and 4% methanol (V/V). The separation voltage was 25 kV and the capillary temperature was 25°C. Samples were injected

under the pressure of 0.5 psi for 10 s. Electropherograms were recorded at 210 nm. For standards separation, the capillary was flushed between two separations with water (2 min) and fresh buffer (2 min). For sample determination, the capillary was flushed between two separations with water (2 min), 0.1 M NaOH (1 min), water (2 min) and fresh buffer (2 min). The capillary tube was rinsed with 0.1 M NaOH for 30 min then with water for 30 min everyday after use.

Preparation of sample

Briefly, dried *Prunella vulgaris L.* was finely homogenized to powder and 1.0 g of sample was immersed with 25.0 mL methanol for 1 h and then sonicated for 60 min. The mixture was centrifuged at 4000 rpm and 4°C for 5 min. The supernatant was filtered by 0.4 μ m pore size filter. 100 μ L of benzoic acid (200 μ g mL⁻¹) was added in 900 μ L sample solution before injection. For beverage analysis, the solution was filtered by 0.4 μ m pore size filter, then 100 μ L of benzoic acid (200 μ g mL⁻¹) was added in 900 μ L sample solution before injection.

RESULTS AND DISCUSSION

Method development

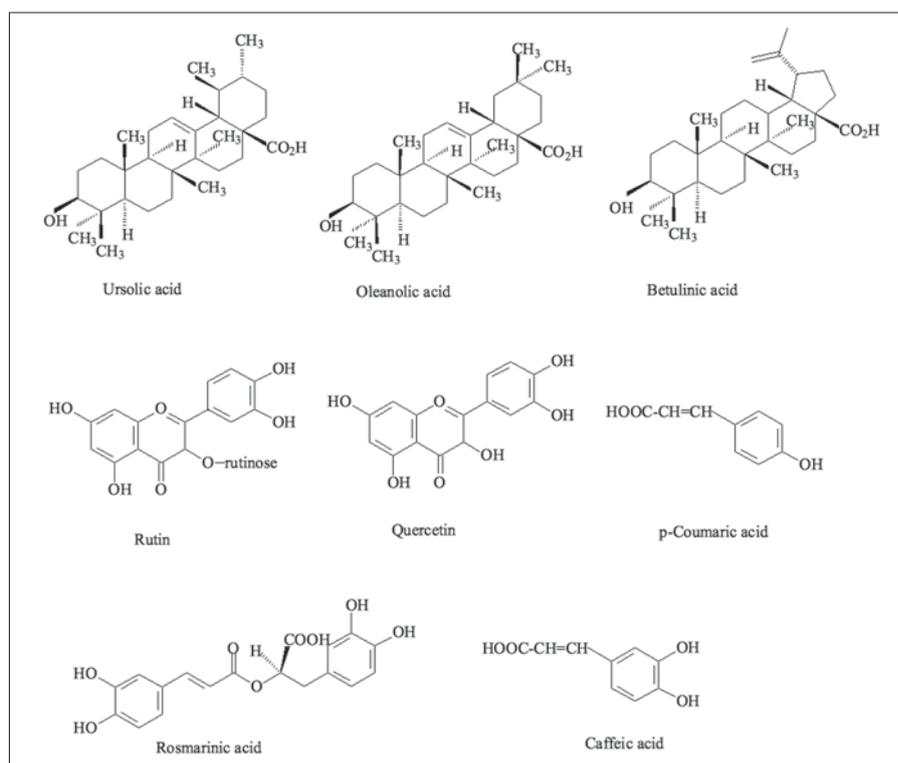


Figure 1. The structure of analytes.

The optimization and separation was achieved by optimizing the wavelength of UV detection, the pH, β -CD, methanol and borax concentration of the buffer. Using a PDA detector, UV spectra of each analyte was obtained. Based on the UV spectra, ursolic acid, oleanolic acid and betulinic acid has no absorbance beyond 225 nm at pH 9.4. Thus, 210 nm was chosen as the optimum UV detection wavelength throughout the experiment.

Effect of β -CD

Ursolic acid, oleanolic acid and betulinic acid are the three isomers with the same molecular weight and net charge, so they can't be separated without buffer modifier. Different concentration of β -CD on the separation of these eight analytes was investigated. The migration time of all analytes decreased with increased β -CD concentration, which mean that all analytes can form inclusion complex with β -CD and cause the electrophoretic mobilities increase. The electrophoretic mobilities of analytes were calculated from the observed migration times with the following equation (1):⁽²⁶⁾

$$\mu_{ep} = \mu - \mu_{eo} = \frac{L_d L_t}{V} \left(\frac{1}{t_m} - \frac{1}{t_{eo}} \right) \dots \dots \dots (1)$$

where μ_{ep} is the electrophoretic mobility of the analytes tested, μ is the apparent mobility, μ_{eo} is the electroosmotic mobility; t_m is the migration time measured directly

from the electropherogram, t_{eo} is the migration time for an unchanged solute (here was methanol); L_t is the total length of capillary, L_d is the length of capillary between injection and detection; and V is the applied voltage. As shown in Fig.2A, the mobility of all analytes increased with the rise concentration of β -CD, which means that β -CD can form complex with these analytes and decreases their net negative charge. It also noted that the mobility of ursolic acid, oleanolic acid and betulinic acid became different with addition of β -CD. And the difference reached maximum at concentration of 1 and 2 mM of β -CD, which cause the baseline separation of these three isomers.

Effect of methanol

Organic solvent can improve the separation performances and selectivity of CE. Our study found that ursolic acid, oleanolic acid and betulinic acid can't be separated just with the addition of β -CD. Thus different concentration of methanol on the separation of these isomers was investigated. As shown in Fig. 2B, the mobility of ursolic acid, oleanolic acid and betulinic acid was the same without methanol, and became different with methanol addition. Increasing of methanol little improve the separation of these three isomers. However, the migration time of other analytes increase notably because the addition of methanol will increase the electroosmotic flow

(EOF). Thus, 4% methanol was chose for subsequent experiments.

Effect of pH

The buffer pH is a very important parameter in capillary electrophoresis for affecting the electro-osmotic flow and the degree of ionization of analytes. The effect of running buffer pH (8.1, 8.5, 9.0, 9.4) in 40 mM borax with 2 mM β -CD and 4% methanol on the analytes separation was investigated. The pK_a of these compounds are ursolic acid: 5.29; oleanolic acid: 5.11; betulinic acid: 5.50;⁽²⁷⁾ caffeic acid: 4.3 and 8.14 and rosmarinic acid: 2.8. And the result showed that the buffer pH has litter influence on the migration time of these analytes. However, to p-courmaric acid (pK_a 4.32, 8.97),⁽²⁸⁾ rutin and quercetin (the pK_a of 7-OH and 4'-OH in flavonoid were about 7.8 and 9.1),⁽²⁹⁾ their migration time gradually increased with the rise of pH. The resolution of these analytes was poor at pH of 8.1, 8.5 and 9.0, and had a better separation at 9.4. Thus pH 9.4 was chose as the optimal running buffer condition (without pH modify).

Effect of borax

Different concentration of borax (20, 30, 40, 50 mM) on the analytes separation was studied. The results found that ursolic acid, oleanolic acid, betulinic acid can't be well separated at 20 and 30 mM of borax, and had a better separation at 40 and 50 mM. The increase of borax concentration remarkably increased the migration time of all analytes. The result is similar to the separation of phenolic acids and flavonoids.^(29,30) It had been reported that borate ion can form negatively charged complexes with hydroxyl groups, but dihydroxyl groups in vicinal position with a *cis* configuration can form stable complexes.⁽³¹⁾ On the other hand, the increase of borax concentration can raise the buffer viscosity and ionic strength, which in turn, decrease the zeta potential and cause the rate of electroosmotic flow decrease. The increase of migration time of the solvent peak (neutral methanol) with increased borax concentration was the proof.

