

HONG KONG PHARMACEUTICAL *JOURNAL*

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News & Short Communications

The Pharmaceutical Services to the Elderly in the Old Aged Homes in Hong Kong: A Scoping Exercise

Drug Wastage among the Elderly Living in Old Aged Homes in Hong Kong

Overview of Targeted Therapies for Renal Cell Carcinoma (2 CE Units)

Over-the-Counter Paracetamol for Management of Fever in Children

Biochemical- and Biological-Based Studies of Asian Ginseng

A letter to the HK Pharmacy Conference Organizing Committee

Brilinta® 90 mg film-coated tablets

Hong Kong Pharmaceutical Journal: For Detailed Instructions for Authors



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The Practising Pharmacists Association of Hong Kong
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1. Lemone P, Guilleminault C, Alvarez E. Improvement of subjective sleep in major depressive disorder with a novel antidepressant, agomelatine: randomized, double-blind comparison with venlafaxine. *J Clin Psychiatry*. 2007;68:1723-1732.
2. Kennedy S.H, Rizvi S, Fulton K, et al. A double-blind comparison of sexual functioning, antidepressant efficacy and tolerability between agomelatine and venlafaxine-XR. *J Clin Psychopharmacology*. 2008;28(3):329-333.
3. Goodwin G.M, Emsley R, Rembray S, et al. Agomelatine prevents relapse in patients with major depressive disorder without evidence of a discontinuation syndrome: a 24-week randomized, double-blind, placebo-controlled trial. *J Clin Psychiatry*. 2009;70:1128-1137.

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INSTRUCTIONS FOR AUTHORS

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

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

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

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

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

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

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No Transformation, No Breakthrough



New breakthrough and innovation normally require some forms of courage and imagination. If people keep on doing the same thing as usual, it is quite unlikely to bring in any advance.

In nature, new features and new dynamic of life are normally achieved by transformation. An insect won't become an adult if it doesn't transform and come out from a cocoon. Through transformation, the insect can fly and reach a higher and further distance. Certainly emerging from a cocoon is not an easy task and it has to pay some prices. The whole process may be difficult, painful and even dangerous. The emergence, acceptance and mature of new horizon of a civilization of human beings is the same. It requires lots of efforts, time and many people's participation.

The influence of pharmacy professionals has been up and down. Pharmacists, or more properly called chemists before the 50s, were also regarded as a medical doctor or the healer. But in the last two centuries, their practices have been cast into the shade due to the outgrowth of medical doctors and become a paramedical professional. It is true for every pharmacist in Hong Kong. But in recent years, some improvements have occurred. In particular, this year is a landmark for all Hong Kong pharmacists; it is a year full of many memorable events. First of all, it marks the 25th Anniversary of inauguration of the Hong Kong Pharmacy Conference and the 20th year of publication of the Hong Kong Pharmaceutical Journal. At the moment of writing this editorial, I have received an invitation to attend another big event, i.e. the inauguration ceremony of the College

of Pharmacy Practice, which will be held on 22nd June, 2013.

Hong Kong Pharmaceutical Journal is a flagship publication of the Pharmaceutical Society of Hong Kong, the Society of Hospital Pharmacists and the Practising Pharmacists Association of Hong Kong. Although the community of pharmacists is relatively small in comparison to other healthcare professionals, the spirit of pharmacists is not small at all. Pharmacists in Hong Kong are always dynamic, enthusiastic, highly motivated and devoted. The launch of this journal some 20 years ago and its continuous presence up to this day is the excellent evidence without saying. Hence, congratulate to members of the editorial board of HKPJ and all its contributors in the past. We would like to thank all of those who have contributed to this journal in the past. Without everyone's effort, it is impossible to make this colorful journal realized. A special thank is given to our advertisers and particularly our regular advertisers for the support they have shown. Our advertisers, along with all subscribers and members of the Pharmaceutical Societies are important contributors to the financial success of this journal. We thank them.

Talking about celebration, the Hong Kong Pharmacy Conference was founded even earlier. This year also marks the Silver Jubilee of its establishment. It was only a month ago that the society under Michael Ling's chairing held an enlightening, spectacular and wonderful annual meeting that probably never took place before. I believe whoever attending this year's conference would agree with me that it was really a joyful, inspiring and educational meeting. In these two days of meeting, many talents have been discovered and their shows were really inspiring and enlightening. These included the opera of Musical-Pharmtom performed by local pharmacists, students and staff from both pharmacy schools, the music played by the PharmCare

Orchestra, the speeches delivered by the keynote speakers, the workshop conducted by Dr. Taylor, the debate etc. I believe all attendants have learned a lot and enjoyed every item. For those who missed this celebration or couldn't turn up, a full report and some photos of this big occasion can be found in p.46-47. I am sure you will catch a glimpse of joy on every participant's face in those two days during the conference.

We are glad to receive more support from the staff and students from both pharmacy schools in Hong Kong. Upon the encouragement of Professor Ian CK Wong, they have provided us with more articles than ever before and it is really a breakthrough. In this issue, Wong et al explored how the aged people in nursing home could be effectively served by pharmaceutical professionals (p.11-15) after surveying the drug wastage by elderly in old aged home (p.16-18). These two reports are indeed the shorter versions of a study sponsored by the Pharmaceutical Society of Hong Kong and MSD Asia last year. We would like to see more sponsorships coming from drug companies for uses in education and research purposes because drug discovery is expensive and time consuming. Today, whatever substances claimed to be effective for the treatment of a health problem requires either proofs of specific effect like the targeted therapies for renal cell carcinoma (p.20-27) or data supports from substantial applications and studies of a substance, such as the Asian Ginseng (p.33-45) or paracetamol for management of fever (p.29-31) reported in the issue.

There are lots of other matters to read in this issue of HKPJ and we hope whoever receiving this issue enjoy the information provided. Of course, we would be most glad for any suggestions, comments or a helping hand!

Cheung Hon-Young
Editor-in-Chief
6th April, 2013

Singapore: Vertical Transmission of Hepatitis B Despite Immunoprophylaxis

Date: December 2012

HSA updated healthcare professionals on several cases of vertical transmission of hepatitis B (HB) despite immunoprophylaxis with both HB immunoglobulin (HBIG) and HB vaccine. The infants were born to HB carrier mothers and had received a single dose of HBIG at birth and completed

a three-dose regimen of HB vaccine. The root cause of vertical transmission of HB could not be ascertained in view of incomplete data and multi-factorial nature of immunoprophylaxis failure. Based on these reports, the rates of immunoprophylaxis failure from 2009 to 2011 were estimated to be within

the expected incidences reported in literature. Healthcare professionals were encouraged to report all cases of HB infection despite immunoprophylaxis to HSA for on-going monitoring of this issue.

Source: www.hsa.gov.sg/publish

US: Lower Recommended Doses for Bedtime Use of Zolpidem Due to the Next-morning Impairment of Certain Activities

Date: January 10, 2013

On 10 January 2013, the Food and Drug Administration (FDA) of the US notified the public of new information about zolpidem. FDA recommended that the bedtime dose be lowered because new data showed that blood levels in some patients may be high enough the next morning to impair activities that required alertness, including driving. This announcement focused on zolpidem products approved for bedtime use. Data showed that the

risk for next-morning impairment was highest for patients taking the extended-release forms of these drugs (Ambien CR and generics). Women appeared to be more susceptible to this risk because they eliminated zolpidem from their bodies slower than men.

FDA therefore required the manufacturers of all zolpidem products to lower the recommended dose. The recommended dose of zolpidem for

women should be lowered from 10mg to 5mg for immediate-release products (Ambien, Edluar, and Zolpimist) and from 12.5mg to 6.25mg for extended-release products. Whereas for men, the labelling should recommend healthcare professionals to consider prescribing the lower doses (5mg for immediate-release products and 6.25mg for extended-release products).

Source: www.drugoffice.gov.hk

Canada: New Labelling Information for All Botulinum Toxin Products

Date: January 21, 2013

On 21 January 2013, Health Canada announced that in order to help prevent medication errors with the use of botulinum toxin products, all manufacturers of these products were requested to revise their product labels so as to reflect that each product had its own individual potency and as such, was not interchangeable with other botulinum products. The labelling changes were due to a risk evaluation of the active ingredients

(Clostridium botulinum toxin type A and type B) within these products. Botulinum toxins were produced by different manufacturing processes, were obtained by different techniques and were derived from different Clostridium strains. As a result of these differences, these products could not be interchanged as these changes could cause unexpected side-effects. In Hong Kong, six pharmaceutical products containing botulinum toxin are

registered, namely Dysport for Inj 500 Units (HK-36983), Botox for Inj 100 Units (HK-41906), Botox for Inj 200 Units (HK-60427), Btxa for Inj 50 Units (HK-51582), Btxa for Inj 100 Units (HK-49886) and Siax Inj 100 Units (HK-56847). They are prescription medicines indicated for the treatment of blepharospasm, hemifacial spasm and strabismus.

Source: www.drugoffice.gov.hk

Canada: New Statins Labeling Update on the Risk of Increased Blood Sugar Levels and Diabetes

Date: January 24, 2013

On 24 January 2013, Health Canada informed Canadians of a labelling update for all cholesterol-lowering drugs ("statins") regarding the risk of increased blood sugar levels and a small increased risk of diabetes among patients already at risk for the disease. Based on the review of all available data, Health Canada concluded that the risk of diabetes appeared to be mainly in patients with pre-existing risk factors for diabetes, such as high levels of glucose or triglycerides, obesity or high blood pressure. Health Canada continued to believe the overall cardiovascular benefits of statin drugs in reducing blood cholesterol outweigh their risks. A new warning about the increased blood sugar levels and the risk of diabetes, including information on how to identify high-risk patients, had been added to the drug labels for the statins currently marketed in Canada.

In Hong Kong, there are 239 registered pharmaceutical products which belong to the class of statins. All are prescription medicines indicated for hypercholesterolemia. The Registration Committee of the Pharmacy and Poisons Board decided that the sales pack or package insert of the following pharmaceutical products should be updated to include the appropriate safety information, examples of wordings to be used are:

A. Statins-containing products:

"It is recommended that liver function tests should be performed before the initiation of [brand name], and thereafter when clinically indicated."

"There have been rare postmarketing reports of cognitive impairment associated with statin use. These cognitive issues have been reported for all statins. The reports are generally non serious and reversible upon statin discontinuation, with variable times to

symptom onset (1 day to years) and symptom resolution (median of 3weeks)."

"Increases in HbA1c and fasting serum glucose levels have been reported with HMG-CoA reductase inhibitors."

B. Atorvastatin-containing products:

"Co-administration of strong CYP3A4inhibitors should be avoided if possible. In cases where co-administration of these medicinal products with atorvastatin cannot be avoided, lower starting and maximum doses of atorvastatin should be considered and appropriate clinical monitoring of the patient is recommended." "In patients taking telaprevir, concomitant use of atorvastatin should be avoided." (Also applicable for telaprevir-containing products) "The dose of atorvastatin should not exceed 40mg daily when taking with boceprevir and close clinical monitoring is recommended." (Also applicable for boceprevir -containing products)

C. Simvastatin-containing products:

"Simvastatin is contraindicated with strong CYP3A4 inhibitors, as well as gemfibrozil, ciclosporin and danazol." "Do not exceed 20mg simvastatin daily with amiodarone." (Also applicable for amiodarone-containing products) "Cases of myopathy/rhabdomyolysis have been observed for simvastatin co-administered with lipid-modifying doses ($\geq 1\text{g/day}$) of niacin. The dose of simvastatin should not exceed 20mg daily in patients receiving concomitant medication with niacin (nicotinic acid) $\geq 1\text{g/day}$." (Also applicable for niacin-containing products) "Cases of myopathy, including rhabdomyolysis, have been reported with simvastatin co administered with colchicine. Caution should be exercised when prescribing simvastatin with colchicine." (Also applicable for colchicine-containing products).

D. Lovastatin-containing products:

"Lovastatin is contraindicated with strong CYP3A4 inhibitors." "The combined use of lovastatin with gemfibrozil or ciclosporin should be avoided." "The dose of lovastatin should not exceed 20mg daily in patients receiving concomitant medication with danazol, diltiazem, verapamil or dronedarone." "The dose of lovastatin should not exceed 40mg daily in patients receiving concomitant medication with amiodarone."

"Grapefruit juice should be avoided inpatients taking lovastatin."

E. Rosuvastatin-containing products:

"The concomitant use with protease inhibitors is not recommended."

"In JUPITER study, there was a significantly higher frequency of diabetes mellitus reported in patients taking rosuvastatin (2.8%) versus patients taking placebo (2.3%). Mean HbA1c was significantly increased by 0.1% in rosuvastatin-treated patients compared to placebo-treated patients. The number of patients with a HbA1c $> 6.5\%$ at the end of the trial was significantly higher in rosuvastatin-treated versus placebo-treated patients."

F. Products containing HIV protease inhibitors:

"Co-administration of atorvastatin should be avoided. In cases where co-administration of atorvastatin cannot be avoided, lower starting and maximum doses of atorvastatin should be considered and appropriate clinical monitoring of the patient is recommended."

"Concomitant use of lovastatin or simvastatin is contraindicated. Rosuvastatin is not recommended to be used with protease inhibitors." (Also applicable for boceprevir-containing and telaprevir-containing products)

Source: www.drugoffice.gov.hk

EU / Canada / Australia: Safety Review of Diane 35 and Its Generics

Date: January 31, 2013

On 31 January 2013, EMA announced that the French medicines agency (ANSM) planned to suspend the marketing authorisation for Diane 35 (cyproterone acetate 2 mg, ethinylestradiol 35 micrograms) and its generics for acne treatment in France within 3 months. In France, these medicines were only authorised for the treatment of acne. However, they were also authorised for the treatment of acne in women who wished to receive oral contraception, as well as for the treatment of other skin conditions, in a number of other Member States in the European Union (EU). The announcement in France came after a review by ANSM that Diane 35 and its generics carried a risk of thromboembolism which had been well known for many years, and while their

effectiveness in treating acne was only moderate and with alternatives available. Although Member States could take unilateral action to suspend the marketing authorisation of a medicine, European legislation required that there was a coordinated European approach in these instances. France had already indicated that it would ask EMA to carry out a European-wide review of Diane 35 and its generics. EMA's PRAC would evaluate all evidence on the benefits and risks of these medicines and give a recommendation on whether their marketing authorisations should be varied, suspended or revoked, in the interest of all patients in the EU. After the meeting in February 2013, EMA stated it was expected that PRAC would adopt a recommendation at its May 2013 meeting.

Both Health Canada and the Therapeutic Goods Administration of Australia announced on 31 January and 5 February 2013 respectively that they were reviewing the safety information on Diane-35, and would advise and take appropriate action as necessary. In Hong Kong, Diane-35 Tab (HK-43330) is registered by Bayer Healthcare Ltd. and there are nine registered generics. All are prescription medicines indicated for the treatment of acne; other registered indications include androgenetic alopecia, mild forms of hirsutism and contraception. The package inserts have included the precaution of blood clot. Letter to healthcare professionals was issued on 31 January 2013 by DH.