Based on all the factors described above, the optimal buffer condition

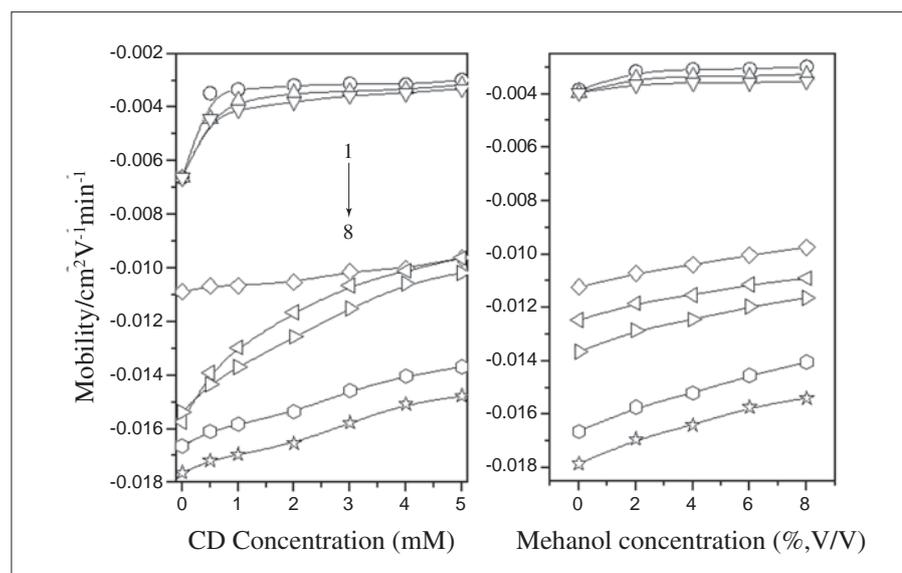


Figure 2. Effect of β -CD and methanol concentration on electrophoretic mobility of the analytes. (A) 40 mM borax with 4% methanol (V/V) at pH 9.4 with different concentration of β -CD; (B) 40 mM borax with 2mM β -CD at pH 9.4 with different concentration of methanol. 1=oleanolic acid, 2=ursolic acid, 3=betulinic acid, 4=rutin, 5=quercetin, 6=p-courmaric acid, 7=rosmarinic acid, 8=caffeic acid.

for separation was chosen as 40 mM borax, 2 mM β -cyclodextrin with 4% methanol (V/V) at pH 9.4. The typical electropherogram for a standard solution of the analytes is shown in Fig. 3A, as we can see baseline separation can be achieved within 18 min.

Method validation

The method precision was investigated by the relative standard deviations (RSD) of migration time and peak area of the analytes at the concentration of 10 and 25 $\mu\text{g mL}^{-1}$. Migration time precision was good for peak identification and peak area precision was significant for the quantitative assay. However, as commonly known, the injection volumes in CE are typically small, which are 5-50 nL, and it is difficult to be precise between injections. Hence, internal standard is always used to overcome this problem. According our experimental results, benzoic acid, which can be well separated with our analytes but not found in *Prunella vulgaris L.*, was selected as an internal standard. As shown in Table 1, The RSD of migration time ranged from 0.25 to 0.74% while those of the peak area ratios (analytes peak area/internal standard peak area) ranged from 2.17 to 4.61% for six determinations of analytes at the concentration of 10 and 25 $\mu\text{g mL}^{-1}$. The results revealed good reproducibility of our method.

The calibration curves for the determination of the eight compounds were constructed under the optimum conditions. Six concentrations were used for each calibration curve. As

shown in Table 1, the correlation coefficients of area ratio equations were all >0.998. As the results implied good linearity at the defined concentration range, it was reliable for quantitative analysis. The LODs and LOQs were

evaluated on the basis of a signal-to-noise ratio (S/N) of 3 and 10.

Samples analysis

The optimum condition was applied

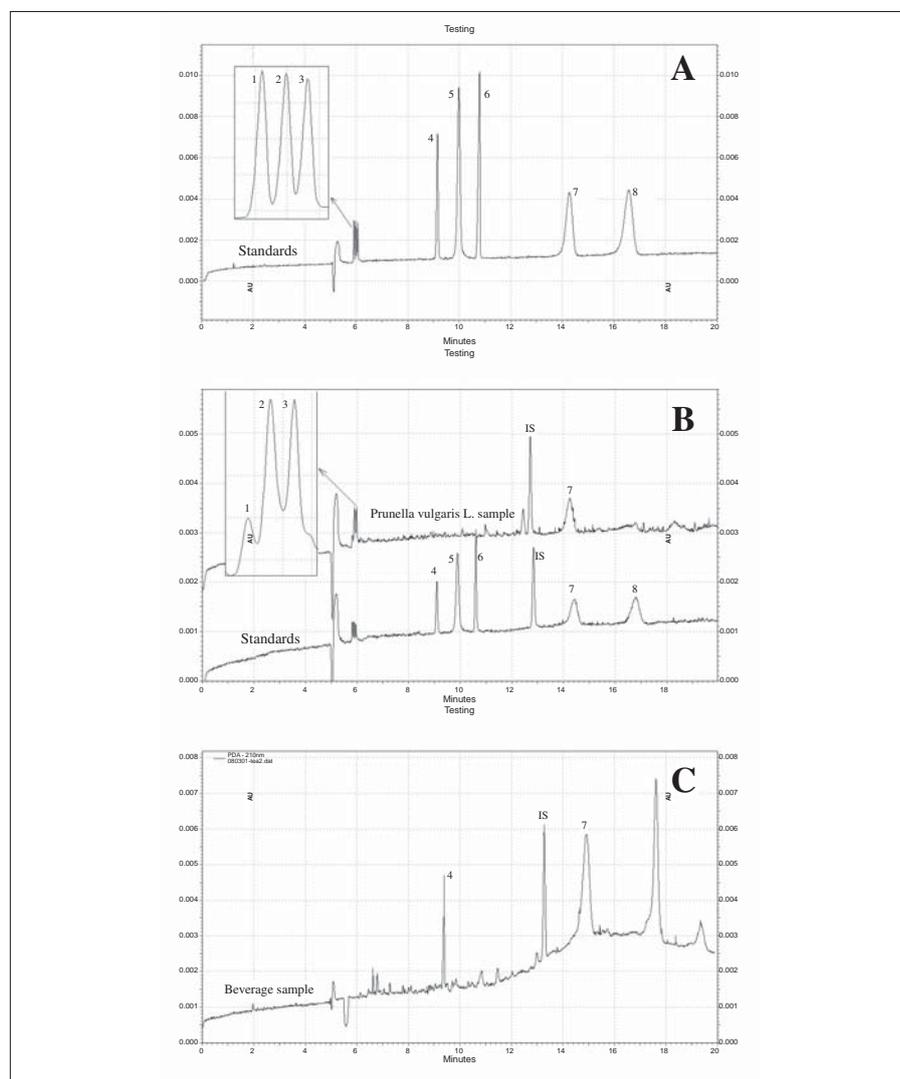


Figure 3. Electropherograms of standard markers, *Prunella vulgaris L.* sample and beverage sample. (A) standard markers (B) *Prunella vulgaris L.* sample (C) Beverage contained *Prunella vulgaris L.* Peaks: 1=oleanolic acid, 2=ursolic acid, 3=betulinic acid, 4=rutin, 5=quercetin, 6=p-courmaric acid, 7=rosmarinic acid, 8=caffeic acid, IS:internal standard.

Compounds	RSD (%)		Regression equation ^c	Linear range $\mu\text{g mL}^{-1}$	LOD ^d $\mu\text{g mL}^{-1}$	LOQ ^d $\mu\text{g mL}^{-1}$	r^e
	Migration time ^b	Peak area ratio ^b					
Oleanolic acid	0.16, 0.25	3.95, 2.17	$Y = 0.0026X + 0.002$	10.0-400	2.65	8.85	0.9985
Ursolic acid	0.17, 0.25	3.64, 2.76	$Y = 0.0026X + 0.005$	10.0-400	2.65	8.85	0.9984
Betulinic acid	0.16, 0.27	2.67, 4.59	$Y = 0.0027X + 0.001$	10.0-400	2.65	8.85	0.9996
Rutin	0.28, 0.44	3.63, 2.24	$Y = 0.031X - 0.010$	2.5-100	0.22	0.73	0.9986
Quercetin	0.40, 0.59	3.67, 2.43	$Y = 0.081X - 0.004$	2.5-100	0.09	0.30	0.9992
p-Courmaric acid	0.53, 0.74	3.82, 4.27	$Y = 0.053X + 0.003$	2.5-100	0.13	0.43	0.9990
Rosmarinic acid	0.37, 0.61	4.61, 3.67	$Y = 0.069X - 0.096$	2.5-100	0.10	0.33	0.9983
Caffeic acid	0.48, 0.74	2.81, 2.97	$Y = 0.091X - 0.122$	2.5-100	0.076	0.25	0.9968

^a Running buffer: 40 mM sodium borate with 2 mM β -CD and 4% methanol (v/v) at pH 9.4.

^b Analytes concentration were 10 and 25 $\mu\text{g mL}^{-1}$, n=6.

^c Area ratio equation, where Y was the area ration between analytes and internal standard and X was the concentration of analytes.

^d LOD, limit of detection (S/N = 3), LOQ, limit of quantification (S/N = 10).

^e r, correlation coefficient, n=6.

to the separation and determination the bioactive components of *Prunella vulgaris L.* and its beverage. Representative electropherograms of extract of sample and beverage are shown in Fig.3 B and C. The peaks were identified by comparison with the UV spectra and the migration times of the standards, and by spiking the sample solution with standards.

The *Prunella vulgaris L.* sample was sonicated in the methanol with different times. Each solution was injected to the capillary and relative peak areas (make the area of internal standard a constant by multiply a factor) were compared. As shown in Fig. 4, the content of ursolic acid, oleanolic acid and betulinic acid was almost unchanged after sonication for 10 min. However, the content of rosmarinic acid increased gradually with the sonication time. And after 60 min, the peak area became unchanged. Thus 60 min of sonication was applied for all the samples.

The calculated contents of the analytes in the samples of *Prunella vulgaris L.* and its beverage are listed in Table 2. The results found that ursolic acid and betulinic acid were the two most dominant active compounds in *Prunella vulgaris L.*, while caffeic acid, p-courmaric acid, rutin and quercetin ferulic acid were too little to be detected or not be present. The content of rosmarinic acid in *Prunella vulgaris L.* is also very high, and can also be detected in its beverage. Because ursolic acid, oleanolic acid and betulinic acid were almost water insoluble,⁽¹⁷⁾ thus they can't be found in the beverage. The beverage also contains other herb, so some compounds don't contain in *Prunella vulgaris L.* can also be detected, such as rutin. Accuracy of the assay could be checked by adding some known standards to the treated samples. Therefore, the samples were spiked with 100 $\mu\text{g mL}^{-1}$ of ursolic acid, oleanolic acid, betulinic acid and 20 $\mu\text{g mL}^{-1}$ of other standards. Corrected peak area

of each standard in the sample after spiking was compared with the sample alone plus the amount spiked. The result demonstrated that the recoveries for the components were in the range of 96.8 to 103.6%.

CONCLUSION

A qualitative and quantitative analytical CE method for simultaneous determination of eight bioactive components including triterpenes, flavonoids and phenolic compounds has been developed. The three structural isomers of oleanolic acid, betulinic acid and ursolic acid were successfully separated simply with the addition of two running buffer modifiers which are β -CD and methanol. The method is simple, reproducible, rapid and reliable and was successfully applied to determine these compounds in herba *Prunella vulgaris* and its processed products. The main advantages of fused silica capillaries compared to packed columns are that plant extracts are directly injected without any pre-separation or purification step, easily washed between runs and free of irreversible contamination of the matrix. The results reveal that ursolic acid, betulinic acid and rosmarinic acid were the three most dominant active compounds in *Prunella vulgaris L.* while caffeic acid, p-courmaric acid, rutin and quercetin ferulic acid were too little to be detected or not present. In contrast, only rosmarinic acid was detected and no any isomeric component of ursolic acid was found in the beverage drinks.

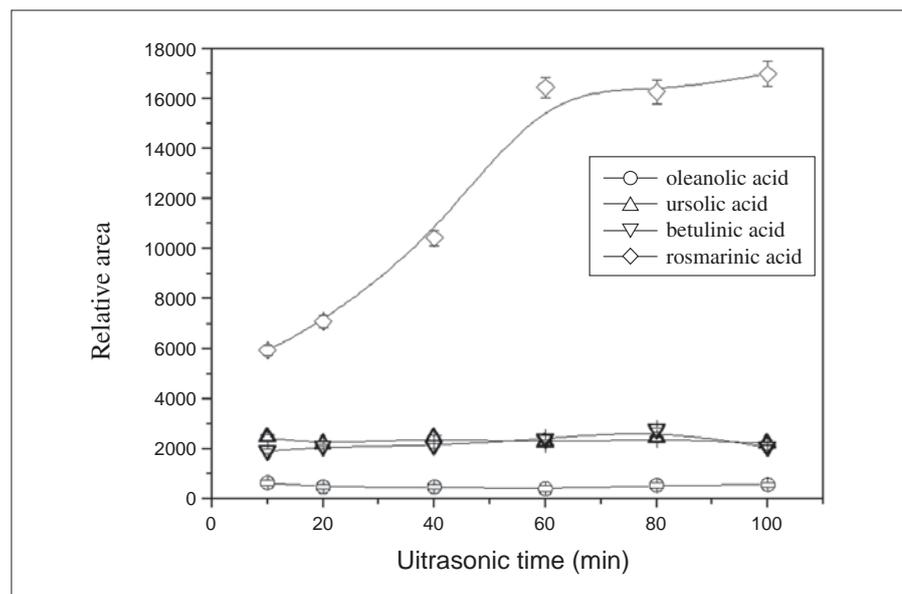


Figure 4. Effect of extraction time on the content of analytes in sample.

Sample	Oleanolic acid	Ursolic acid	Betulinic acid	Rosmarinic acid	Rutin
Sample 1	517 \pm 20	2177 \pm 12	4788 \pm 330	514 \pm 29	NF
Sample 2	281 \pm 10	1546 \pm 321	5538 \pm 128	756 \pm 17	NF
Sample 3	385 \pm 17	3386 \pm 58	7200 \pm 193	1929 \pm 54	NF
Sample 4	903 \pm 37	4023 \pm 67	4717 \pm 98	1177 \pm 24	NF
Beverage 1	NF	NF	NF	39 \pm 2	NF
Beverage 2	NF	NF	NF	46 \pm 2	13 \pm 1
Beverage 3	NF	NF	NF	62 \pm 5	15 \pm 2
Recovery(% , n=3)	98.2 \pm 1.7	103.6 \pm 2.2	101.4 \pm 3.5	96.8 \pm 2.9	

NF: not found.

Recovery (%) = 100 \times (amount found – original amount) / amount spiked.

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Authors' background

Mr ZHANG Qing-Feng is research student currently doing his PhD degree in City University of Hong Kong. Dr CHEUNG Hon-Yeung is corresponding author. He is an Associate Professor of Pharmaceutical Microbiology & Biotechnology.

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A Pattern of Shift in Vaccine Production

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ABSTRACT

Subunit vaccines that do not require cold chain support and which can be produced quickly in large quantities, may be an attractive option for less-capital intensive drug manufacturers in Asia.

Keywords: Vaccine; Production; Attenuation; Subunit vaccine; Genetic engineering; Infectious diseases

INTRODUCTION

Vaccines have been designed and manufactured in essentially the same manner for more than 200 years. In fact there are indications that primitive forms of vaccination were practiced in China and India from as early as 2000 years ago. Modern vaccinations are generally credited to Edward Jenner for his cowpox vaccine against smallpox in 1796.

Vaccines work by inducing an immune response via the introduction of a foreign antigen. This can be accomplished in a variety of ways, four of which now present the basis for modern vaccines.

Vaccinations against infectious diseases have traditionally involved the use of the entire virus of a pathogen, either inactivated or attenuated. Inactivated vaccines involve the production of the infectious virus, which is then killed so it cannot replicate. This method presents certain risks if not all of the virus are killed, as it can cause the vaccine to induce an infection from the virus.

INNOVATIVE APPROACHES IN VACCINE PRODUCTION

In more recent times, live viral pathogens have been genetically attenuated to remove or reduce their virulence. Attenuation is achieved by replacing virulent genes with similar but less virulent genes. Injecting a whole attenuated virus is an effective method

to induce immunity against the pathogen since the body's antibody and T-cell responses to the vaccine are comparable to that of the infectious pathogen. This is because the immunogenic surface proteins of the attenuated virus which induce the immune response, retain the three-dimensional structure found in the infectious virus.