Source: www.drugoffice.gov.hk

US: Safety Review Update of Codeine Use in Children; New Boxed Warning and Contraindication on Use After Tonsillectomy and/or Adenoidectomy

Date: February 20, 2013

The FDA of the US reminded healthcare professionals about the risks of death and respiratory depression of using codeine in children, particularly in those who had undergone tonsillectomy and/or adenoidectomy for obstructive sleep apnoea. These children, who were two to five years old, had evidence of an inherited ability to convert codeine into life-threatening or fatal amounts of morphine in the body. On 20 February 2013, FDA updated the public about labelling changes of codeine-containing products to address the issue.

Healthcare professionals should prescribe an alternate analgesic for post-operative pain control in children who were undergoing tonsillectomy and/or adenoidectomy. In the US, a new Boxed Warning would be added to the drug label of codeine containing products about the risk of codeine in postoperative pain management in children following tonsillectomy and/or adenoidectomy. A Contraindication would be added to restrict codeine from being used in this setting. The Warnings/Precautions, Paediatric Use, and Patient Counselling Information sections of the drug label would also be updated in Hong Kong,

there are about 360 registered codeine-containing pharmaceutical products and most of them are in syrup form. Majority are indicated to relieve cough and a few are used as pain reliever. DH had not received any adverse event report in connection with the use of the products. A letter to healthcare professionals was issued on 16 August 2012 regarding this issue. In view of FDA's recommendations, the matter will be discussed in the meeting of the Registration Committee of the Pharmacy and Poisons Board.

Source: www.drugoffice.gov.hk

Announcement of Results of Registration Examination for Pharmacists

Date: March 8, 2013

On 8 March 2013, the Pharmacy and Poisons Board of Hong Kong announced the results of the Registration Examination for Pharmacists held in December 2012. There were 95, 83 and 145 candidates sitting for examinations in "Pharmacy Legislation in Hong Kong",

"Pharmacy Practice" and "Pharmacology" respectively, with corresponding pass rates of 31.6 per cent, 36.1 per cent and 23.4 per cent. Apart from meeting other requirements prescribed by the Board, any pharmacy graduate outside Hong Kong intending to be registered as a

pharmacist in Hong Kong is required to pass the above three subjects. The Board conducts its Registration Examination twice a year, usually in June and December.

Source: www.dh.gov.hk

Notification of Three Human Cases of H7N9 in Shanghai and Anhui

Date: March 31, 2013

On 31st March 2013, the Centre for Health Protection (CHP) of the Department of Health received notification from the National Health and Family Planning Commission (the Commission) concerning three confirmed human cases of influenza A (H7N9). The two cases in Shanghai were two men aged 87 and 27, who passed away on March 4 and March 10 respectively. As regards the case in Anhui, the 35-year-old female patient is now in critical condition. Laboratory tests on the three patients' specimens yielded a positive result for H7N9. The 27-year-old man was a butcher while the 35-year-old

woman had exposure history to poultry before the onset of symptoms. So far, no abnormality was detected among the 88 close contacts of three cases.

Influenza A (H7) is a statutorily notifiable infectious disease in Hong Kong. CHP is maintaining close liaison with the Mainland health authorities to obtain more information on the cases. A spokesman for the DH urged travellers not to visit wet markets with live poultry in the affected areas, and to avoid direct contact with poultry, birds or their droppings. If contact has been made, people should

wash their hands thoroughly with soap and water.

As of 25 April, 2013, a total of 111 cases have been laboratory confirmed with avian influenza A (H7N9) in the Mainland, which included Zhejiang (44 cases), Shanghai (33 cases), Jiangsu (24 cases), Anhui (4 cases), Henan (4 cases), Beijing (1 case) and Shandong (1 case). Locally, no confirmed human case of avian influenza A(H7N9) has been recorded so far

Source: www.dh.gov.hk

Hypertension Is Preventable and Treatable- World Health Day 2013

Date: April 2, 2013

On 2 April, 2013, the Director of Health, Dr Constance Chan held a press conference to launch an upcoming public education campaign on hypertension led by the Department of Health (DH) in collaboration with partners in the health-care sector. The campaign echoes "High Blood Pressure", the theme of World Health Day 2013 chosen by the World Health Organization (WHO), with the aim of reducing heart attacks and strokes. Locally, the Thematic Household Survey conducted by the Census and Statistics Department in the last five years revealed that the prevalence of diagnosed hypertension in Hong Kong has been on a rising trend from 9.3 per cent in 2008, to 10.3 per cent in 2009/10, and 11 per cent in 2011/12. However, many adults in Hong Kong actually do

not realise that they have hypertension. Hypertension is a silent killer. Uncontrolled or untreated hypertension can lead to serious or even fatal diseases, including coronary heart disease, heart attack, heart failure, stroke, dementia, kidney failure, and retinal disease. Dr Chan said, "Hypertension does not usually give rise to symptoms. Many patients with hypertension may not be aware of their disease. Therefore, it is important to monitor blood pressure regularly for early detection of hypertension. Healthy adults aged 18 years or above should have their blood pressure checked at least every two years. Hypertension is preventable. The risk of developing high blood pressure can be reduced by maintaining a healthy lifestyle such as reducing salt (sodium)

intake as part of a balanced diet, engaging in regular physical activity, maintaining an optimal body weight, refraining from smoking and drinking.

Dr Donald Li, the President of the Hong Kong Academy of Medicine, said that hypertension is a chronic disease which occurs when blood pressure is persistently elevated. It can be controlled with medication, but the objective of treatment is to prevent complications and not to seek a cure. Patients need to continue with the treatment and lifestyle modifications as advised by doctors and attend regular medical follow up.

Source: www.dh.gov.hk

HK Law Undermines TCM Exhibition

WONG Albert

Modernized Chinese Medicine International Association (email: mcmia@mcmia.org)

Dear Editor,

Our own law is undermining Hong Kong's only international Chinese medicine exhibition-conference gala event (ICMCM) that has been held for the past 11 years at the HK Convention and Exhibition Center.

Ever since the full implementation of the *HK Chinese Medicine Ordinance* in 2010, some of ICMCM's exhibitors began to abandon the exhibition because the *Ordinance's* Clause 119 prohibits the sale, importation and possession of unregistered proprietary Chinese medicine (pCM中成藥). The clause is reasonable in a general sense but becomes incongruous and unreasonable in the context of an international exhibition.

Chinese medicine exhibitors from different parts of the world congregate annually to HK to showcase their latest products. Most of these exhibits are brought into HK solely for promotional purpose and they will only be registered later when local distributors are found to sell them in HK. Some of the products might not even be intended for sale in HK but to a third country or region. Hence, it is unreasonable for an *Ordinance* to require exhibits to be registered prior to exhibitions.

The *ordinance* also prohibits local merchants from displaying their newly developed, but yet unregistered, products. Furthermore, even legitimate distributors who received unregistered product samples at the exhibitions might violate the law because of possession.

Hence the prohibition of exhibitors' unregistered pCM samples amounts not only to a prohibition of pCM exhibitors to come to HK's Chinese medicine trading platform but also restricts other international traders to use HK as a center to trade among themselves.

Five years ago, long before the implementation of the *ordinance*, MCMIA (Modernized Chinese Medicine International Association) and HKTDC (HK Trade Development Council) brought this issue to the attention of the Department of Health (DH) to seek the addition of an exemption clause to the *ordinance's* Exemption Section or to grant a temporary waiver of Clause 119 in legitimate exhibition environments. Unfortunately, the request was rejected right off hand as the department claimed itself to be a law enforcement agency and not a policy maker. Last month, MCMIA took the issue to the Food and Health Bureau (FHB), expecting a more sympathetic and understanding audience. To our disappointment, the issue was promptly referred back to DH for further consultation.

MCMIA's proposal to FHB was very simple. Exhibitors will be allowed to bring only a small number of exhibition samples (≤ 6 units) of each displayed product into HK after their exhibition lists are approved by DH ahead of time. The samples will be restricted to be displayed at the designated location and time with the remainder samples to be brought back to its country of origin after the exhibition. All legitimate distributors or buyers who receive samples must leave behind their personal and company information

so that the samples are traceable. The distribution of the unregistered product samples to ordinary citizens is forbidden.

It is clear that the procedure proposed above protects the general public from exposing to unregistered samples. With practically no risk to the public, the government's implementation of an unreasonable *clause* in an exhibition environment amounts to the inhibition of free-trade and the impairment of HK's reputation as a world trading center.

It took MCMIA and HKTDC a dozen year since 2002 to build the event to its current international prominence. ICMCM is now an aggregate of events and activities that include an international medical/scientific professional conference, a trade exhibition, a whole-day TCM forum for the general public, an international graduate student symposium and a student TCM educational display. The 3-day event is anchored onto the exhibition. Once the exhibition crumbles, all the other activities will follow.

It is sad to look back at MCMIA-HKTDC's 12 years of hard work to build up ICMCM with no government support, only to see it meeting its potential demise in a couple of years, ironically, because of our own outdated law and intransigent government policy makers rather than losing at the hands of our competitions !

Sincerely,
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A New Gateway of Treatment

A New Way of Life

Predictable...

- Metabolism independent of CYP2D6 pathway in the liver¹⁻³
- Low potential for CYP2D6-mediated drug-drug interaction⁴

Reliable...

- Discontinuation rate due to adverse events comparable to placebo⁴

Convenient...

- One simple 50 mg dose⁴

PRISTIQ® ABBREVIATED PACKAGE INSERT. TRADE NAME: PRISTIQ® PRESENTATION: Pristiq is formulated as an extended-release tablet which contains 75 mg of desvenlafaxine succinate equivalent to 50 mg of desvenlafaxine. Light pink, square pyramidal one-sided tablet debossed with "W" (over) "50" on one side. **INDICATIONS:** Pristiq is indicated for the treatment of major depressive disorder (MDD). **DOSEAGE & ADMINISTRATION:** The recommended dose for Pristiq is 50 mg once at approximately the same time daily, with or without food. Pregnant women during the third trimester, child & adolescent must balance the potential risks with the clinical needs. No dosage adjustment in patients with mild renal impairment but the recommended dose in patients with moderate renal impairment is 50 mg per day. The recommended dose in patients with severe renal impairment or end-stage renal disease (ESRD) is 50 mg every other day. Supplemental doses should not be given to patients after dialysis. No adjustment of the starting dosage for patient with hepatic impairment. No dosage adjustment is required solely on the elderly patients but the possibility of reduced renal clearance of Pristiq should be considered when determining the dose. **CONTRAINDICATIONS:** Hypersensitivity to desvenlafaxine succinate, venlafaxine hydrochloride or to any excipients in the Pristiq formulation. Must not be used concurrently in patients taking MAOIs or in patients who have taken MAOIs within the preceding 14 days. **WARNINGS & PRECAUTIONS:** All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behaviour, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Not approved for use in treating bipolar depression. Serotonin syndrome or NMS-like reactions. Activation of mania/hypomania. Elevated blood pressure & abnormal bleeding. Serum cholesterol & triglyceride elevation. Narrow-angle glaucoma. Renal impairment. Seizure. Hyponatremia. Interstitial lung disease & eosinophilic pneumonia. New symptoms and various discontinuation symptoms were reported in discontinuation of treatment. Caution is advised to patients with cardiovascular, cerebrovascular, or lipid metabolism disorders. Co-administration of drugs containing desvenlafaxine & venlafaxine is not recommended. **SIDE EFFECTS:** Most commonly observed adverse reactions in short-term fixed-dose studies were: nausea, dizziness, insomnia, hyperhidrosis, constipation, anorexia, decreased appetite, anxiety, and specific male sexual function disorders. Hypersensitivity effects on blood pressure, abnormal bleeding, mydriasis, hypomania & mania, serum cholesterol & triglyceride elevation, and seizure were also reported. **INTERACTIONS:** Risk in combination with other CNS-active drugs has not been systematically evaluated and caution is advised. MAOI: Serotonergic drugs. Drugs that interfere with hemostasis. Not increase the impairment of mental and motor skills caused by ethanol but advised to avoid alcohol consumption. Concurrent use with potent inhibitors of CYP3A4 may result in higher concentrations of Pristiq. Inhibitors of other CYP enzymes are not expected to have significant impact on the pharmacokinetic profile of Pristiq. Minimal inhibitory effect of desvenlafaxine on CYP2D6. Not inhibit or induce the CYP3A4 isozyme. Not inhibit CYP1A2, 2A6, 2C8, 2C9 & 2C19 isozymes & not expected to affect the pharmacokinetics of drugs that are metabolized by these CYP isozymes. Not a substrate or an inhibitor for the P-glycoprotein transporter. No clinical data establishing the risks and/or benefits of electroconvulsive therapy combined with Pristiq treatment. **PREGNANCY AND LACTATION:** Pregnancy Category C. Carefully consider the potential risks and benefits of treatment when treating a pregnant woman during the third trimester, labor and delivery. Excreted in human milk, breastfeed if the expected benefits outweigh any possible risk. **DRUG ABUSE AND DEPENDENCE:** Not systematically studied in preclinical/clinical studies for its potential for abuse. Physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of Pristiq. Limited clinical experience with desvenlafaxine succinate overdose in humans. **Reference:** WH1829C005-HK 04/08 **Date of preparation:** MAY/2010 **Identifier number:** PRIS0510 **FULL PRESCRIBING INFORMATION IS AVAILABLE UPON REQUEST.**

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- Further information is available upon request.



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The Pharmaceutical Services to the Elderly in the Old Aged Homes in Hong Kong: A Scoping Exercise

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ABSTRACT

Various models of pharmaceutical services have been provided by pharmacists to old aged home residents, however, these models have never been summarised and compared. The aim of this scoping exercise is to identify different kinds of pharmaceutical services currently available to the old aged home residents, by means of systemic literature review, qualitative in-depth interviews with service providers in order to understand their models and qualitative semi-structured interviews with non-pharmaceutical service users in an attempt to investigate reasons why some homes do not subscribe to these services. The results showed that none of the pharmaceutical services currently available can uproot the causes of medication errors, and there is a need to elaborate the roles of pharmacists in a primary care setting.

Keywords: Aged; Elderly; Pharmaceutical Services; Nursing Homes; Homes for the Aged; Hong Kong

INTRODUCTION

There is a rapidly growing ageing population in Hong Kong^[1, 2] and there is an issue of polypharmacy among the elderly.^[3] According to a 5-year evaluation report published in 2012,

approximately 46.4% of medication errors happen in the old aged homes (OAHs) are drug administration error.^[4] (Table 1) In order to optimise drug treatments among the elderly, various pharmaceutical services are provided to the elderly living in the old aged homes in Hong Kong. The aim of this scoping exercise was to identify different kinds of pharmaceutical services currently available to them and to ascertain opinions from pharmaceutical service users and non-users (i.e. those who are not current users of pharmaceutical services but may be future potential users).

METHODS

This scoping exercise is a 3-part study comprises of:

Part 1: Systematic literature review

Aim to identify published services in the literature, conference materials and the internet (web-based sources).

Part 2: Qualitative in-depth interviews with service providers

Interviews were conducted to study the service nature, resources to start and to sustain the services; and the key facilitators and barriers in running the services.

Part 3: Qualitative semi-structured interviews

Telephone interviews with pharmaceutical service users and non-users were also conducted to determine the perceptions of users on the pharmaceutical services including benefits, shortcomings, economics, potential improvement and long-term future, as well as to identify the current service provision gaps by comparing the opinions of users with non-users.

All interview data was transcribed and analysed separately by two independent reviewers.