Two methods to produce vaccines have gained attention. Virus-Like Particle (VLP) vaccines are made from small immunogenic portions of the viral protein - which self-assemble into particles resembling the infectious virus but lack certain key components of the virus which allow it to replicate. In this way, VLP vaccines are safe because they cannot replicate. A limitation of VLP vaccines is that not all human pathogens have self-assembling immunogenic proteins.

The second method is recombinant protein subunit vaccines (Figure 1). Subunit vaccines are similar to VLP vaccines in that they contain only small immunogenic portions of the viral protein (antigens) which induce the immune response to the virus. Unlike VLP, these antigens do not need to self-assemble. This makes subunit vaccines applicable for a wider range of pathogens. However, segments of the antigens tend to be unstable.

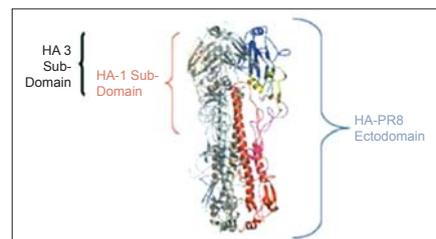


Figure 1. Subunit segments of the influenza Puerto Rico & Hemagglutinin. Representation of Trimeric HA. (Source: Palese: Fields, 5th Edition)

This has led to the common belief that subunit vaccines are not sufficiently immunogenic since the antigens fail to retain the precise three dimensional structure of the virus' surface proteins. They may induce an immune response but not one that is protective against the target pathogen.

PROBLEMS ASSOCIATED WITH LARGE SCALE PRODUCTION OF VACCINES

The production of vaccines has traditionally taken place in large, complex and expensive vaccine plants. Production of a whole virus inactivated or attenuated vaccine can be a long process, especially for rapidly mutating viruses such as the influenza virus. Growing whole viruses efficiently requires first optimizing the virus and growth conditions in order to achieve acceptable levels of viral production. The production of live, infectious pathogens also presents a risk and requires a high level of safety containment for the production process - which adds to the cost of the manufacturing process.

The development of mammalian cell lines has enabled whole virus manufacturers to reduce the time to optimize and produce their virus from several months to just a few.

Technological considerations

Two factors have limited the potential of subunit vaccines to supplant whole virus vaccines. One is the difficulty in growing properly folded small immunogenic portions of the viral protein in a large-scale, cost efficient manner. It was previously believed that cell based growth media, whether mammalian, insect or bacteria, could not be used to mass produce the subunit proteins due to the former's inability to maintain the proper folding or glycosylation of the antigens outside the context of other viral components. Without the ability to mass produce the antigens, large quantities of subunit vaccines were commercially impractical.

This problem has been solved by researchers who have developed subunit protein constructs that can be successfully grown in bacteria. Because bacteria are the fastest growing recombinant protein media, massive amounts of properly folded antigen can be produced without inclusion bodies.

Mammalian cells and insect cells double in number every 24 hours, while bacteria double every 40 minutes. This means that with a starting base stock of 100,000 mammalian or insect cells, there would be 200,000 cells available after 24 hours to produce recombinant proteins. In comparison, starting with 100,000 bacteria, there would be nearly 70 billion bacteria after the same period of time, each producing a recombinant protein subunit.

By maintaining a plasmid bank of various strains of infectious pathogens such as influenza, it is possible to produce a plasmid for an emerging pathogen within a few days after the identification of the Deoxyribonucleic Acid (DNA) structure of the new subunits. The production of vaccine antigens can begin within a few weeks. The first batch of the subunit vaccines against a new strain of flu can be ready for testing and market approval in less than six weeks using these techniques.

The second factor that was thought to limit the viability of subunit vaccines was the belief that subunit vaccines could not provide efficient levels of immunity against a pathogen. The denaturing of the antigen caused by organic solvents or the harsh processing conditions that are required to attach the protein fragments to polymers, often resulted in the loss of the precise three-dimensional structure required of the protein subunits. Furthermore, antigens that had been injected without a stabilizing moiety also lose their desired three dimensional confirmation. The result of these failures was a belief that an immune response against the desired pathogen could not be achieved by a subunit vaccine.

This problem has been overcome by the use of a protein-like synthetic polymer that binds the antigenic proteins and maintains their three-dimensional conformation. This is achieved through the use of an ion-chelating property of the polymer and by processing in a mild solution which produces antigen-bound nanoparticles that are similar to VLPs.

Because of the polymer's ability to maintain the bound water that is necessary for the proper folding of the antigens, the vaccine nanoparticles can be dried, stored, transported and administered at ambient temperatures. This technology eliminates the cold storage and therefore the entire cold chain that is required of virus-based

vaccines. This makes subunit vaccines viable for much of the world's population.

THE ECONOMICS OF VACCINE PRODUCTION

Whole virus vaccine plants tend to be large, costly to build and operate. This is primarily due to the high levels of risk that are associated with the production of live viruses and the infrastructure that are necessary to provide the economies of scale - in order to be cost effective. The cost of traditional vaccine plants often runs into several hundred million dollars. Such costs make locating a vaccine plant in a small or less economically developed country prohibitive.

The result is that these countries often find themselves at the end of a long line of buyers for vaccines. In addition, the vaccines that they buy may not even be the best vaccine for their local needs, as the strains included in the vaccine may have been determined as being those that are the most appropriate for the large, Northern Hemisphere markets such as the US, Europe and Japan. The decision to make the world's supply of the H1N1 (swine flu) vaccine from the A/California/07/2009 strain may be appropriate for the US market but may be inappropriate for markets in Asia.

Small or less economically developed countries, especially those in the tropical zones, may also have special vaccine requirements that are not met because such vaccines are not cost effective for pharmaceutical companies to produce, since the disease may not exist in the latter's primary markets.

A different type of vaccine plant may solve that problem and may bring the local production of vaccines to virtually every country. Small recombinant protein production facilities which use disposable (single-use) technology can be the cornerstone of a highly efficient and low cost vaccine plant. Companies such as Xcellerex (Marlborough, Massachusetts) produce modular recombinant protein production lines such as the FlexFactory that are Good Manufacturing Practice (GMP) approved for manufacturing within one year after ordering the equipment (Figure 2).

Since recombinant protein subunit vaccines do not involve the production of dangerous pathogens, the cost of the vaccine facility is a fraction of that of a



Figure 2. An Xcellerex FlexFactory installation for vaccine production. (Source: MediVas)

traditional vaccine plant. Since the subunit vaccines that utilize the proprietary polymer technology do not require cold storage or cold transportation, this also provides a reduction in the cost of building and maintaining the vaccine production facility.

Another advantage of a subunit approach to vaccines using a single-use production line is that it is capable of producing relatively small amounts of a variety of vaccines efficiently. The production of a new antigen can begin within hours after the completion of the production of a previous antigen. This allows the vaccine plant to produce a variety of subunit vaccines to meet more local needs.

CONCLUSION

The ability to produce vaccines quickly in large quantities, provides another financial advantage. Vaccines such as those for influenza, have a short life such that they must be changed each year. This means any vaccine that has been produced but not sold, must be destroyed at a loss to the company. Conversely, if too small a quantity of influenza vaccine is produced, the company will be unable to meet the local demand. This is the ongoing dilemma that faces influenza vaccine manufacturers.

With a recombinant protein-based subunit vaccine technology and a rapid production method using bacteria, it is possible to produce vaccines closer to the time when they are needed, so that quantities of vaccines do not need to be stockpiled in advance. This advantage can mean the difference between making or losing money each year.

Author's background
Mr. CARPENTER Kenneth is the Chairman & CEO of MediVas, a biotechnological company based in California, USA.

The Morphological Features, Chemical Constituents and Biological Effects of *Fritillaria Hupehensis* Bulbus (湖北贝母)

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Official Name: *Fritillariae Hephensis* Bulbus

Chinese Name: 湖北贝母

Chinese Phonetic Name: Hubeibeimu

Plant Family: liliaceae

Botanical Name: *Fritillaria hupehensis* Hsiao et K. C. Hsia

Pharmacopoeia Name: *Fritillariae Hephensis* Bulbus

Other Names:

Part Used: bulbus

ABSTRACT

Hubei-Beimu, as a traditional Chinese medicinal herb, is derived from the dry bulbs of *Fritillaria hupehensis* Hsiao et K. C. Hsia, which is a perennial plant found in Hubei province, China. It has been used as an antitussive and expectorant herbal drug in China by folk people for a long time and is recorded in Chinese pharmacopoeia. It is an important medicinal bulb available in the market along with two other species of the Genus, namely *Fritillaria cirrhosa* D. Don and *Fritillaria thunbergii* Miq. It contains at least 10 steroidal alkaloids, 2 diterpenes and 3 diterpenoid dimers. Many chemical and pharmacological studies demonstrated that the alkaloids are responsible for its antitussive and expectorant activity. The biological effect based on modern research of this herb coincides with its traditional uses by the Chinese. However, further research on its molecular pharmacology is necessary in order to maximize its uses and exploit even further the resource of Hubei-Beimu.

Keywords: *Fritillariae hepehensis*; Steroid alkaloids; Antitussive effect; Expectorant activity

INTRODUCTION

Fritillariae Bulbus (Beimu in Chinese),

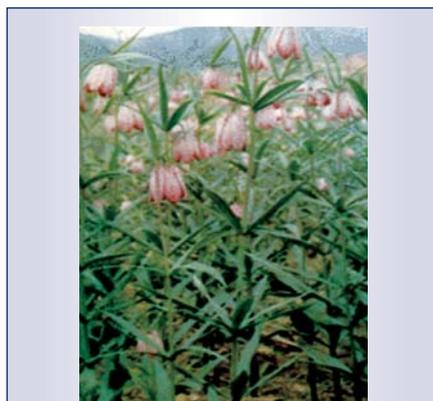


Figure 1. *Fritillariae hepehensis* with blooming flowers.



Contraindications:

No obvious contraindications reported.

Undesirable Effects

No obvious toxicity effect reported.

Interaction with Conventional Drugs

No obvious adverse event reported in combination with other drugs. But it can not be mixed to decoct with *Aconitum carmichaeli* Debx

belonging to the family Liliaceae, has been used as an antitussive and expectorant herb in traditional Chinese medicine (TCM) for more than 2000 years.⁽¹⁾ In recent years, the study of *Bulbus Fritillariae* has attracted more and more attention.⁽²⁻⁴⁾ Chuan-Beimu (*F. cirrhosa* D. Don, *F. unibracteata* Hsiao et K. C. Hsia, *F. przewalskii* Maxim. ex Batal. and *F. delavayi* Franch.), Zhe-Beimu (*F. thunbergii* Miq.), Hubei-Beimu (*F. hupehensis* Hsiao et K. C. Hsia), Ping-Beimu (*F. ussuriensis* Maxim.), and Yi-Beimu (*F. walujewii* Regel and *F. pallidiflora* Schrenk), a total of five groups of Beimu, altogether comprising of nine *Fritillaria* species, are officially recorded in the 2010 edition of the Chinese Pharmacopoeia.⁽⁵⁾ What is more, the

bulbs of more than 30 other species were used locally as substitutes for *Fritillariae Bulbus* in some native areas of China.^(6, 7) Although some of these species may share some chemical components and bioactivities with each other, they have distinctive differences in chemical constituents and pharmacological properties.⁽⁸⁾ Hubei-Beimu, as one of the important Beimu crude drugs in market, was firstly recorded in "Shenlong Bencao Jing". Its chemical constituents and pharmacological effects have been reported.⁽⁹⁾ This article reviews and summarizes some of the recent studies and discoveries on the resource and application of Hubei-Beimu.

DESCRIPTION AND IDENTIFICATION

Hubei-Beimu (Fig. 1) is distributed mainly in the Chinese provinces of Hubei, Sichuan, Hunan, and is mostly cultivated.⁽¹⁰⁻¹²⁾ The stem of this herb is 20-60 cm high. There are 3-7 leaves on the stem. They are whorled and the blade is oblong-lanceolate to lanceolate, of 5-12 × 1.5-3 cm in dimension. The apex of the leaves is curled. Each plant has 1-4 flowers. Flowers are inflorescence with 1-3 bracts and often cirrus in shape. The flower is nodding, tubular-campanulas; pedicel 1-2 cm. Petals are greenish yellow to pale purple, tessellated or spotted with yellowish brown or dark purple, sometimes very heavily so, oblong-obovate to oblong, 3.5-5 × 1-2 cm, apex obtuse; nectaries projecting abaxially. Stamens are about 2 mm; filaments glabrous or slightly papillose. Style 3-lobed; lobes 3-8 mm. Capsule is broadly winged of approximately 6-8 mm width. Flowering normally occurs in April to June. Fruiting takes place in June to July.

MACROSCOPIC APPEARANCE OF THE DRIED BULBS

The bulbs, in general, are oblate, 0.8-2.2 cm in height, 0.8-3.5 cm in diameter and

externally whitish to brownish. There are two outer scale leaves in each bulb. They are fleshy, nearly reniform, or varying considerably in size. The large scale closely embraces the small one. The apex is closed or opened with 2~6 scales and shrunken stem remained. The color of the internal side is yellowish to whitish. Base is depressed, with remains of brownish epidermis and a few fibrous roots. The single scale leaf is reniform-shoe-shaped, 2.5~3.2 cm in length, 1.8~2 cm in diameter. Texture fragile, fracture whitish, starchy. Odour, slight; taste, bitter. The bulb of Hubei-Beimu is comprised of 2 to 3 scales which are 1.2~2 cm in diameter.



Figure 2. Dried crude drug of *Fritillariae Hepehensis Bulbus* (Scale bar = 1 cm)

MICROSCOPIC FEATURES OF THE TRANSVER SECTION OF THE DRIED BULBS

Epidermis of scale leaves consists of 3-5 rows of cells, slightly lignified, their outer wall thickened with cuticle (Fig. 3). Parenchyma cells are filled with starch granules. Sometimes crystals of calcium oxalate are visible. Vessels small, scattered in parenchyma tissue.

MICROSCOPIC FEATURES OF THE POWDER OF THE DRIED BULBS

Powder of the dried bulbs is pale brownish-yellow. Starch granules are fairly abundant, broadly ovoid, long ellipsoidal or sub-spheroidal, 7~54 μm in diameter, hilum pointed, V-shaped, slit-shaped, striations fine and dense, distinct. Epidermis cells are sub-square or polygonal. Anticlinal wall is irregularly beaded; sometimes stomata are visible, oblate, 54~62 μm in diameter, with 4~5 subsidiary cells. Crystals of calcium oxalate are rhombic, sub-square, granular or clustered, up to 50 μm in diameter. Vessels are spiral.

CHEMICAL CONSTITUENTS

In recent years, research on the bioactive constituents of *Fritillariae Hepehensis Bulbus* has attracted more and more

attentions. Isolation and identification of the chemical compounds in the bulb of *Fritillariae hepehensis* has been carried out continually with the development of analytical separation techniques. The

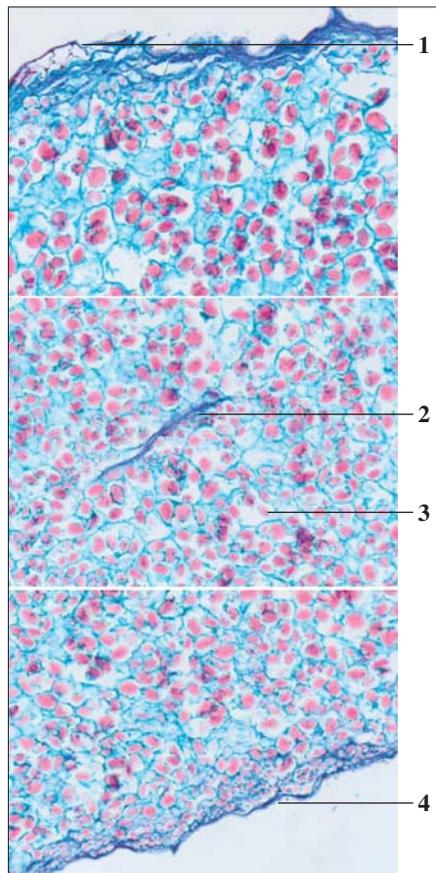


Figure 3. Microscopic features of the transverse section of *Fritillariae Hupehensis Bulbus*.