Table 1. Five-year review report of accreditation scheme for old aged homes from 2005-2010

Common problems reported	Percentage of recommendations among the 69 recommendations in 56 OAHs(%)
Drug administration procedures	46.4
Drug storage procedures	26.1
Drug disposal	7.2
Special event reporting and following-up procedures	7.2
Staff education and training on drug management	4.3
Residents' self-purchased medicines and residents' discharge medication management	8.8

The Hong Kong Association of Gerontology. The Project on Accreditation System for Residential Care Services for the Elders in Hong Kong - Five-year review report (2005-2010). Hong Kong, 2012 1-83.

RESULTS

Part 1: Systematic literature review

All services identified were categorised into the following according to the patient cohorts the services serve. There were two services serving the elderly living in OAHs (Old Age Homes) including Monitored Dosage System (MDS) by pharmacy,^[5] and visiting pharmacist service (VPS).^[6-8] Moreover, three services serving all elderly in Hong Kong were identified including pharmacy online drug enquiry platform,^[9, 10] elderly drug counselling programme in a local hospital,^[11] and drug knowledge exchange via mass media.^[12]

Part 2: Qualitative in-depth interviews with service providers

The qualitative in-depth interviews were conducted with three main pharmaceutical service providers, namely MDS by pharmacy, in-house pharmacist, MDS by OAH staff. Service providers of in-house pharmacist and MDS by OAH staff were identified through snowballing technique. VPS, being as one of the service providers, refused to be interviewed.

Drug delivery model

Without any pharmaceutical service, the usual drug delivery model is represented in Figure 1. Drugs would be dispensed from medical institutes (including Hospital Authority institutes,

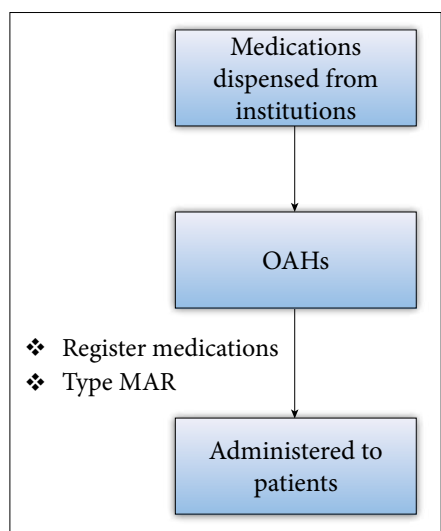


Figure 1. Usual practice of drug delivery model in old aged homes without the subscription to any pharmaceutical service

private sectors, such as private hospital and general practitioners). When the drugs arrive at the OAHs, healthcare workers would register the drugs manually into their in-house record, and they might be computer type-written by their clerk into medication administration record (MAR) for signing during the drug administration process.

Unlike usual drug delivery model, MDS by pharmacy allows repacking of the oral solid drugs for OAHs residents. When the dispensed drugs arrive at the OAHs, they would be transported to the delegated pharmacy, who would electronically update and document the medications of each resident and repack the oral solid dosages into MDS weekly pack. The prepacked MDS packs would be transported back to the OAHs for drug administration to the residents. The whole process is monitored by a bar-

code system and shall minimise the steps handled by non-medical professionals. (Figure 2)

Similar to MDS by pharmacy, in-house pharmacist is also responsible for the repacking of the drugs for OAHs residents. When the dispensed drugs arrive at the OAHs, they would be transported to the in-house pharmacy, who would electronically update and document the medications of each resident and repack the dosages into MDS weekly pack. The prepacked MDS packs would be transported to each floor of the OAH for drug administration to the residents. This model shall minimise the steps handled by non-medical professional. (Figure 3)

However, MDS by OAH Staff does not affect the drug delivery model, but

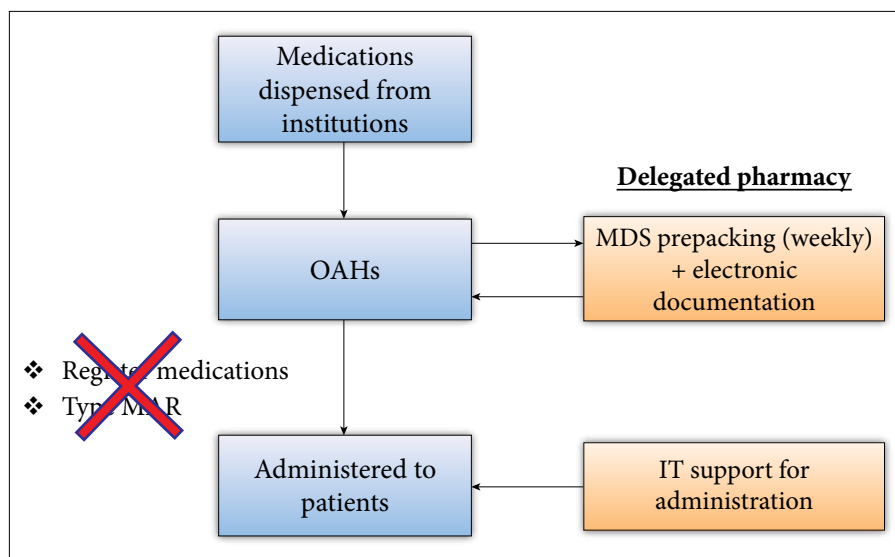


Figure 2. Drug delivery model for old aged homes subscribed to the MDS service packed by delegated pharmacy.

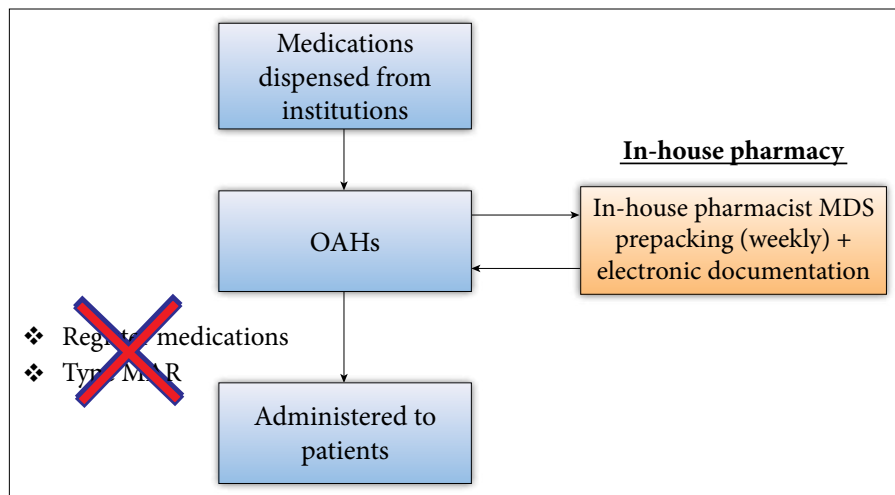


Figure 3. Drug delivery model for old aged home having an in-house pharmacist

the service provider supplement the OAHs with a centralised computerised system for their easy documentation and typing into MAR. Hardware for the repacking of medications into MDS would be supplied by the service provider to allow the OAH staff to do that by themselves. The service provider also offers a mobile application for the documentation of electronic signatures during drug administration process. (Figure 4)

Part 3: Qualitative semi-structured interviews

Nine non-users were interviewed. The understanding of the services, services gaps perceived and the gap of understanding pharmacists' roles by non-users were identified. (Table 2) The interviews were carried out until data saturation is achieved.

From the results, it seems that most of the interviewees do not perceive the need to have pharmacists' input in their drug delivery model. Most of them only see the dispensing role of a pharmacist, and when pharmacist are not being an "extra pair of hand" or when the services require additional charges, they do not see the need for such "investment". It is therefore important to elaborate and promote the roles of pharmacists in primary care to the general public.

DISCUSSION

The Medicine Management Process

Figure 5 illustrate the usual medicine management process. The process begins from a physician prescribing onto a prescription/medication record, which would be dispensed in the pharmacy. The medications would be issued and the OAH nurses/health-care assistants would store the medication away, and administer to the patients according to the instructions written on the prescriptions/ medication records.

Errors could occur at any stage of the medication management process.

- 1) **Prescribing error** could arise during the prescribing process, which is subdivided into:
 - i) errors in prescribing decision, and

- ii) errors in prescription writing process;
- both could lead to the wrong prescribing instructions printed on the prescription/medical record.

- 2) When the prescription arrives at the pharmacy, **dispensing error** could occur, which could lead to the wrong medication being issued to the patient.
- 3) When the medications arrive at the

OAH, their efficacy could be affected severely due to **sub-optimal storage** conditions.

- 4) When the nurse/health-care assistant administer the drugs to the patient, **administration error** could occur, which might be caused by:

- i) the wrong documentation in the medical record (due to wrong prescription writing process as discussed) or

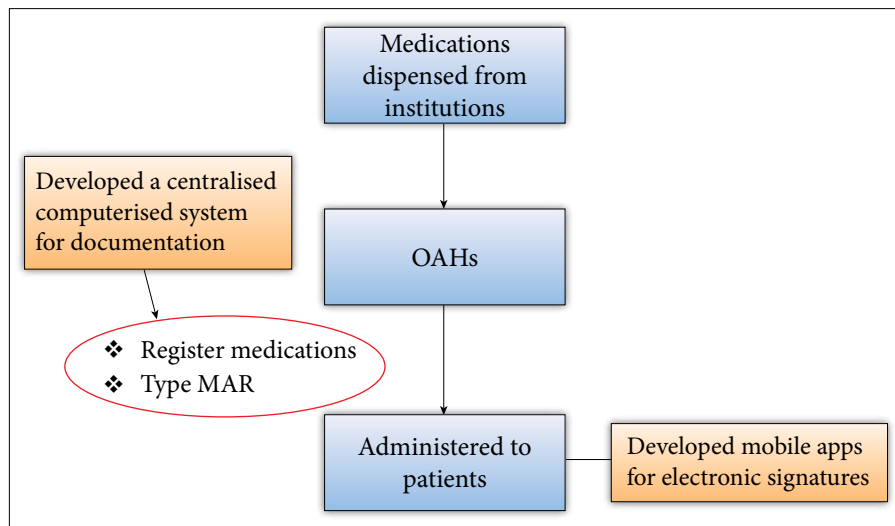


Figure 4. Drug delivery model for old aged homes subscribed to the MDS repacking by OAH staff.

Table 2. Reasons for non-pharmaceutical services users not subscribing to services	
Responses	Counts (N=9)
No perceived need	6
Financial concern	4
Doubted the usefulness of the services	3
Complicated communication cascade	3
Reluctant to change	2
Not heard of the services	1

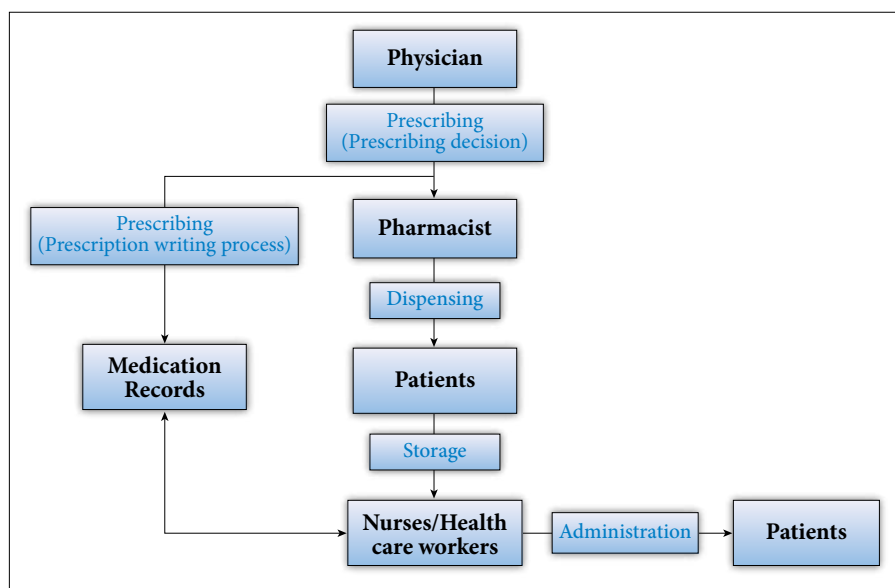


Figure 5. The medicine management process adopted to Hong Kong old aged home settings.

- ii) failure to identify the correct patient/drug, which leads to the patient being administered the wrong medication.

Ideally, the errors that occur at various stages of the medication management process could be prevented by the involvement of pharmacists, which is illustrated in Figure 6.

1. Pharmacist bed-side patient care

A pharmacist could provide clinical bed-side patient care on clinic days or clinical rounds together with the on-duty physician(s) and could prevent prescribing errors due to wrong prescribing decision and errors arise during the prescription writing procedures.

2. Pharmacist supervised MDS system

MDS system has been widely used both locally and globally. Prior to the start of the dispensing process, pharmacist could clinically check the prescriptions for legibility to prevent errors from the prescribing process and oversees the dispensing process to ensure the correctness of the dispensed medications. If the dispensing pharmacy locates on-site or has close collaboration with the OAH, all of the medications could also be stored at the pharmacy, where the storage conditions would be optimised and closely monitored.

3. Information technology monitored check in drug administration

The use of information technology is the global direction as that off-loads the checking procedures that could be tedious from the nurses/health-care assistants, which minimise the administration errors due to human factors.

Pharmaceutical Services

Various pharmaceutical services designed to reduce medication errors in Hong Kong were identified. In summary, all the services serving patients in OAHs could not uproot the problems of prescribing error since all the pharmaceutical service providers are not working closely enough with the doctors during the prescribing process. However, most of the services in OAHs could detect (but could not prevent) the discrepancies in the prescription writing process (which could lead to potential medication errors). Although drug administration is a high risk procedure in OAHs, only some of the services such as IT Supported MDS by Pharmacist, OAH in-house MDS, and IT supported MDS for OAH staff could potentially reduce it. In terms of storage and drug dispensing (i.e. re-dispensing) errors, services with dispensing component could reduce storage and administration errors by taking the responsibilities away from non-healthcare professionals.

In addition, services involving re-dispensing cannot address the problem of drug wastage due to duplication of prescription, which arise from the changes in medications between

clinic visits, transitions of care and unsynchronised prescribing. As a result of the current practice, drug labels cannot be changed when there is a change in the regimen. Hence, drugs cannot be reused or set aside for later use. This could potentially lead to a significant economic burden on the local healthcare system.

Generalisability and limitations

To our knowledge, this is the first study identifying the pharmaceutical services provided to the elderly in Hong Kong and examining the perceptions of service users and non-users towards those services.

The quality of this scoping exercise heavily relied on the information available from the literature and participating pharmaceutical service providers. In general, major limitations included scarce published literature and refusals of interview participation. However, triangulation was used to cross examine the data collected from multiple sources. There are also limited solid data available concerning the medication errors and effectiveness of the pharmaceutical services in Hong Kong.

The generalisability of study results is limited by the nature of qualitative study design. For the purpose of increasing generalisability, interviews were stopped when there was a saturation of themes. Interviewer bias and the 'Hawthorne effect' might also be induced during the interviews and observations. Efforts were made to ensure the objectivity of the interviewers and reduce the bias from the 'Hawthorne effect' by explaining that their identities would be kept confidential.