1= Upper epidermis; 2 = Vessels; 3 = Starch granules; 4 = Lower epidermis.

content of total alkaloid of this herb is 0.3922 % ~ 0.4289 % (W/W).^(13, 14) It was found that steroidal alkaloid is the main type of bioactive components in *Fritillariae hepehensis*. Today, more than ten steroidal alkaloids have been isolated and identified. These include verticine (or peiminine), verticinone (or peiminine) hupehenine, hupehenoside, hupehenirine, hupehenizine, hupehensine, hepehenidine, hupehemonoside, ebeiensine and so on.⁽¹⁵⁻¹⁹⁾ The content of verticine, verticinone, hupehenine and hupehenoside are higher than others. These four constituents are considered as the main ingredients responsible for all the unique applications of this herb. The content of hupehenine as specified in the Chinese Pharmacopoeia (2010 edition) is required to be more than 0.020%. Other ingredients that have been isolated and identified from *Fritillariae hepehensis* included β -sitosterin, adenosine, ent-kauran-16 α ,17-diol, ent-kauran-16 β , 17-diol. In recent years, three polymorphic diterpene (fritilleide A, fritillebin C, fritillebin D) were also isolated.⁽²⁰⁻²³⁾ Fig. 4 shows the chemical structures of some steroidal alkaloids that have been isolated and identified in *Fritillariae hepehensis*.

PHARMACOLOGICAL ACTIVITIES

Antitussive and expectorant effects

Antitussive and expectorant effects are the most important activities of the extracts of *Fritillariae Hupehensis Bulbus*. When 57 mg of total alkaloids of the bulb

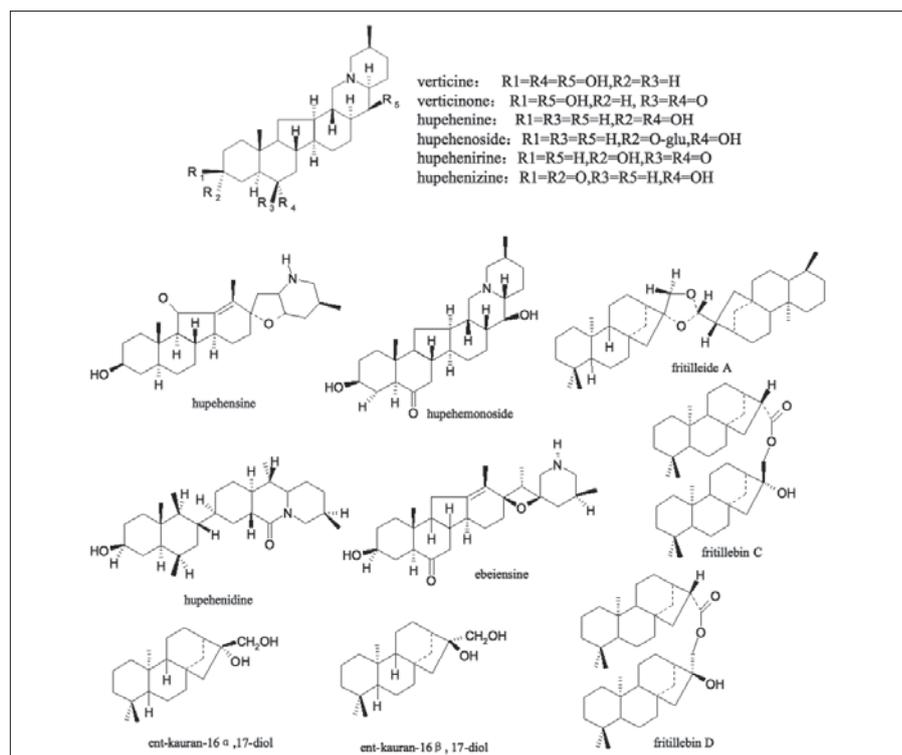


Figure 4. Chemical structure of some steroidal alkaloids isolated from *Fritillariae Hupehensis Bulbus*

was orally given to mice which has cough induced by the phenolsulfonphthalein and ammoniae aqua, the cough was satisfactory subdued. It was found that the amount of phenolsulfonphthalein increased in the trachea of mice and in their glands. Hence, it was confirmed that the total alkaloids obviously have an expectorant effect. The antitussive effect of the total alkaloids extracted from the bulb has also been verified by intraperitoneal injection.⁽⁸⁾

Anti-asthmatic effects

The antiasthmatic effect of the alkaloids of *Fritillariae hepehensis* was investigated through observing the latent period of asthma induced by acetylcholine-histamine in guinea pigs. By *in vitro* measuring the tension of isolated guinea pig tracheal strips, the influence of the alkaloids from *Fritillaria hupehensis* was found effective on both the basal tension and the contraction induced by acetylcholine, histamine and 5-HT. Results in Fig. 5 and 6 demonstrated four mg / kg (i.g.) of the total alkaloids could significantly prolong the latent period of asthma in guinea pigs. In the isolated guinea pig tracheal smooth muscle experiments, though the total alkaloids from *Fritillaria hupehensis* could not change the basal tension and the contraction induced by histamine and 5-HT, it could antagonize the contraction induced by acetylcholine. Moreover, the cumulative concentration-response curves of acetylcholine were shifted to the right in a concentration-dependent manner, and the maximal contraction was not changed significantly. The total alkaloids from

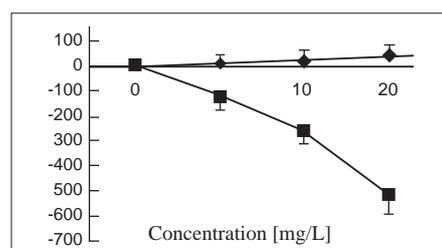


Figure 5. The effect of the total alkaloids from *Fritillaria hupehensis*, compared with aminophylline on the basal tension in the isolated tracheal smooth muscle of guinea pig. Symbol: ■ = aminophylline; ◆ = Total alkaloids

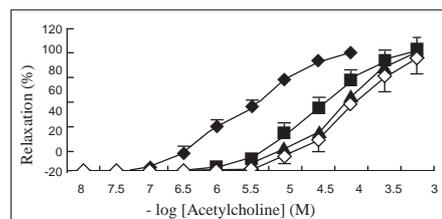


Figure 6. The cumulative concentration-response curves of the total alkaloids from *Fritillaria hupehensis* in response to varying concentrations of acetylcholine. Concentration (mg/L) of acetylcholine used: ◆ = control; ■ = 20; ▲ = 40; ◇ = 80.

Fritillaria hupehensis may be a novel and good antiasthmatic agent.⁽²⁴⁾

Blood pressure-lowering

The intravenous administration of 30 mg of total alkaloids of *Fritillariae hepehensis* resulted in moderate degree of short-term hypotension in cats accompanied by a lower heart rate.⁽²⁵⁾

Other pharmacologically effects

The total alkaloids of *Fritillariae hepehensis* can significantly improve hypoxia tolerance in mice. They can reduce the oxygen needs of the organization and extend the survival time of cells. On the other hand, when the total alkaloids were dropped to the eyes of rabbit, they had dilation effects on the corneal of their eyes.⁽²⁵⁾

Toxicity

The LD₅₀ of the alkaloids of *Fritillariae Hephensis* Bulbus given intraperitoneally to mice was 13.71±1.24 g/kg. If the alkaloids were given orally, the LD₅₀ was 1025 mg/kg. Therefore, extract of the *Fritillariae Hephensis* Bulbus has extremely low toxicity.⁽²⁵⁾

CONCLUSION

Fritillariae hepehensis has a long history in traditional Chinese medicine, and modern research shows extracts of the herb have explicit antitussive, expectorant and anti-asthmatic effects. In addition, toxicity is very low. The current application is similar to the use of traditional Chinese medicine theory. In addition to the total alkaloids, other ingredients, such as the non-basic parts of β -sitosterol and adenosine also have certain pharmacological effects.

The total alkaloids, as the mainly ingredients in Hubei-Beimu, have many similar properties, but it has many different properties with other Beimu species including Chuan-Beimu, Zhe-Beimu, Hubei-Beimu, Ping-Beimu, and Yi-Beimu. So it has been suggested that Hubei-Beimu may be considered as Zhe-beimu or as a replacement product of other beimu species. We think that it should be used according to necessity. It is not suitable to misuse them.

In conclusion, Beimu crude drug can not completely meet the needs of the medical market currently, thus to study and develop the Hubei-Beimu, and constantly improve its production quality is still of very importance to its application.

Author's background

Both Dr ZHANG Zhi-feng and Mr LAM Li-Wing are currently working as research supporting staffs in City University of Hong Kong; Xu Yan is a research student working on a Chinese Medicine project. Dr CHEUNG Hon-Yeung is the corresponding author. He is an Associate Professor of Pharmaceutical Microbiology & Biotechnology in City University of Hong Kong.

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Screen for latent TB prior to starting therapy; treat latent TB with standard therapy before initiating Actemra

Hepatic transaminase elevations:

Not recommended in patients with baseline ALT or AST > 5xULN; use with caution in patients with ALT or AST > 1.5xULN. Monitor ALT/AST levels according to Prescribing Information, if raised follow recommendations for dose modification. **Haematological abnormalities:** Not recommended in patients with ANC < 0.5 x 10⁹/l or platelet count < 50 x 10⁹/µl.

Diverticulitis:

Use with caution in patients with a history of intestinal ulceration or diverticulitis. Patients with symptoms of complicated diverticulitis should be evaluated promptly.

Drug Interaction:

Co-administration with MTX had no significant effect on MTX exposure. MTX, NSAIDs or corticosteroids had no effect on tocilizumab clearance. Patients taking medicines

which are individually adjusted and metabolized via CYP450 3A4, 1A2, 2C9 or 2C19 should be monitored when starting or stopping Actemra, as doses may need to be adjusted. Actemra is not recommended for use with other biological agents due to lack of experience.

Side Effects:

URTI, nasopharyngitis, headache, hypertension and increased ALT. Other events listed as common were cellulitis, pneumonia, oral herpes simplex, herpes zoster, mouth ulceration, gastritis, rash, pruritis, dizziness, leucopenia, neutropenia, hypercholesterolaemia, conjunctivitis.

Forensic Classification:

P1S1S3

Galvus® (Novartis)

Active Ingredient:

Vildagliptin

Presentation:

Each tablet contains 50 mg Vildagliptin
White to light yellowish round tablet

Pharmacological Properties:

Vildagliptin is a member of the islet enhancer class, is a potent and selective dipeptidyl-peptidase-4-(DPP-4) inhibitor that improves glycaemic control. The administration leads to rapid and complete inhibition of DPP-4 activity. In type 2 diabetes, administration of Vildagliptin led to inhibition of DPP-4 activity for 24 hour period and also resulted in increase fasting and postprandial endogenous levels of the incretin hormones GLP-1 (glucagon-like peptide 1) and GIP (glucose-dependent insulinotropic polypeptide). By increasing, the endogenous levels of these incretin hormones,

Vildagliptin enhances the sensitivity of beta cells to glucose resulting in improved glucose dependent insulin secretion. By increasing endogenous GLP-1 levels, Vildagliptin enhances the sensitivity of the alpha cells to glucose resulting in more glucose appropriate glucagon secretion. The enhanced increases in secretion in the insulin/glucagon ratio during hyperglycaemia due to increased incretin hormone levels results in a decrease in fasting and postprandial hepatic glucose production, leading to reduced hyperglycaemia.

Indications:

Vildagliptin is indicated as an adjunct to diet and exercise to improve glycaemia control in patients with type 2 diabetes mellitus as monotherapy and in dual combination with metformin, a sulphonylurea, a thiazolidinedione (TZD) or insulin when diet, exercise and a single antidiabetic agent do not result in adequate glycaemic control.

Dosage and Administration:

The recommended dose is 50 mg or 100 mg daily for monotherapy and in dual combination with metformin, a TZD or insulin. The 50mg dose should be administered in the morning whilst the 100 mg dose should be administered as two divided doses of 50 mg in the morning and evening. When used in dual combination with sulphonylurea the recommended dose is 50 mg daily in the morning and 100 mg was no more effective. Vildagliptin is not recommended in hepatic impairment including patients with a pre-treatment ALT and AST >2.5X the upper limit of normal. It is not recommended in patients with moderate to severe renal impairment.

Contraindications:

Vildagliptin is contraindicated

in patients with known hypersensitivity to it and its excipients.

Precautions:

They are not a substitute for insulin in insulin requiring patients and should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis. Galvus contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Interactions:

Vildagliptin has low potential for drug interactions. Since it is not a cytochrome P(CYP)450 enzyme substrate nor does it induce or inhibit the CYP450 enzymes. It is not likely to interact with co-medications that are substrates, inhibitors or inducers of these enzymes.

Side Effects:

Dizziness, headache, constipation, oedema peripheral, asthenia, nausea, flatulence, GERD, rare cases of angioedema and hepatic dysfunction including hepatitis have been reported,

List of Excipients:

Lactose anhydrous, microcrystalline

cellulose, sodium starch glycolate, magnesium stearate these may vary between countries.

Forensic Classification:

P1S1S3

ISENTRESS®
(MSD)

Active Ingredient:

Raltegravir

Presentation:

400 mg tablets

Pharmacological Properties:

ISENTRESS is an HIV integrase strand transfer inhibitor active against the Human Immunodeficiency Virus (HIV-1).

Indications:

ISENTRESS is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adult patients.

The use of other active agents with ISENTRESS is associated with a greater likelihood of treatment response.

The safety and efficacy of ISENTRESS

have not been established in pediatric patients.

Dosage & Administration:

For the treatment of patients with HIV-1 infection, the dosage of ISENTRESS is 400 mg administered orally, twice daily with or without food. During coadministration with rifampin, the recommended dosage of ISENTRESS is 800mg twice daily with or without food.

Hepatic Insufficiency

Raltegravir is eliminated primarily by glucuronidation in the liver. No dosage adjustment is necessary for patients with mild to moderate hepatic insufficiency. The effect of severe hepatic insufficiency on the pharmacokinetics of raltegravir has not been studied.

Renal Insufficiency

Renal clearance of unchanged drug is a minor pathway of elimination. There were no clinically important pharmacokinetic differences between patients with severe renal insufficiency and healthy subjects. No dosage adjustment is necessary. Because the extent to which ISENTRESS may be dialyzable is unknown, dosing before a dialysis session should be avoided.

Forensic Classification

P1S1S3



MSc in Clinical Pharmacy*

This is a 2 years' part-time programme in HK delivered through distance learning. Tutorials / workshops are run by visiting academics from the University of Sunderland.

Features:

- Updated specialist modules
- Training in research skills
- Realistic project workload for timely completion
- High and timely completion rate

Course content is under review.

Teaching and Assessment:

Teaching is conducted through lectures, tutorials, seminars, group work and structured practical experience. Project work is required on a topic relevant to patients' needs from the students' area of study.

Assessment is mainly by coursework, including reports, seminar presentations, case studies and project report (dissertation).

* This is an exempted course under the Non-Local Higher and Professional Education (Regulation) Ordinance. It is a matter of discretion for individual employers to recognize any qualification to which this course may lead.

Entry Requirements:

A minimum of lower second class honours degree in pharmacy (or equivalent) and registration as a pharmacist in HK. Applicants who obtained their bachelors degree in pharmacy from Australia, Canada, New Zealand and Taiwan are also welcomed to apply. The programme is open to both hospital and community pharmacists.