Implications for practice

Prescriptions could be sent directly to the local/delegated community pharmacies after the process of prescribing to avoid the duplicated procedures of dispensing process of the current MDS packing systems. The community pharmacies can become a point for medication reconciliation when the prescriptions are presented. Community pharmacies may be contracted to specific nursing homes so that there is ownership for the roles of medication reconciliation and medication review. However, a

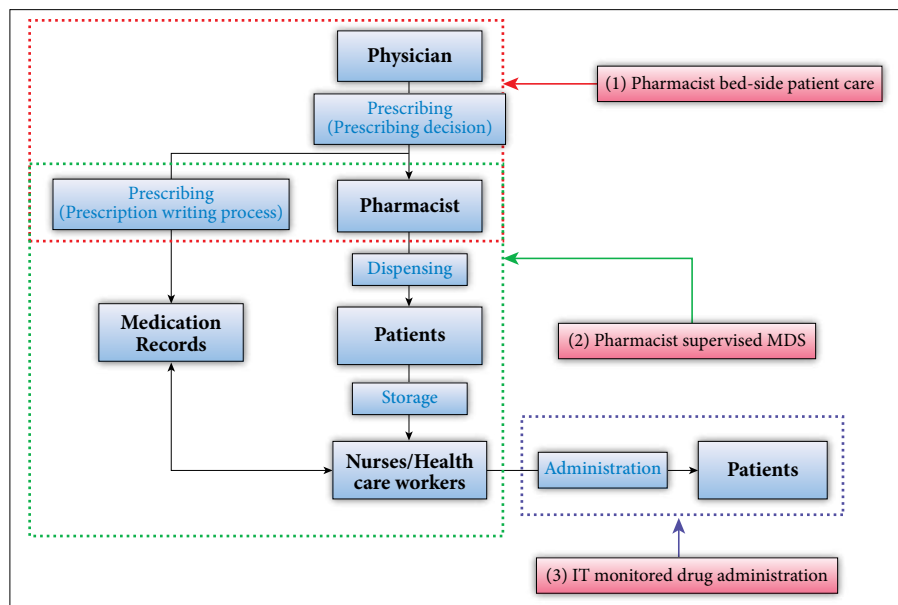


Figure 6. Medication errors could be prevented by pharmacists' involvements.

centralised remuneration mechanism for the community pharmacies is required to streamline reimbursement from the government healthcare body. Further, from a clinical perspective, there is a need for consistency with respect to the availability and access to patients' full medical history including the patient's medication records, diagnostic and laboratory reports which are pertinent for complete and thorough pharmaceutical care. This would require the granting of access to patient's information including the upcoming Electronic Health Record, to community pharmacies.

The mandatory printing of discharge and post-clinic summaries for every patient is recommended since it could facilitate the communications during the transition of care and allow the staff at each point of care to have a comprehensive profile of the care plan and medication record. Importantly, any change to the medication list needs to be adequately highlighted, documented and importantly communicated between health care providers. There is a need for more consistent procedures with the communication of any changes made to drug management at transitions of care.

Pre- and post-clinic patient and medication record screening can potentially prevent prescribing errors. It can possibly be achieved by several service models, e.g. VPS, outreach services and in-house pharmacist in OAH; however, modification of current service may be necessary. In an ideal situation, the physical presence of a pharmacist on clinic day can prevent prescribing error.

RECOMMENDATIONS FOR FUTURE RESEARCH

Firstly, a monitoring surveillance system with OAHs, doctors and nurses should be developed to systematically record and collect data. Currently, the prevalence of medication incidents in the OAHs of Hong Kong could not be measured systematically due to the sub-optimal record keeping practices among doctors and nurses. There is a need for a monitoring surveillance system for recording the data to measure the prevalence of medication incidents so as to offer an evidence-based view to reflect the condition of medication errors in Hong Kong.

Secondly, high quality studies such as randomised controlled trials are highly recommended to evaluate the effectiveness of the interventions. Collaboration between the OAHs, pharmaceutical service providers and academics, is of utmost importance for the success of future studies.

Thirdly, economic studies should be conducted to evaluate the feasibility of the implementation of the services on a large scale. In light of our study, it could be seen that most of the interventions were on a small scale. Therefore, future research should investigate the monetary benefits and costs by measuring the cost-effectiveness of the interventions so as to estimate the feasibility of implementation of larger scale interventions to achieve higher coverage in Hong Kong.

Fourthly, quantitative studies on the volume of drug wastage as a result of duplicate dispensing based on current service models are highly recommended. The financial implications can further be analysed.

CONCLUSION

Various pharmaceutical services were identified in this scoping study. The natures of these pharmaceutical services were different and help reduced different medication errors. However, none of the available services can uproot the causes of medication errors. Insufficient data were available for evaluate the effectiveness of the services in tackling medication errors. Moreover, problems of double dispensing, the lack of comprehensive discharge and post-clinic summaries, and drug wastage were noted in this study. Future studies are warrant to evaluate the cost-effectiveness of the services and quantify the volume of drug wastage. There is also a need to elaborate the roles of pharmacists in a primary care setting.

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Drug Wastage among the Elderly Living in Old Aged Homes in Hong Kong

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ABSTRACT

The extend of drug wastage among elderly living in old aged homes was never investigated. Upon the completion of the previous study on pharmaceutical services provided to elderly living in old aged homes, the amount of drugs wasted from 3,020 residents in one of the delegated pharmacies over a 4-month period were counted and their costs were calculated. The total cost of wasted drugs amounted to be HKD\$96,924, with drugs acting on the central nervous system contributed to the highest cost of HKD\$26,872 (27.7%), followed by respiratory drugs of HKD\$23,875 (24.6%) and alimentary tract & metabolism of HKD\$22,965 (23.7%). The results showed that for health institutes dispensing prescriptions of long duration to the elderly could lead to considerable amount of drug wastage and this issue should be addressed.

Keywords: Aged; Elderly; Nursing Homes; Homes for the Aged; Hong Kong

INTRODUCTION

The concept of medicines waste has not been comprehensively studied in Hong Kong. However, the overseas experiences suggest that it can place considerable burden on the health care system through a waste of resources and lead to economic and environmental concerns.^[1-5] The aim of this descriptive study was to quantify the volume and corresponding costs of

wasted drugs in old age homes (OAHs) in Hong Kong.

METHODS

The audit was performed using the data collected in a delegated community pharmacy. According to Social Welfare Department, the population of elderly aged 60 or above was 2,292,190 at 2011. Among which, there were 60,406 living in old aged homes as of March 2012. (Social Welfare Department, personal communication, December 13, 2012) Data in 3,020 elderly patients such as unique patient identification number designated for each patient by the community pharmacy, trade names, generic names, strengths, and dosage forms of the drugs were collected from September 2012 to January 2013. Unit prices of the drugs were derived from Hospital Authority (HA) drug formulary in Hong Kong. Prices without listing from the HA drug formulary were derived from MIMS Hong Kong.^[6]

RESULTS

A total value of HK\$96,924 consisting of

173,790 units of oral solid preparations, 80.86 litres of oral liquid preparations, 500 inhaler preparations, 5.384 kilograms of external preparations (including cream, gel and ointment), 427 parenteral preparations and 2,979 other preparations (including patch, sachet, drops, enema, spray and rectal suppository) in 3,020 residents. (Table 1) It is estimated that 10,428,435 units of oral solid preparations, 4,852 litres of oral liquid preparations, 30,002 inhaler preparations, 323 kilograms of external preparations, 25,622 parenteral preparations and 178,757 other preparations will require disposal annually for all elderly living at OAHs in Hong Kong. The total extrapolated cost was HK\$5,816,017. Of the total discarded drugs, the prices of 258.5 drug items could not be found in HA drug formulary nor MIMS Hong Kong. There was also approximately 1-2% of drugs that could not be identified so they were not included in the calculation.

The drug wastes were sorted in accordance with the Anatomical Therapeutic Chemical (ATC) classification system. The predominant groups of the cost were group N (Nervous system) with

Table 1. The number of discarded drugs and the corresponding costs

	No. of discarded drugs	Cost (HKD)
Oral solid preparations	173,790 units	\$50,769
Oral liquid preparations	80,860 millilitres	\$7,066
Inhaler preparations	500 units	\$20,429
External preparations	5,384 grams	\$1,379
Parenteral preparations	427 units	\$7,718
Others (including patch, sachet, drops, enema, spray, suppository)	2,979 units	\$9,562
Grand Total	---	\$96,924

Table 2. The cost of drug wastes sorted by Anatomical Therapeutic Chemical classification system (ATC)

Anatomical Therapeutic Chemical classification system	Cost (HKD) (%)
(A) Alimentary tract and metabolism	\$22,965 (23.7%)
(B) Blood and blood forming organs	\$5,496 (5.7%)
(C) Cardiovascular system	\$9,944 (10.3%)
(D) Dermatologicals	\$1,149 (1.2%)
(G) Genito-urinary system and sex hormones	\$1,328 (1.4%)
(H) Systemic hormonal preparations	\$1,579 (1.6%)
(J) Antiinfectives for systemic use	\$794 (0.8%)
(L) Antineoplastic and immunomodulating agents	\$496 (0.5%)
(M) Musculo-skeletal system	\$1,062 (1.1%)
(N) Nervous system	\$26,872 (27.7%)
(P) Antiparasitic products, insecticides and repellents	\$36 (0.04%)
(R) Respiratory system	\$23,875 (24.6%)
(S) Sensory organs	\$1,320 (1.4%)
(V) Various	\$0.3 (0.0003%)
Grand Total	\$96,924 (100%)

27.7%, group R (Respiratory system) with 24.6% and group A (Alimentary tract and metabolism) with 23.7%. (Table 2)

Of the disposed drugs in group N, anticonvulsants and antipsychotic drugs were expensive and in high volumes which constituted 30.4% (HKD\$8,167) and 20.5% (HKD\$5,511) of the total cost in group N respectively. In group R, inhalers had high value per drug item which ranged from HKD\$30 to HKD\$300 and accounted for 85.6% (HKD\$20,429) of cost in group R. In group A, laxatives had high volumes which accounted for 36.9% (HKD\$8,467) of the cost in group A. Moreover, proton pump inhibitors (PPIs) were some of the most expensive drugs, constituted 26.9% (HKD\$6,184) of the cost in group A. Insulin preparations were found to contain 11.6% (HKD\$2,653) of the cost in group A due to their high cost per item. (Table 3)

In terms of great volumes of oral solid preparations, there were paracetamol (31,519 units), tramadol hydrochloride

(5,760 units), and betahistine mesylate (2,616 units) in group N. Bromhexine hydrochloride (2,744 units) and chlorpheniramine maleate (2,580 units) were found to have great frequency for disposal in group R. Senna (11,335 units), famotidine (6,594 units) were found to have great frequency in group A. (Table 4)

DISCUSSION

The total amount of disposed drugs, especially the number of oral solid preparations was high which create burden to the environment. The estimated cost of the drug wastes was also high without taking the salaries of dispensers and pharmacists for dispensing the medicines which was wasted eventually and the disposal cost of the waste into account in this study.

The medication wastes due to intentional and unintentional non-adherence of medications were not the primary causes of drug wastes in

this study as health care workers in OAHs are responsible for ensuring high adherence to drugs among study subjects. Changes in medications between clinic visits, transitions of care and unsynchronised prescribing during long prescription period might account for the significant proportion of drug wastes.

Generalisability and limitations

To our knowledge, this is the first study quantifying the volumes of drug wastes and measuring the total cost of the wastes.

There were three major limitations in our study. Firstly, drug wastes due to death are largely inevitable. However, the drug wastes of dead patients were included in the analysis. It was due to the limited and incomplete records to identify the dead patients. Secondly, prices of some drugs could not be found in HA nor MIMS so their costs were not included in the result. There were also small quantities of drugs which could not be identified and were not included in the calculation. It could lead to underestimation of the total cost of discarded drugs. However, the quantities of these drugs were insignificant and would not greatly alter the result. In addition, the findings in this study were only extrapolated for the elderly living in OAHs, the amount of drug wastage for those living at home remains unknown.

Implications for practice

The mean prescription duration for public health providers is about six months and sometimes even up to a year per visit to ease the pressure resulting from long queues. Long prescription duration could lead to medicines waste

Table 3. The top cost of drugs according to therapeutic classes for disposal

Drugs (Nervous system)	Cost (HKD)
Anticonvulsants	\$8,167
Antipsychotics	\$5,511
Narcotic drugs	\$2,201
Benzodiazepines	\$1,505
Drugs (Alimentary tract and metabolism)	Cost (HKD)
Laxatives	\$8,467
PPIs	\$6,184
Insulin	\$2,653
Drugs (Respiratory system)	Cost (HKD)
Inhalers	\$20,429

Table 4. The number of discarded drugs with great frequency for disposal and the corresponding costs

Drugs (Nervous system)	No. of discarded drugs	Cost (HKD)
Paracetamol	31,519	\$1,261
Tramadol HCl	5,760	\$1,464
Betahistine mesylate	2,616	\$387
Drugs (Alimentary tract and metabolism)	No. of discarded drugs	Cost (HKD)
Senna	11,335	\$1,471
Famotidine	6,594	\$361
Aluminium hydroxide, magnesium hydroxide, simethicon	3,958	\$394
Drugs (Respiratory system)	No. of discarded drugs	Cost (HKD)
Bromhexine HCl	2,744	\$247
Chlorpheniramine maleate	2,580	\$111

whenever there are any changes to treatments. The deployment of repeat prescriptions scheme, allowing patients with stable clinical conditions to obtain drugs on monthly basis from community pharmacies after the first attendance at health institution(s), such as hospital and out-patient clinics is recommended. It could be a much improved way in reducing wastes and meeting the on-going needs of the patients. By outsourcing the dispensing and supply of repeat prescriptions to community pharmacies, it could also relieve the heavy burden of public health care sector. Moreover, the community pharmacists can also monitor the conditions of the patients more frequently and provide them with appropriate drug advice and better monitoring of drug compliance.

There is a lack of awareness among elderly patients to discard the obsolete drugs. It is recommended that the unused and expired drugs should be returned to health care institutes for proper disposal in Hong Kong. It can be achieved by the collaboration between government and health care institutions to establish an integrated mechanism for the collection and disposal of drug wastes. Moreover, public education campaign should also be launched to raise the awareness on proper disposal of medicines waste.

Since there is no mechanism for the collection and disposal of drug wastes in the community, there may potentially be inappropriate disposal methods among the elderly living at their homes.

On the other hand, elderly are also very likely to store large stocks of obsolete drugs at their homes for later use due to inadequate knowledge. Patient safety concerns may also arise from taking expiry drugs among them. Further research on exploring the problem of medicines waste among the elderly living at homes is needed.

CONCLUSION

The scale of economic and environmental problems of medicines waste was found to be substantial. Wastes could be reduced if the long prescription duration is cut short simply by issuing repeated prescriptions instead and the supply logistics could be effectively managed if dispensing service is provided by community pharmacies. The establishment of an integrated mechanism for collection of drug wastes in the community should be encouraged. Public education campaign should also be launched to raise the awareness of proper disposal of medicines waste. Further research on exploring the problem of medicines waste among the elderly living at homes is needed.