Application Deadline: May 28, 2010

Enquiries: 3762 0096

Fax: 2151 0720

Email: sheri.ip@hkuspace.hku.hk



Hong Kong Pharmaceutical Journal: Detail Instructions for Authors

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The manuscript is required to be written in English, with numbered pages, single-spaced, using Arial 9 point font, and in a suitable word-processing format. Each page should have adequate margins (4 cm) and liberal spaces at top and bottom of the manuscript. All textual elements should begin flush left, with the second paragraphs onwards indent, and should use the wrap-around end-of-line feature, i.e. no returns at the end of each line. Place two returns after every element such as title, headings,

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The content of manuscripts must be arranged as follows: (1) a Title Page with authors name(s) and address(es); (2) an Abstract, in which contents are briefly stated; (3) a 4 to 6 Key Word Index, (4) Introduction, and (5) the Results and Discussion (preferably combined). Although each section may be separated by headings, they should form one continuous narrative and only include details essential to the arguments presented. If a discussion is separately provided, it should not include a repetition of the results, but only indicate conclusions reached on the basis of them, and those from other referred works; (6) Conclusions or Concluding Remarks; (7) the Experimental should include brief details of the methods used such that a competent researcher in the field may be able to repeat the work; (8) Acknowledgments; (9) References; (10) Legends, Formulae, Tables and Figures.

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address should also be indicated for the corresponding authors. No academic or professional membership title is allowed.

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Key Words: Authors must give four to six "key words" or phrases, which identify the most important subjects covered by the paper.

INTRODUCTION should give the minimum historical data needed to give appropriate context to the author's investigation and its relationship to other similar research previously or currently being conducted. Only information essential to the arguments should be presented. Much data can be taken for granted or quoted in abbreviated form. Specific term (genus, species, authority) of all experimental works must be given at first mention and preferably be in the form adopted by the International Scientific Community.

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Nomenclature: Chemical nomenclature, abbreviations and symbols must follow IUPAC rules. Whenever possible, avoid coining new trivial names; every effort should be made to modify an existing name. For example, when a new compound is described, it should be given a full systematic name according to IUPAC nomenclature and this should be cited in the Abstract or in the Experimental section.

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- (1) Cabello-Hurtado F, Durst F, Jorin JV, Werck-Reichhart D. et al. (1998). Coumarins in *Helianthus tuberosus*: characterization, induced accumulation and biosynthesis. *Biochemistry*, 49(1):1029-1036.

- (2) Mabry T, Markham KR, Thomas MB. (1970). *The Systematic Identification of Flavonoids*. 2nd Ed, pp. 79-105. Springer Verlag, New York.
- (3) Harborne JB. (1999). Plant chemical ecology. In: Barton D, Nakanishi K, Meth-Cohn O, (Eds.), *Comprehensive Natural Products Chemistry*, Vol. 8. pp. 137-196. Pergamon, Oxford.

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Abbreviations

About, approximately: ca.
Anhydrous: dry (not anhyd.)
Aqueous: aq.
Circular dichroism: CD
Concentrated (or mineral acids): conc.
Concentrations: ppm (or ppb), μ M, mM, M, %, mol
Dry weight: dry wt; fresh weight: fr. wt
Electricity: V, mA, eV
Force due to gravity (centrifugation): g; rpm (revolutions min⁻¹)
Gas chromatography: GC
Gas chromatography-mass spectrometry: GC-MS
Trimethylsilyl derivative: TMSi (TMS cannot be used as this refers to the internal standard tetramethylsilane used in ¹H NMR)
High performance liquid chromatography: HPLC
Infrared spectrophotometry: IR
Length: nm, μ m, mm, cm, m
Literature: lit.
Mass spectrometry: m/z [M]⁺ (molecular ion, parent ion)
Melting points: uncorr. (uncorrected)
Molecular mass: Da (daltons), kDa
Molecular weight: M,
Nuclear magnetic resonance: ¹H NMR, ¹³C NMR, Hz, δ
Numbers: e.g. 1, 10, 100, 1000, 10000; per or ⁻¹
Optical rotatory dispersion: ORD
Paper chromatography: PC
Precipitate: ppt.
Preparative thin-layer chromatography: prep. TLC
Radioactivity: dpm (disintegrations per min), Ci (Curie), sp. act (specific activity), Bq (1 becquerel = 1 nuclear transformation sec⁻¹)
Repetitive manipulations: once, twice, x3, x4, etc.
RR_t (relative retention time), R_t (Kovat's retention index), ECL (equivalent chain length- term frequently used in fatty acid work)
Saturated: satd.
Solution: soln.
Solvent mixtures including chromatographic solvents: abbreviate as follows n-BuOH-HOAc-H₂O (4:1:5)
Statistics: LSD (least significant difference), s.d. (standard deviation), s.e. (standard error)
Temperature: (with centigrade), mp, mps, mmp, bp
Temperature: temp.
Thin-layer chromatography: TLC, R_f
Time: s, min, h, day, week, month, year
Ultraviolet spectrophotometry: UV, A (absorbance, not aD-optical density)
Volume: l, (litre), μ l, ml
Weight: wt, pg, ng, μ g, mg, g, kg

Inorganics, e.g. AlCl₃ (aluminum chloride), BF₃ (boron trifluoride), Cl₂, CO₃, H₂, HCl, HClO₄ (perchloric acid), HNO₃, H₂O, H₂O₂, H₂SO₄, H₃BO₃ (boric acid), He, K₂CO₃ (potassium bicarbonate), KMnO₄ (potassium permanganate), KOH, K-Pi buffer (potassium phosphate buffer), LiAlH₄ (lithium aluminium hydride), Mg²⁺, MgCl₂, N₂, NH₃, (NH₄)₂SO₄, Na⁺, NaBH₄

(sodium borohydride), NaCl, NaIO₄ (sodium periodate), NaOH, Na₂SO₃ (sodium sulphite), Na₂SO₄ (sodium sulphate), Na₂S₂O₃ (sodium thiosulphate), O₃, PPI (inorganic phosphate), SO₄²⁻, Tris (buffer).

Organics, e.g. Ac₂O (acetic anhydride), n-BuOH (butanol), C₆H₆ (benzene), CCl₄ (carbon tetrachloride), CH₂Cl₂ (methylene chloride), CHCl₃ (chloroform), CH₂N₂ (diazomethane), CM (carboxymethyl), DEAE (diethylaminoethyl), DMF (dimethylformamide), DMSO (dimethyl sulphoxide), EDTA (ethylene-diaminetetraacetic acid), Et₂O (diethyl ether), EtOAc (ethyl acetate), EtOH (ethanol), HCO₂H (formic acid), HOAc (acetic acid), iso-PrOH (iso-propanol), Me₂CO (acetone), MeCOEt (methyl ethyl ketone), MeOH (methanol), NaOAc (sodium acetate), NaOMe (sodium methoxide), petrol (not light-petroleum or petroleum ether), PhOH (phenol), PrOH (propanol), PVP (polyvinylpyrrolidone), TCA (trichloroacetic acid), TFA (trifluoroacetic acid), THF (tetrahydrofuran).
¹H NMR solvents and standards: CDCl₃ (deutero-chloroform), D₂O, DMSO-d₆ [deuterodimethylsulphoxide not (CD₃)₂S], pyridine-d₅ (deuteropyridine), TMS (tetramethylsilane).

For further terms used in biochemistry and molecular biology the authors should see the websites of the nomenclature committees (www.chem.qmul.ac.uk/iubmb/).

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LIPITOR[®]
atorvastatin calcium – crystalline form
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patients?

Consider what you
would take.

LIPITOR remains the statin widely preferred by the majority of physicians....

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✓ **LIPITOR** is the **#1 choice of Physicians** (especially when they need treatment)¹.

...for their loved ones

✓ **Five times more Physicians** surveyed would recommend **LIPITOR** to their own family members over other cholesterol-lowering medications.²

✓ **Three times more Cardiologists** surveyed would recommend **LIPITOR** to their own family members over other cholesterol-lowering medications.³

...for their patients

✓ **LIPITOR** is the most prescribed statin in the world.⁴

✓ **Evidence** on broad range of patients for primary and secondary prevention.⁵



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Reference : 1. Results based on a subset of a blinded, national, random survey of 597 physicians representative of the AMA master file, conducted by Harris Interactive Inc from November 17, 2003, through January 9, 2004. 2. Results are based on a blinded, national, random survey of 493 physicians representative of the AMA master file, conducted by Harris Interactive Inc. April-June 2007. 3. Based on a response from 57 cardiologists in a Harris Interactive Survey of 489 physicians, sampled from the American Medical Association master file, conducted from April 2007-June 2007. 4. IMS Top 15 Global Products (2008). 5. Lipitor Hong Kong Packing Insert (Dec 2007). Detailed information is available upon request.