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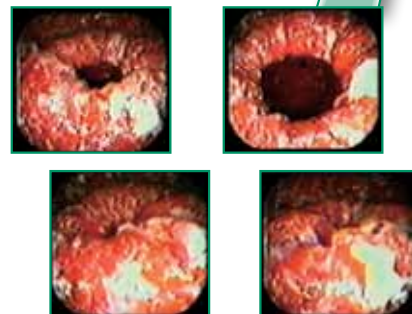
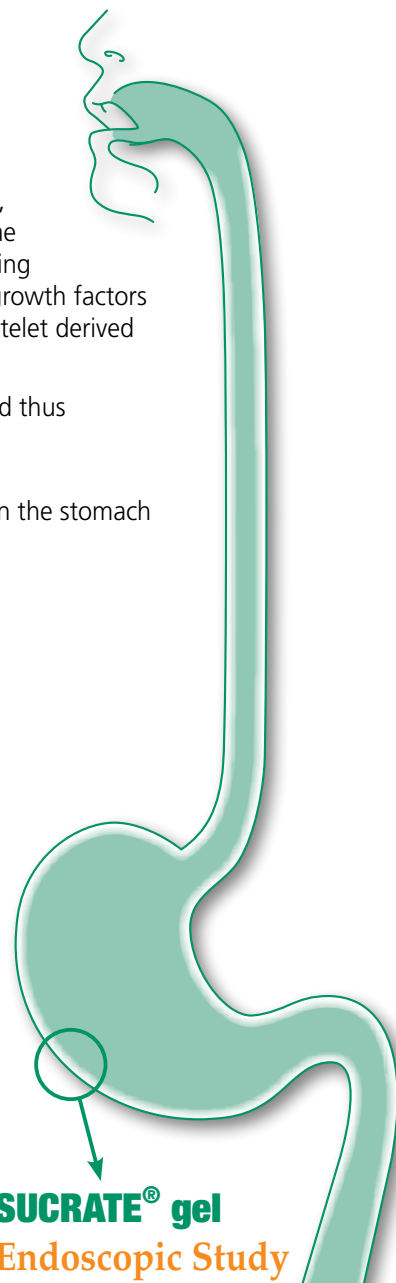
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Overview of Targeted Therapies for Renal Cell Carcinoma

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ABSTRACT

Before 2005, systemic treatment options for metastatic renal cell carcinoma (RCC) were limited to cytokine therapy. Recently, development of novel treatment selections have been possible due to an improved understanding of disease biological pathways including vascular endothelial growth factor (VEGF) and mammalian target of rapamycin (mTOR). Uncovering these novel targeted biomarkers enables the establishment of several targeted therapies available for metastatic RCC with an improved efficacy and safety profile. These drugs include sorafenib, sunitinib, pazopanib, bevacizumab (plus Interferon- α), temsirolimus and everolimus. The different adverse events caused by targeted therapies and their management strategies are discussed. Further research studies on a head-to-head comparison, combination therapy and therapy in adjuvant setting as well as novel agents are currently in progress and as a result are initiating a new era of RCC treatment.

Keywords: Renal cell carcinoma, targeted therapy, VEGF inhibitor, mTOR inhibitor

INTRODUCTION

Renal cell carcinoma (RCC) is relatively rare and among the most drug-resistant malignancies,⁽¹⁾ only recently has impressive progress in surgical and systemic treatment strategies revolutionized the disease management profile. Surgical innovation such as laparoscopic and robotic nephrectomy has minimized invasiveness so that maximum renal function may be preserved.⁽²⁾ Until 2005, only a single treatment, high-dose interleukin-2, has been approved by the FDA for the treatment of this disease despite its high toxicity and low response rate.⁽³⁾

Recently, specific biological targets essential to the pathophysiology of RCC such as vascular endothelial growth factor (VEGF) and mammalian target of rapamycin (mTOR) have been discovered. New drugs acting on those specific biological pathways have been emerging in the market and offer new therapeutic options for patients with metastatic RCC. RCC sets a good example for developing targeted therapy based on the discovery of biological tumor targets for other treatment resistant malignancies. Thus, biological targeted therapies have initiated a new era of oncology drug research and development.

Epidemiology

There were 505 newly diagnosed cases (314 in men and 191 in women) of kidney and other related urinary organ carcinomas in Hong Kong in 2009,⁽⁴⁾ contributing to 1.94% of all malignant diseases. The age standardized incidence rate between 2000 and 2009 was 4.38 per 100,000 person years. (Fig. 1) illustrates that an increasing trend in incidence of kidney carcinoma has been observed over the past two decades.⁽⁴⁾ Improved imaging techniques and widespread use of abdominal imaging scans may explain the increasing trend in renal cell carcinomas, however, an increase in the number of people with risk factors (Table 1) must also be considered. Kidney cancer is most commonly detected after 45 years of age, comprising nearly 90% of

patients with RCC.⁽⁴⁾ The male to female ratio is about 2:1 and thus males have a higher risk of developing RCC. The 5-year overall survival rate is about 70% in the last decade⁽⁵⁾ however is expected to improve with recent development of targeted therapies.

Etiology

There are several established risk factors for RCC including smoking, obesity, analgesic use and hypertension (Table 1).^(6,12)

Hereditary cases of RCC account for 2-3 % among all RCC cases.⁽⁶⁾ Approximately 35% of patients with Von Hippel-Lindau (VHL) disease,⁽¹³⁾ which is characterized by a defect on both allele of the tumor suppressor VHL gene on chromosome 3p25-26,⁽¹⁴⁾ may develop clear cell RCC which tend to be early onset and multifocal. For sporadic

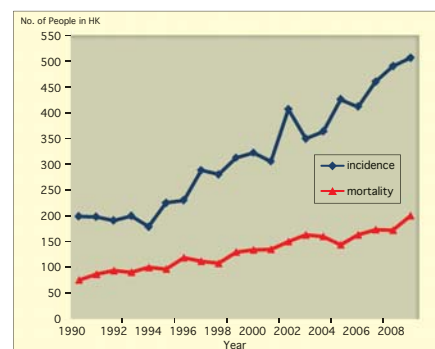


Figure 1. Incidence and mortality of renal cell carcinoma cases in Hong Kong from 1990-2009.⁽⁴⁾

Active and passive smoking	Relative risk of about 2-3 comparing with non-smokers. ^(7, 8) Smoking cessation could reduce the risk of RCC with 20%-30% after cessation for 10-15 years and 50% if quit for more than 30 years. ⁽⁹⁾
Obesity	Body Mass Index >25 kg/m ² : Relative risk of 1.5-2.5 comparing with normal weight ⁽¹⁰⁾
Prolonged poorly controlled hypertension ⁽¹¹⁾	Diastolic Blood Pressure (>90 mmHg): Relative risk of 2 comparing with normal diastolic Blood Pressure (<70 mmHg) Systolic Blood Pressure (>150 mmHg): Relative risk of 1.6 comparing with normal systolic Blood Pressure (<120 mmHg)
Long term analgesic use ⁽¹²⁾	Acetaminophen: 33% increase in risk Non-Steroidal Anti-Inflammatory Drug: 26% increase in risk

RCC cases, clear cell RCC patients would acquire inactivation in both VHL alleles, leading to destruction of tumor suppressing VHL protein. Thus sporadic clear cell RCC tends to be late in onset and unifocal.

Classification

Despite its predominance, clear cell RCC is not the only kidney carcinoma subtype present. It accounts for 75% among all RCC cases. Other named subtypes⁽¹⁵⁾ include papillary type I (5%), papillary type II (10%), chromophobe (5%), oncocytoma (5%), and also rare but aggressive subtype collecting duct carcinoma (<1%). Those subtypes differ in histopathologic and cytogenetic features eg. clear cell RCC subtype is characterized with cystic architecture, clear cytoplasm as well as chromosome 3p loss.⁽¹⁵⁾ Also they may vary in prognosis and aggressiveness. For example, renal oncocytoma subtype has excellent prognosis and is relatively benign and rarely metastatic,⁽¹⁶⁾ but collecting duct carcinoma is very aggressive.

Pathology

Von Hippel-Lindau (VHL) tumor-suppressor gene undergoes inherited or sporadic inactivation in at least 60% of these tumors.⁽¹⁷⁾ The defective gene fails to produce VHL protein, which is an important regulator of hypoxia inducible factor (HIF). HIF is degraded upon VHL protein binding through polyubiquitination and hence proteasome degradation in condition of abundant oxygen supplies.⁽¹⁸⁾ HIF is a heterodimeric protein transcription factor of over 100 genes that promotes adaptation and survival under hypoxic conditions.⁽¹⁹⁾ However, HIF upregulates with normal oxygen supply since failure in degradation by proteasome through binding with VHL protein. Thus hypoxia inducible proteins, including vascular endothelial growth factor (VEGF), platelet derived growth factor (PDGF), transforming growth factor α (TGF- α) etc, that promote angiogenesis and tumor development are overexpressed and hence renal cell carcinoma may develop (Fig. 2).^(17,19) Also, mammalian target of rapamycin (mTOR) is another key inducing factor in development of RCC. Since activation of mTOR is associated with upregulation of HIF and mTOR regulates protein translation, mTOR may also predispose RCC.⁽¹⁷⁾ Improved knowledge in molecular biology and pathway of RCC enables development of novel therapeutic targeted therapies.

Recent research⁽²⁰⁾ in TNF receptor-associated factors shows that it may have a role in apoptosis of RCC and is currently under study.

Clinical presentations and diagnosis

Widespread use of imaging modalities such as computed tomography (CT) scans contributes to early incidental detection of renal masses during radiographic imaging of neighbouring organs. Those incidentally diagnosed renal masses are usually smaller in size and more localized as compared with those patients with symptoms such as the classic triads of flank pain, hematuria, and palpable abdominal mass present in less than 10% of RCC patients.⁽²¹⁾ Other systemic symptoms^(6, 21) include bone pain, fatigue, weight loss, anemia, hypertension, fever, hypercalcaemia and lower extremity edema which may

be due to metastatic growth in other organs. Complete Blood Count (CBC), comprehensive metabolic panel, including LDH, urinalysis and also CT or MRI imaging of chest, abdomen and pelvis is required as initial workup to characterize the renal tumor and determine staging and prognosis factors when suspicious masses are discovered.⁽²²⁾

Staging and Prognosis

Staging of RCC was introduced by the American Joint Committee on Cancer (AJCC) and was recently updated in 2010.⁽²³⁾ The staging classification mainly encompasses the extent of tumor (T), involvement of lymph node (N) and presence of metastases (M). For AJCC staging (Table 2), estimated average 5 year survival rates in RCC⁽²⁴⁾ is 96% for stage I, 82% for stage II, 64% for stage III and 23% for stage IV.

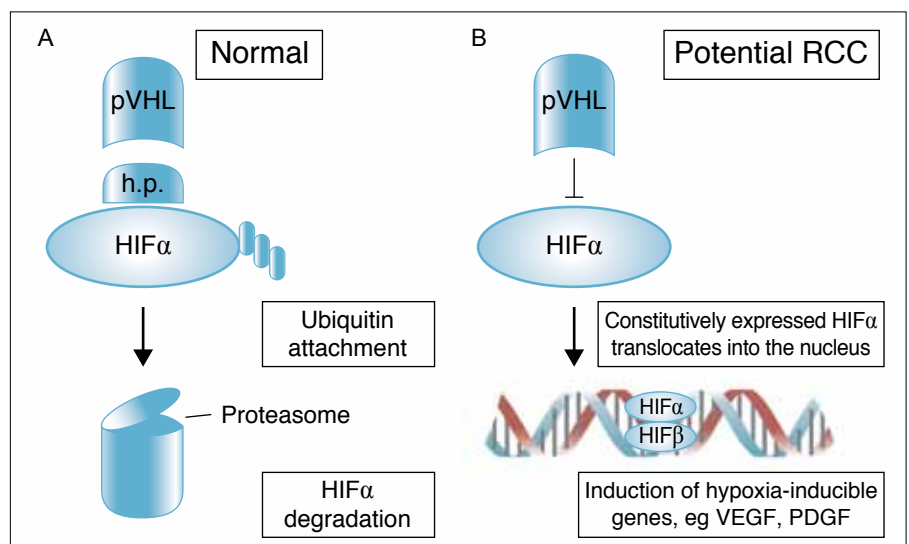


Figure 2. (A) Under normal pVHL, HIF α degrades with pVHL binding through ubiquitin attachment in proteasome. (B) Under impaired pVHL condition, accumulation of HIF α leads to overexpression of hypoxia inducible genes. [Modified from Rini & Small]⁽¹⁹⁾

Primary Tumor (T)		Regional Lymph Nodes (N)			
Involvement	Extent of disease	NX	Regional lymph nodes cannot be assessed		
TX	Primary tumor cannot be assessed	N0	No regional lymph node metastasis		
T0	No evidence of primary tumor lymph node(s)	N1	Metastasis in a single regional		
T1a	Tumor \leq 4 cm	Distant Metastasis (M)	M0		
T1b	Tumor \geq 4 cm to \leq 7 cm		No Distant Metastasis		
T2a	Tumor $>$ 7cm to \leq 10cm		M1		
T2b	Tumor $>$ 10 cm		Distant Metastasis		
		Staging			
T3a	Into renal vein or its segmental branches	Stage I	T1	N0	M0
T3b	into vena cava	Stage II	T2	N0	M0
T3c	Into vena cava or invades wall of vena cava	Stage III	T1 or T2	N1	M0
T4	invades beyond Gerota's fascia	Stage IV	T3	N0 or N1	M0
	Including contiguous extension into the ipsilateral adrenal gland		T4	Any N	M0
			Any T	Any N	M1

Table 3. MSKCC prognostic factors⁽²⁷⁾

MSKCC Prognostic Factors
Karnofsky Performance Score (KPS) ≤ 70
≥2 sites of organ metastasis
Interval of less than a year from original diagnosis to the start of systemic therapy
Corrected serum calcium level > 10 mg/dl (2.5 mmol/L)
Hemoglobin level < lower normal limit (<13 g/dL for men and <11.5g/dL for women)
Lactate dehydrogenase level > 1.5 times upper normal limit (300U/L)

For metastatic RCC patients, the Memorial Sloan-Kettering Cancer Center (MSKCC) model (Table 3)⁽²⁵⁾ is commonly used to determine prognosis of patients. Low risk was defined as presence of none or one risk factor, intermediate risk as two risk factors, and high risk or poor prognosis as three or more risk factors. Corresponding two year overall survival rate for low, intermediate and high risk groups were 75%, 53%, and 7% respectively.⁽²⁶⁾

Treatment

For local RCC (stage I to III), open, laparoscopic, or robotic surgical excision is the primary method of disease control.⁽²²⁾ In patients with advanced or metastatic disease (stage IV), systemic treatment options following cytoreductive nephrectomy are immunotherapies including high dose interleukin-2 or Interferon-alpha and more recently targeted therapies (Table 4).⁽²²⁾ Six new drugs for metastatic RCC have been approved in Hong Kong either as first or second line therapy: sunitinib, sorafenib, pazopanib, bevacizumab (with Interferon-α), temsirolimus and everolimus. Axitinib,⁽²⁸⁾ a novel drug approved recently by FDA in US in 2012, is also indicated for metastatic RCC after failure of one prior systemic therapy. Enrolling in clinical trial is also another treatment option for RCC patients.

Immunotherapy

Prior to emergence of targeted therapies the only systemic therapies available against metastatic RCC were high dose bolus IL-2 or IFN-α. With both IFN-α and

IL-2, objective response rate (ORR) was reported to be between 9.9%-23.2%.⁽²⁹⁻³¹⁾ No direct comparison of high dose bolus IL-2 or IFN-α has been performed. National Comprehensive Cancer Network (NCCN) guidelines include high dose IL-2 as a category 2A recommendation for selected patients with excellent organ function and no comorbidities.⁽²²⁾ Also, clear cell histology, carbonic anhydrase-9, and favorable score on MSKCC and University of California Los Angeles (UCLA) Survival After Nephrectomy and Immunotherapy (SANI) scale may be predicted as benefiting from cytokine therapy.⁽³²⁾ However, interleukin-2 use has markedly declined⁽³³⁾ since currently available targeted therapies show an improved benefit in both efficacy and safety. IFN-α is rarely used as a single agent in metastatic RCC, but it is usually used in combination with bevacizumab in a regimen that has shown better progression-free survival (PFS) than IFN-α alone.⁽³⁴⁾ One study⁽³⁵⁾ suggested that patients receiving high dose IL-2 after VEGF therapy experienced lack of antitumor activity as well as high rate of severe cardiac toxicities (40%).

Targeted therapies

The six biological targeted therapies available in Hong Kong are all for palliative treatment of either treatment-naïve or previously-treated RCC. Table 5 summarizes the recommendation by guidelines of different authorities and key efficacy data from pivot clinical trials of the targeted therapies.^(22, 36-49) Table 6 summarizes the dose, route, dose adjustment, drug interaction and adverse event (AE) profiles of different targeted

therapies. Moreover, Fig. 3 shows the specific therapeutic targets for different targeted therapies of metastatic RCC.

Tyrosine Kinase Inhibitors (TKI)

Sorafenib, sunitinib and pazopanib are multikinase inhibitors indicated for metastatic renal cell carcinoma. They have similar mechanism of actions, blocking tumor angiogenesis by inhibiting multiple receptor tyrosine kinases such as vascular endothelial growth factor receptor (VEGFR), platelet derived growth factor receptor (PDGFR), cytokine receptor (c-KIT), fms-like tyrosine-kinase 3 (FIT3).

All of these drugs are available in oral form and whilst Sorafenib and sunitinib can be taken with or without food. Pazopanib should be taken one hour before or two hours after meals since absorption and therefore systemic exposure of pazopanib increases with food.⁽⁵³⁾ Moreover, TKIs are all CYP3A4 substrates and therefore pharmacists should be aware of those drug interactions between TKIs and both CYP3A4 inducers and inhibitors. Pharmacists should advise on dose adjustments in the event of any potential drug interaction. In addition, both the herbal preparation St. John's Wort and grapefruit juice are common CYP3A4 inducers and inhibitors respectively and RCC patients taking TKI medications should be counselled appropriately.

Hypertension is a frequent adverse event associated with TKIs and must be carefully monitored and managed.⁽⁵⁶⁾ Cardiac toxicity such as heart failure, QT wave prolongation and an increased risk of bleeding due to inhibition of VEGF which has a role in maintaining vascular structure of endothelial cell has also been associated with TKIs. Hepatotoxicity is another serious adverse event associated with the administration of sunitinib and pazopanib and the FDA has added a black box warning to their labels.

Other common adverse events include dermatological AEs (hand foot skin reaction), gastrointestinal AEs (diarrhoea, vomiting), fatigue and headache (Table 5).

Sorafenib

Sorafenib was the first oral multi-kinase inhibitor to be approved by US FDA in 2005 for the treatment of patients with metastatic RCC and it is recommended as second-line therapy after cytokine therapy failure.⁽⁵⁰⁾ As described in Table

Table 4. Treatment options of clear cell Renal Cell Carcinoma⁽²²⁾

Stage	Treatment Options
Ia	Partial Nephrectomy(Preferred) Radical nephrectomy(If partial not feasible or tumor in centralized location) Active surveillance Thermal ablation therapy for non-surgical candidates
Ib	Partial Nephrectomy Radical Nephrectomy
II, III	Radical Nephrectomy
IV	(Cytoreductive) nephrectomy + Possible surgical metastasectomy Systemic therapy (Immunotherapy or targeted therapy) Clinical Trial

5, its approval was based on a pivotal phase III randomized, double blinded and placebo-controlled TARGET trial in which 903 cytokine-refractory patients were studied.⁽³⁷⁾ The result of this study showed a significant superiority in Progress-Free Survival (PFS) and Objective Response Rate (ORR) but no benefit for Overall Survival (OS).^(37,38) It has been suggested that if patients in the placebo arm of this study were switched to the sorafenib arm, then there would be an improvement in overall survival (17.8 months vs 14.3 months, p=0.03).⁽³⁸⁾ The safety profile of sorafenib was generally good and the drug was well tolerated. Sorafenib was moved towards second-line therapy after market launch of sunitinib, another multikinase inhibitor with superiority efficacy.⁽²²⁾

Sunitinib

Sunitinib is another oral multi-kinase

inhibitor that was approved by the FDA in 2007. It was administered⁽⁵⁰⁾ in a 6-week cycle and the clinical trial that encouraged this registration was a phase III study that compared sunitinib with IFN- α in 750 treatment-naïve patients.⁽³⁹⁾ Sunitinib demonstrated a significant improvement in PFS, ORR and OS rate and an overall benefit over IFN- α alone with a comparatively increase in adverse events. The adverse events such as hand-foot skin reaction, hypertension and gastrointestinal toxicity caused by sunitinib were similar to sorafenib but appeared more frequently.⁽³⁹⁾ Additional severe adverse events other than those experienced with sorafenib namely, hepatotoxicity (<1%), cardiac toxicity (<1%) and hypothyroidism (9.7%)⁽⁵⁰⁾ have been observed with the use of sunitinib and therefore related routine laboratory biochemical testing and monitoring the signs of congestive heart failure should be implemented as

standard practice. Due to its acceptable toxicity as well as its promising result in first-line RCC treatment study, it has been recommended by NCCN and EAU^(22, 36) as first-line therapy in treatment-naïve patients.

Pazopanib

Pazopanib is the latest multi-kinase inhibitor approved by FDA in 2009. The clinical trial⁽⁴⁵⁾ pivotal in the acceptance of this drug into RCC treatment was a randomized, double-blinded, placebo-controlled phase III study of 435 either treatment-naïve or cytokine-pretreated patients with metastatic RCC. Pazopanib showed a significant difference in PFS and ORR compared to placebo regardless of MSKCC risk score, age, sex or Eastern Cooperative Oncology Group (ECOG) performance status.⁽⁴⁵⁾ However, pazopanib does not show an overall survival (OS) advantage.⁽⁴⁶⁾ It appears

Table 5. Summaries of National Cancer Comprehensive Network® (NCCN) and European Association of Urology (EAU) guideline recommendation and pivotal clinical trials of the six approved targeted therapies plus axitinib^(22, 36-49)

Drug Name	Class	NCCN Guidelines ⁽²⁰⁾	EAU Guidelines ⁽³⁵⁾	Patient Population	Compare against	Median PFS vs compar-ator (months)	ORR vs compa-rator	OS vs comparator (months)
Sorafenib ^(36, 37)		First-line for selected patients (Cat 2A) and Second-line following cytokine therapy (Cat 1) and following other TKIs (Cat 2A)	Second line following cytokines	Progressed Disease after 1 systemic therapy	Placebo	5.5 vs 2.8 p<0.001 HR= 0.44	10% vs 2% p<0.001	17.8 vs 15.2 p=.146 HR=0.88
Sunitinib ^(38, 39)	VEGFR and PDGFR tyrosine kinase inhibitor	First-line (Cat 1) and Second-line following cytokine therapy (Cat 1) and following other TKIs (Cat 2A)	First-line for low or immediate risk	No prior systemic therapy	IFN- α	11 vs 5 p<0.001 HR=0.42	47% vs 12% p<0.001	26.4 vs 21.8 p=.051 HR=0.821
Bevacizumab+ IFN- α ⁽⁴⁰⁻⁴³⁾		First-line (Cat 1) and Second-line following cytokine therapy (Cat 2A) and following other TKIs (Cat 2B)	First-line for low or immediate risk	No prior systemic therapy	A IFN- α + Placebo	10.2 vs 5.4 p=0.001 HR=0.63	31% vs 13% p=0.001	23.3 vs 21.3 p=.1291 HR=0.86
					B IFN- α	8.5 vs 5.2 p<0.001 HR=0.71	25.5% vs 13.1% p<0.001	18.3 vs 17.4 p=.069 HR=0.86
Pazopanib ^(44, 45)		First-line (Cat 1) and Second-line following cytokine therapy (Cat 1) and following other TKIs (Cat 3)	First-line for low or immediate risk Second line following cytokines	With or without prior cytokine therapy	Placebo	9.2 vs 4.2 p<0.001 HR=0.46	30% vs 3% p<0.001	22.9 vs 20.5 p=.224 HR=0.91
Temsirolimus ⁽⁴⁶⁾	mTOR inhibitor	First-line for poor prognosis patients (Cat 1) and Second-line following cytokine therapy (Cat 2A) and following other TKIs (Cat 2B)	First-line for high risk	No prior systemic therapy Poor-prognosis	IFN- α	3.8 vs 1.9	8.6% vs 4.8% p<0.01	10.9 vs 7.3 p=.008 HR=0.73
Everolimus ⁽⁴⁷⁾		Second-line following TKI (Cat 1)	Second line following VEGFR TKI	Prior VEGFR TKI therapy	Placebo	4.9 vs 1.9 p<0.001 HR=0.33	1.8% vs 0%	14.8 vs 14.4 p=.162 HR=0.87
Axitinib (yet approved in HK) ⁽⁴⁸⁾	VEGFR inhibitor	N/A	N/A	Prior systemic therapy	Sorafenib	6.7 vs 4.7 p<0.0001 HR=0.665	19% vs 9%	Not yet released

Note: ORR= Objective Response Rate, PFS= Progression Free Survival, OS=Overall Survival, HR=Hazard Ratio, VEGFR= Vascular Endothelial Growth Factor Receptor, PDGFR= Platelet-Derived Growth Factor Receptor, mTOR= Mammalian Target of Rapamycin, TKI= Tyrosine Kinase Inhibitor NCCN categories.⁽²⁰⁾

Cat 1=Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate
 Cat 2A=Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate
 Cat 2B=Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate
 Cat 3=Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate

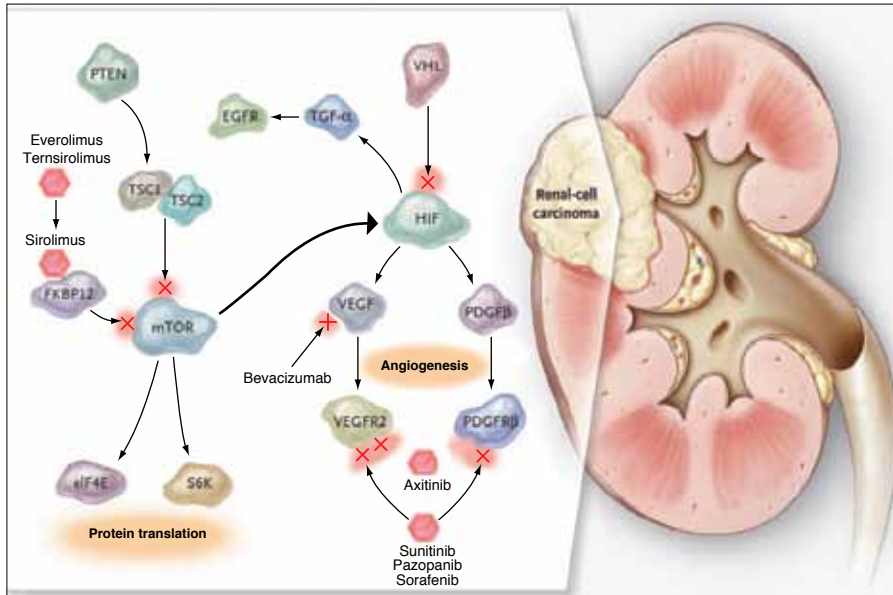


Figure 3. Therapeutic targets in renal cell carcinoma. Abbreviations: VHL, von Hippel-Lindau protein; HIF, hypoxia-induced factor; TGF- α , transforming growth factor α ; mTOR, mammalian target of rapamycin; VEGF, vascular endothelial growth factor; PDGF β , platelet-derived growth factor β ; EGFR epidermal growth factor receptor; PTEN, phosphatase and tensin homologue; TSC1 and TSC2 tuberous sclerosis complex 1 and 2, FKBP12 FK506-binding protein 12 kD; eIF4E eukaryotic translation initiation factor 4E; S6K, S6 kinase. [Modified from Brugarolas]⁽¹⁷⁾

Pazopanib is also recommended by the NCCN and EAU^(22,36) as first-line therapy in treatment-naïve patients due to its promising efficacy in PFS and ORR with a well-tolerated safety profile.

Anti-VEGF Monoclonal Antibody - Bevacizumab + IFN- α

Bevacizumab is an I.V. administered humanized monoclonal antibody and is given in combination with subcutaneous injected IFN- α . This combination was approved by the FDA in 2009 for first-line treatment of patients with metastatic RCC. Bevacizumab⁽⁵⁰⁾ binds to circulating VEGF and inhibits its action upon VEGF receptors, thus blocking the process of angiogenesis. Two clinical trials helped establish bevacizumab as a useful agent in RCC, these comprised of a randomized, double blinded phase III AVOREN study of bevacizumab plus IFN- α versus placebo plus IFN- α and a randomized, open-labelled phase III CALGB study of bevacizumab plus IFN- α versus IFN- α . In both trials, bevacizumab plus IFN- α showed superiority in PFS and ORR versus comparator and had a trend of longer OS but no significant difference was shown. The combination is also recommended by NCCN and EAU^(22, 36) as first-line therapy of metastatic RCC.

to have similar but lower frequency of AEs compared with sorafenib and sunitinib from clinical trial result.⁽⁴⁵⁾ More comprehensive and extensive safety profile study on pazopanib is required to establish its safety profile since different

AEs or increased frequency of AEs may possibly appear with prolonged drug experience. Also, a lower frequency of common AEs does not necessarily mean a lower risk of serious AEs requiring intervention or discontinuation.

Table 6. Summary of route, dose, dosage adjustment, drug interaction and adverse event profiles of different targeted therapy for metastatic renal cell carcinoma.⁽⁵⁰⁻⁵⁵⁾

Name	Route	Dose	Dose adjustment		Drug Interaction	Common Adverse Event	Serious Adverse Event that may need intervention or discontinuation
			Renal	Hepatic			
Sorafenib	Oral	400mg BD	No	No	CYP3A4 inducers (↓), neomycin (↓)	Dermatologic (rash, hand-foot skin reaction, alopecia), GI(constipation, diarrhea, nausea, vomiting), hypertension, fatigue, headache	Cardiac ischemia, Bleeding, GI perforation, QT prolongation
Sunitinib	Oral	50mg QD, 4 weeks on followed by 2 weeks off in a 6-week cycle	No	No	CYP3A4 inducers (↓), CYP3A4 inhibitors (↑)	Dermatologic (rash, hand-foot skin reaction, alopecia, skin discoloration), GI(diarrhea, nausea, stomatitis, vomiting), dyspnea, fever, peripheral edema, extremity pain, hypothyroidism, anorexia, anemia, hypertension, fatigue, headache	Hepatotoxicity, Cardiac toxicity, Bleeding, GI perforation, Hypothyroidism
Pazopanib	Oral	800mg QD without food	No	200mg QD (moderate impairment)	CYP3A4 inducers (↓), CYP3A4 inhibitors (↑)	Dermatologic (rash, hand-foot skin reaction, hair color changes), GI (diarrhea, nausea, vomiting), fatigue, hypertension, anorexia, headache, ALT/AST increase	Hepatotoxicity, QT prolongation, Bleeding, arterial thromboembolism, GI perforation, Hypothyroidism, proteinuria
Bevacizumab + IFN- α	I.V. + SC	10mg/kg every 2 weeks	No	No	No	Dermatologic (dry skin, skin discoloration), GI (constipation, diarrhea, nausea, vomiting), epistaxis, hypertension, fatigue, headache, neutropenia, rhinitis, back pain	GI perforation, Wound healing complications, Bleeding, Arterial thromboembolism, Reversible posterior leukoencephalopathy syndrome, proteinuria
Temsirolimus	I.V.	25 mg IV infusion once a week	No	mild: ↓to 15mg bilirubin>1.5x ULN=contraindicated	CYP3A4 inducers (↓), CYP3A4 inhibitors (↑)	Dermatologic (Rash, pruritus, acne, nail disorder), GI (Diarrhea, mucositis, vomiting, nausea), infections, edema, asthenia, dyspnea, cough, hyperglycemia, hyperlipidemia	Infusion reactions, neutropenia, thrombocytopenia , infections, GI perforation, renal failure, intracerebral bleeding
Everolimus	Oral	10mg QD	No	moderate: ↓to 5mg	CYP3A4 inducers (↓), CYP3A4/Pgp inhibitors (↑)	Dermatologic (Rash, pruritus, dry skin, nail disorder), GI (Diarrhea, stomatitis, vomiting, nausea), fatigue, edema, infections, cough, dyspnea,epistaxis, hyperglycemia, hyperlipidemia	Non-infectious pneumonitis, infections, neutropenia, thrombocytopenia, renal failure

Proteinuria (7%), wound healing problems (1%), gastrointestinal perforation (1%) and cardiovascular events (1%) are all possible life threatening side effects of bevacizumab which need monitoring and prompt management should they arise. Other common side effects include gastrointestinal AEs (constipation, diarrhoea), fatigue and headache (Table 5).

Moreover, pharmacists may need to monitor the compliance of this treatment which currently necessitates a combination of IFN- α injected subcutaneously three times a week and bevacizumab which is injected intravenously every 2 weeks. Phone calls or an injection calendar may help to remind patients to adapt to injection scheme with good compliance in an outpatient setting.

Mammalian target of rapamycin (mTOR) inhibitors

Temsirolimus and everolimus are mTOR inhibitors indicated as alternative treatment options of metastatic RCC. They have similar mechanism of action to achieve treatment target,^(54, 55) binding to an intracellular protein FKBP-12 and the protein-drug complex inhibits mTOR which controls protein translation. They down-regulate the activity of S6 ribosomal protein kinase (S6K1) and eukaryotic elongation factor 4E-binding protein (4E-BP1), which are involved in protein synthesis. Also, mTOR inhibition leads to the inhibition of hypoxia-inducing factor α (HIF- α) and thus VEGF, leading to anti-angiogenesis effect. Both mTOR inhibitors are CYP3A4 substrates. Thus drug-drug/drug-herb/drug-food interactions with mTOR inhibitors may occur and those drugs affecting CYP3A4 enzymes should be avoided.

Due to their immunosuppressive properties, mTOR inhibitors are associated with drug-induced infections such as urinary tract infections, pneumonia and reactivation of hepatitis B, etc. Non-infectious pneumonitis⁽⁵⁷⁾ is another class effect of mTOR inhibitors in which more than one quarter of RCC patients' treatment with mTOR inhibitors had pneumonitis. Metabolism disorders such as hyperlipidemia and hyperglycemia are specific effects of mTOR inhibitors which pharmacists need to be aware of and routine lab monitoring is required. Other common side effects include fatigue, asthenia, rash and cough (Table 5). Moreover, live vaccination and close contact with those who have

received live vaccines should be avoided for patients treated with mTOR inhibitors.

Temsirolimus

Temsirolimus⁽⁵⁴⁾ is an mTOR inhibitor administered through 30-60 minute I.V. infusion once weekly and was approved by the FDA in 2007 for first line treatment of metastatic RCC patients with at least three of six prognostic risk factors in MSKCC criteria (Table 2). One major trial⁽⁴⁷⁾ was a randomized phase III study of 626 patients with a poor prognosis. Temsirolimus showed significant benefits in PFS, ORR as well as OS compared to IFN- α . The results of this trial supported the use of temsirolimus in the treatment of metastatic RCC patients with a poor prognosis and thus it is recommended by both NCCN and EAU^(22,36) for this indication.

Since temsirolimus is administered via IV infusion, pharmacists should be aware of possible hypersensitivity and infusion site reactions and if required antihistamine prophylaxis should be given before infusion. Moreover, temsirolimus should be withheld if grade 3 or above neutropenia or thrombocytopenia occurred and restarted with a lower dose. Temsirolimus should be stored in a refrigerator between 2-8°C and protected from light.⁽⁵⁴⁾

Everolimus

Everolimus is an oral form mTOR inhibitor approved by the FDA in 2009 for second-line therapy of metastatic RCC after failure of TKI therapy. The pivotal clinical trial in the adoption of this drug into clinical use⁽⁴⁸⁾ was a randomized, double-blinded, placebo-controlled phase III study of 416 metastatic RCC patients with prior failure of VEGF therapy. Everolimus showed significant improvements in PFS and ORR, but no OS significant difference against placebo. Thus, NCCN and EAU^(22, 36) recommend its use for second-line therapy of metastatic RCC after failure of systemic therapy. Everolimus should be protected from light and moisture in order to prevent reduced efficacy.⁽⁵⁵⁾ Monitoring signs of infections and lab result should be done routinely to minimize risk of life threatening adverse events.

Adverse Events Management Strategies

Dermatologic toxicities

Dermatologic AEs frequently appear in targeted therapies for RCC including

rash, hand-foot skin reaction (HFSR), alopecia and pruritus. HFSR may not be life threatening but a dose reduction may be required as symptoms progress and affect the daily activities of patients. Prevention strategies such as pedicure before treatment may be effective in reducing risk and the severity of HFSR in patients with plantar hyperkeratosis.⁽⁵⁸⁾ Pharmacists may also counsel patients to reduce exposure of extremities to hot water, to avoid excess rubbing and not wear constrictive clothing. Similarly to wear shoes with padded insoles and use emollients such as moisturizing cream which should be applied to the hands and feet. For the treatment of rash, topical emollients, topical corticosteroids (short-term) and antihistamines may be used to relieve symptoms. Also, mild, non-deodorant soaps may be used and hot showers should be avoided.

Gastrointestinal toxicities

Patients under targeted therapies for RCC may experience some of the gastrointestinal adverse events such as diarrhoea, constipation, stomatitis, vomiting and nausea. Educating patients about the likelihood of these events is a major step in managing any gastrointestinal adverse events which would be elucidated below.⁽³²⁾

To manage diarrhoea, patients should be educated to avoid foods that may aggravate diarrhoea such as dietary fibre and favour foods that may slow gastrointestinal motility such as banana and toast, etc. Also, rehydration after an episode of diarrhoea is essential and intensive oral rehydration with fluids containing water, salt and sugar is encouraged.⁽⁵⁹⁾

Pharmacological intervention with standard dose loperamide (4 mg, followed by 2 mg/4h or after every loose stool) may be helpful with relieving diarrhea.⁽⁵⁹⁾

For the management of nausea and vomiting, pharmacists should ask patients to eat small amount frequently and they should take plenty of fluids. Premedication with antiemetics like dimenhydrinate to limit drug-induced nausea and vomiting may be helpful.⁽⁵⁹⁾

Hypertension

Hypertension is a common adverse event associated with VEGF inhibitors treatment. Risk assessment of hypertension and CV events should

be conducted before starting VEGFR TKI treatment. Active monitoring of blood pressure throughout treatment especially in first 6 weeks of treatment is required. Healthcare professionals should be aware of “white coat hypertension” and this factor should be carefully evaluated.⁽⁶⁰⁾ The goal for BP control of VEGFR TKI treated patients should be 140/90 mmHg at maximum. However, the targets should be lowered with other preexisting comorbidities such as diabetes or chronic kidney disease.⁽⁶⁰⁾ BP control should be carried out aggressively so as to avoid the development of complications (such as CV events) associated with prolonged elevation. Normal antihypertensives (ARB, ACEI, diuretics etc.) may be useful in controlling BP⁽⁵⁹⁾ and its choice is up to prescribers. However, pharmacists should be aware of potential drug-drug interactions due to the CYP3A4 substrates nature of most targeted therapy for RCC.

Hematological toxicities

Serious hemorrhage and infections are possible severe adverse events caused by anticancer targeted therapy. CBC and physical examination should be conducted routinely to assess platelet, white blood cell and hemoglobin counts. Patients should be educated to avoid cuts, bruises and burns by avoiding physical activities with increased risk of bleeding.⁽⁵⁹⁾ Also, constipation should be treated and medications that may cause bleeding such as nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided.⁽⁵⁹⁾ Also, systemic therapy especially bevacizumab which may cause wound healing problems should be discontinued before surgery and not restarted until adequate wound healing has occurred.⁽⁶¹⁾

Respiratory toxicities

Pneumonitis and interstitial lung diseases are complications associated with mTOR inhibitors treatment. Patient education is important to encourage reporting of symptoms such as cough and dyspnea. Once pneumonitis is diagnosed, differentiation between infectious and non-infectious pneumonitis is important as different treatment strategies would be used.⁽³²⁾ Corticosteroid and antibiotics could be used as treatment and dose interruption may be required in symptoms progression.

Lab abnormalities

Hypothyroidism is a class adverse effect

caused by sunitinib and pazopanib treatment. Thyroid function has to be monitored regularly and patients should be educated about signs of thyroid dysfunction for reporting to physicians. Levothyroxine may be given to symptomatic patients with elevated TSH and dose adjustment should be based on lab results.⁽⁵⁹⁾

Hyperlipidemia and hyperglycemia are associated with mTOR inhibitors treatment.^(47,48) Pharmacists and healthcare professionals should be aware of the current medical history of patients, patients with diabetes and hyperlipidemia should be monitored more closely and assess whether current diabetes and lipid medications are sufficient.⁽⁵⁹⁾ Lipid-lowering medication and oral diabetes agents may be started or increased in dose to obtain control in cholesterol level and glucose level respectively. Also, pharmacists should advise patients to report excessive thirst or increase in volume or frequency of urination.⁽⁵⁹⁾ Moreover, hepatotoxicity may develop after long-term exposure of sunitinib and pazopanib,^(51,53) thus bilirubin, ALT/AST level should be routinely monitored.

FUTURE TRENDS

Axitinib is an oral VEGFR TKI approved by the FDA in 2012 but has not yet been registered in Hong Kong. It is a VEGFR only inhibitor and indicated as second-line treatment option for RCC after failure of prior systemic therapy. A randomized phase III study of 723 patients and axitinib showed significant benefit in PFS and ORR against sorafenib in treating refractory RCC patients and its safety profile is comparable to sorafenib.⁽⁴⁹⁾

Tivozanib,⁽⁶²⁾ another oral VEGFR TKI undergoing a phase III clinical trial involving 517 patients, demonstrated significant improvement in PFS and ORR when compared with sorafenib without causing significant toxicity based on preliminary data.⁽⁶³⁾ Dovitinib, also another oral VEGF inhibitor demonstrated anti-tumor activity in a phase I study⁽⁶⁴⁾ targeting previously anti-VEGF treated patients. A phase III study is in progress to compare the efficacy with sorafenib in third-line RCC treatment.⁽⁶⁵⁾ Novel agents targeting new biomarkers are under development, including vorinostat,⁽⁶⁶⁾ a histone deacetylase inhibitor, which is used in combination with anti-VEGF agents to exhibit antitumor effect, is under phase I/II study.

Other than investigational drugs, clinical trials on combination therapy and adjuvant use of existing drugs are also under investigation. Head-to-head comparison⁽⁶⁷⁾ of sunitinib and pazopanib as first-line treatment for RCC patients is also undergoing to compare their efficacy and safety profile.

CONCLUSION

Recent molecular targeted therapies have increased the treatment options available for metastatic RCC patients to prolong their survival. Future research will focus on further understanding of biological pathways and identifying phenotype involved in drug response and resistance, thus novel agents could be developed to optimize treatment efficacy and safety. Moreover, current systemic treatment is limited to palliative care which aims to prolong progression free survival and improve quality of life but not curative. Uncovering adjuvant use of targeted therapy may further raise the role of systemic therapy in decreasing relapse rate of disease after nephrectomy, or even to attain complete remission.

Author's background

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Questions for Pharmacy Central Continuation Education Committee Program

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

1. Which reason may not explain the increasing trend in renal cell carcinoma (RCC) patients?

- a Better imaging techniques
- b Increasing overall survival rate of RCC
- c Rising number of people with risk factors
- d Popularity in abdominal imaging scans

2. Which risk factor contributes to potential development of renal cell carcinoma (RCC)?

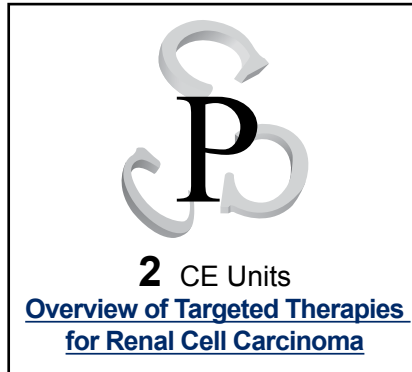
- a Alcohol abuse
- b Long term opioid use
- c Defect in Von Hippel-Lindau (VHL) gene
- d Female

3. Which of the factor is least related in over-expression throughout the development of renal cell carcinoma (RCC)?

- a Platelet derived growth factor (PDGF)
- b Mammalian target of rapamycin (mTOR)
- c Vascular endothelial growth factor (VEGF)
- d Human epidermal growth factor receptor 2 (HER2)

4. Which of the following statement about Renal Cell Carincoma (RCC) staging is incorrect?

- a If the tumor size is less than 7cm with regional lymph node involvement, the estimated average 5 year survival rates in RCC is about 96%.
- b Distant metastasis to any visceral organ indicates a stage IV carcinoma.
- c If the tumor invades into vena cava with no lymph node involvement, the estimated average 5 year survival rates in RCC is about 64%.



d The Memorial Sloan-Kettering Cancer Center (MSKCC) model is adopted to determine prognosis of patients.

5. Which of the therapeutic option is considered reasonable in stage III renal cell carcinoma (RCC)?

- a Radical Nephrectomy
- b Thermal ablation therapy
- c Targeted therapy
- d Clinical trials

6. Which of the following statement about Renal Cell Carcinoma (RCC) therapeutic options is correct?

- a Immunotherapy such as Interleukin-2 use is a viable treatment option in treating RCC based on its benefit in efficacy and safety.
- b Temsirolimus should be used as first-line treatment option regardless of risk.
- c Bevacizumab should be used in combination with IFN- α to maximize its efficacy in treating RCC.
- d After approval of pazopanib, sunitinib was moved second-line therapy due to its inferior efficacy.

7. Which of the following therapeutic agent involves in least drug-drug interaction?

- a Sunitinib
- b Temsirolimus
- c Sorafenib
- d Bevacizumab

8. Which of the adverse effect may be specifically related to sunitinib compared with sorafenib?

- a Hand-Foot skin reaction (HFSR)
- b Anemia
- c Hypothyroidism
- d GI perforation

9. Which of the adverse events management strategy may not regarded as appropriate?

- a Intensive oral rehydration with electrolytes after an episode of diarrhoea is essential.
- b Short-term application topical corticosteroids may be efficacious for relieve dermatology symptoms such as rash.
- c Medications that carry bleeding risk such as nonsteroidal anti-inflammatory drugs (NSAIDs) and aspirin should be strictly forbidden.
- D Levothyroxine may be a possible treatment option to sunitinib or pazopanib induced hypothyroidism.

10. Which of the following therapeutic agent is not a potential candidate for targeted therapy of Renal Cell Carcinoma (RCC)?

- a Axitinib
- b Tivozanib
- c Ruxolitinib
- d Dovitinib

Answers will be released in the next issue of HKPJ.

Over-the-Counter Paracetamol for Management of Fever in Children

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ABSTRACT

Paracetamol has long been the drug of choice for relieving fever in children due to its easy accessibility, acceptable use in infants ≥ 3 months of age, and low side effect profile. However, as with any medication paracetamol is not exempt from errors due to incorrect doses and the potential for overuse. One possible reason for excessive use is fever phobia among parents. This phobia is largely due to misconceptions regarding the dangers of childhood fever and is reflected in studies which demonstrate parents' tendency for lower temperature threshold in the definition of fever and associated harmful effects. Medication errors which have been documented include too frequent administration of paracetamol and administration of incorrect dose. Both present areas which pharmacists may contribute to improve medication safety among children. By counseling parents and caregivers regarding implications of fever, appropriate goals of therapy, and alert them on potential harmful effects associated with the use and misuse, we can ensure paracetamol maintains its status as the safe and effective drug of choice for the management of fever among children in the out-patient setting.

Keywords: *Over-the-Counter: Over-the-Counter Paracetamol, Fever, Children*

INTRODUCTION

Over-the-counter antipyretic agents account for majority of medications used by children. Paracetamol in particular ranks as the single most commonly

used over-the-counter medication in children in the outpatient setting. Although local data regarding the use of paracetamol among children in Hong Kong is currently unknown, overseas studies have documented the frequency of its use. In the United Kingdom, paracetamol accounted for 48.4% of total over-the-counter medications for children < 16 years of age.⁽¹⁾ In the United States, paracetamol (known as Acetaminophen) represented 23% of the most used single-ingredient medications in infants ≤ 23 months of age, and the most used active ingredient among all children < 12 years old.⁽²⁾ Paracetamol's popularity extends to children in Hong Kong as well due to its accessibility as an over-the-counter medication and its favorable safety profile. It is worthwhile to revisit the aspects regarding its use as an antipyretic among such population. This article explores paracetamol's use/misuse, associated harmful effects and ways by which pharmacists may improve the primary care provided to parents caring for children with fever in the community setting.

ANTIPYRETIC OF CHOICE OR CHOOSING TO OVER USE ANTIPYRETICS?

The presence of fever in a child has the tendency to illicit excessive concern among parents in Hong Kong- a phenomenon long recognized as fever phobia. A term coined by Schmitt, B. in 1980, fever phobia described his observations of parental behavior in children presenting with fever.⁽³⁾ Despite its recognition 20 years ago, fever phobia remains a fully universal occurrence among parents with a febrile child.⁽⁴⁻⁶⁾ Although difficult to establish an explicit causal relationship, fever phobia may be the underlying

factor leading to aggressive treatment and over use of antipyretics such as paracetamol.

Fever is a symptom and not a disease itself. However, parents' misperception of it as a disease is not uncommon. Reducing an elevated body temperature regardless of the degree of elevation becomes a primary focus rather than the overall condition of the child. The clinical definition of fever is a rectal temperature $\geq 38.0^{\circ}\text{C}$ or an oral temperature $\geq 37.8^{\circ}\text{C}$.^(7,8) Research regarding caregivers' definition of fever have shown the tendency for parents to provide lower threshold temperature for the definition of fever with most assigning fever as any temperature above $37.5-37.9^{\circ}\text{C}$.^(9,10)

In addition to a lower threshold temperature for fever, parents' were also found to regularly use medications to achieve normothermia when temperature readings are $< 38.5^{\circ}\text{C}$. This has been demonstrated by the persistence and increased frequency of use of antipyretics despite temperatures being only mildly elevated. Parent interviews have suggested this to be due to the perceived harm to the child as a result of elevated temperatures. The three most commonly cited harmful effects of fever (and thereby serve as the basis for fever phobia) include seizure, brain damage and death. A comparison of the findings from several studies looking into parents' perceptions is listed in Table 1.

The lowest temperature threshold believed to pose a threat was 40°C with a good majority of parents believing that fever alone could damage a child.⁽¹⁰⁻¹³⁾ Additional factors such as ethnicity appear to play a role as well in the overall fever management with parents

Table 1. Comparative findings of parents 'perceived harmful effects of fever

Harmful Effects of Fever	Crocetti et al (n= 340)	Poirier et al (n=230)	Karwowska et al (n=209)	Betz et al (n=264)
Seizure	32%	32%	69.9%	19.4%
Brain Damage	21%	15%	53.1%	24.4%
Death	14%	18%	35.4%	5.3%
Dehydration	4%		80.4%	

of East Asian origin more likely to seek clinician assistance immediately rather than attempting to first manage their child at home.^(12,13) Against common misconception, fevers between 37.8°C to 40°C are actually less often considered a threat. The risk for harm increases when temperatures reach at least 41.7°C. Adverse physiologic events begin to occur at temperatures above 41°C to 42°C rather than the widely held belief of temperatures above 40°C. In practice though, few fevers escalate past this point due to our brain's natural capability to regulate temperature.

TO GIVE OR NOT TO GIVE

Benefits of using antipyretics for fever reduction include relief of patient discomfort and minimizing insensible water loss to prevent dehydration. Additionally, paracetamol is also an analgesic. Benefits of its use include improved comfort in the child that then extends to improvements in activity, feeding, and reduced irritability. This allows the clinician to better assess the child's condition.

It is important to note that the degree of fever does not always correlate with severity of illness or risk for febrile seizures, another common misconception. Additionally, antipyretic therapy may not necessarily decrease the recurrence of febrile seizures.⁽⁷⁾ Deciding to initiate anti-pyretic therapy largely depends on several factors. Often clinicians may have a higher threshold of starting therapy when the child appears to be quite well, with eating and drinking patterns not too far from their usual norm. Unless the child is uncomfortable, antipyretics may not be necessary in patients with low grade fever. The age limit for use of paracetamol among infants is ≥3 months old unless under the care and instruction of a health care provider subsequent to clinical examination. The MHRA guidelines in

the UK noted that paracetamol may be given to children as young as 2 to 3 months old in the community setting only if the child experiences post-vaccination fever or if other causes of pain or fever exist and the infant weight >4 kg and was born after 37 weeks.⁽¹⁴⁾ The drug also demonstrates a favorable safety profile compared to ibuprofen although their differences are quite marginal.⁽¹⁵⁾

With all the benefits of fever reduction, the presence of fever does pose some advantages. Fever is a physiological adaptive response to external pyrogens such as micro-organisms which causes the body to enhance elimination of certain bacteria and decrease bacterial and viral growth rates. Additionally, fever may assist the clinician in assessing the child's condition and thereby preventing the delayed identification of the underlying diagnosis and initiation of treatment.

MANAGEMENT OF CHILDHOOD FEVER IN THE OUTPATIENT SETTING

Recommendations for Paracetamol Dosing

Paracetamol at doses of 10 to 15 mg/kg per dose given every 4 to 6 hours orally is generally regarded as a safe and effective dose range. Approximately 80% of children will experience the onset of antipyretic effect within 30 to 60 minutes.⁽⁷⁾ The maximum recommended dose as well as maximum

number of times paracetamol may be given in children vary. A comparison of recommendations set forth by leading health organizations is shown in Table 2. Although some authorities have accepted higher paracetamol doses, such as in the range of 90 mg/kg/day, this dosing is regarded as supra-therapeutic. Reminding parents that paracetamol will lower the fever but may not necessarily bring the child's body temperature to normal may prevent over treatment. Parents may also be informed that if the child's condition is stable, there is no need to awaken them during sleep to administer a dose. The benefit of allowing the child full interrupted rest outweighs dose administration.

Currently, there are no specific dosing recommendations for Hong Kong regarding use of over-the-counter paracetamol. Moreover, package labeling often indicate an age-based dosing guideline rather than the recommended weight based approach. Discrepancies in dose given may occur due to differences in weight among children's even within a few years apart. To illustrate, a population based study done to determine the median age of Hong Kong boys at 3 years of age was found to be 14 kg while those 5 years of age was 17kg.⁽¹⁶⁾ If the same amount, for example 6 mL of paracetamol 120 mg/5mL was given to children of both ages, a 3 year old boy will receive the recommended 10 mg/kg dose while a 5 year old boy will receive a dose of 8 mg/kg. This may cause a sub-therapeutic antipyretic effect leading to parents to give doses sooner than recommended or seek alternative measures. In products where weight based dosing indicates the approximate volume to administer, pharmacists should emphasize on the appropriate dose frequency to ensure the maximum daily limit is not reached.

Table 2. Comparison of Paracetamol Recommendations

	American Academy of Pediatrics ⁽¹⁴⁾	Medicines and Healthcare Products Regulatory Agency (UK)	Therapeutic Goods Administration (Australia)
Maximum Daily Dose	75mg/kg	Dosing based on age	60mg/kg (without medical advice)
Maximum Number of dose/ Day	≤5 doses	4 doses	4 doses
Maximum days before seeking medical advise	-	3 days	2 days
Age cutoff for use	<3 months	<2 months	<1 month

Alternating between paracetamol and ibuprofen or use of them in combination has been noted in practice to reduce body temperature. Experts agree that currently there is insufficient evidence to either accept or refute this practice. Clinicians who choose to recommend this approach should thoroughly counsel parents regarding proper formulation, appropriate dose and dosing frequency of each antipyretic.⁽⁷⁾

Risks associated with use

When administered appropriately, paracetamol at doses of up to 75mg/kg/day has not been associated with hepatotoxicity based on the results from a recent meta-analysis. However when used in an outpatient setting, dose accuracy is often compromised, as administration is dependent on accuracy of measurement by parents or caregivers. Inaccuracy of dose given by caregivers has been documented in numerous studies. In one study, 62% of patients who received acetaminophen were given an incorrect dose- 47% were given too little while 15% received too much.⁽¹⁷⁾ This could be attributed to the parents' lack of knowledge regarding appropriate dose to administer. A study by Li et al reported that although 55% of caretakers obtained dosing information from their physician, 28% of the caregivers followed package labeling with 8% of them resorting to guessing.

Incorrectly using standard measuring devices has also been documented. Proposed measures to reduce dosing errors include the use of color-coded devices and pictograms.^(9,18,19) These approaches have shown marked improvement from conventional methods in the caregivers' ability to correctly determine and measure the appropriate dose for the child.^(18,19) Interestingly, caregivers who correctly stated that paracetamol dosing is based on weight of the child were less likely to give an incorrect dose of medication.⁽¹⁸⁾

Despite its good safety profile, paracetamol has also been linked to toxicity cases. Due to its popularity paracetamol has become a staple in most household's medicine cabinet. This makes it readily accessible to young children. A review of hospital admissions in a local tertiary hospital during a 6 year period observed paracetamol to

account for 14 hospital admissions due to unintentional poisoning.⁽²⁰⁾ Fever has been documented to be predisposing factor for doctor shopping in the local paediatric population. The prevalence of this behavior was as high as 53% among paediatric in-patients.⁽²¹⁾ Doctor shopping is associated with potential dangers such as polypharmacy from use of multiple medications often with multiple ingredients. Patients may inadvertently be taking several medications which contain paracetamol leading to toxicity. Pharmacists should be reminded to extend their counseling to include proper storage and avoidance of doctor shopping to prevent accidental over-ingestion.

TAKE HOME MESSAGE

Paracetamol is a widely accessible drug often passed off as relatively safe due to its appropriateness of use in children <6months of age and negligible side effects. However research has documented areas where pharmacists may provide improved patient care. When counseling parents' regarding fever, emphasis should be made on the primary goal of antipyretic use, which is improving the child's comfort rather than achieving normothermia. Pharmacists may also remind parents that the height of a child's fever does not necessarily reflect seriousness of the illness. Rather, it is how sick the child behaves that clinicians tend to weigh more heavily in their assessment. Fever is a symptom of a disease rather than a disease in itself and often times once the disease has been treated or addressed, the fever abates. If antipyretics are to be used, the recommended dose for infants and children is 10 to 15 mg/kg per dose every 4 to 6 hours at a maximum of 4 doses per day. Fevers that persist beyond 48 hours despite use of paracetamol warrants medical attention. Educating parents on correct measurement and appropriate dosing frequency are additional areas where pharmacists can further enhance safety in the use of paracetamol for the management of childhood fever within the community setting.

Author's background

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*96% of patient on Dexlansoprazole 60mg achieved 24-h heartburn-free days⁵



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Biochemical- and Biological-Based Studies of Asian Ginseng

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Botanical name: *Panax ginseng* C. A. Mey.

Family: Araliaceae.

Common names/other names: Asiatic Ginseng, Chinese Ginseng, Korean Ginseng, Red Korean Ginseng, Ren Shen, Wonder-of-the-World, Bio Star, Cimexon, Energy Rise, Fast Lane Herbo Tea, Gincosan, Ginsana, Ginsatonic, Ginseng Action, Neo Ginsana

Chinese Name: 人參 *rénshēn*

Part Usually Used: roots, leaves, stems, fruits, flower heads

Common Uses: Increasing strength, vitality and immune function; lowering high blood pressure aphrodisiac; stimulating type II diabetes treatment; treating erectile dysfunction.

ABSTRACT

Panax ginseng C. A. Mey (*P. ginseng*), one of the most popular and best-selling herbs worldwide, has been used as a valuable folk medicine for thousands of years. It contains triterpenoid saponins, polysaccharides, volatile oils, polypeptides, polysacetylenes, amino acids and other bioactive compounds. The major bioactive components of this herb are triterpenoid saponins, including ginsenosides R_{b1}, R_{b2}, R_c, R_g, R_e and R_f. Of which ginsenoside R_f is the most characteristic component. Biological vice, the herb has CNS-regulating, substance metabolism improving, age-delaying, immune system boosting, hematopoiesis promoting, anti-myocardial-ischemia, endocrine-enhancing and anti-tumor effects. In this review, an emphasis has been placed upon the biological activity and clinical applications associated with ginsenosides, particularly with respect to some new discoveries based on recent studies from chemoprophing studies and system biology.

INTRODUCTION

Herbal products are commonly used in developing and developed countries for medicinal purposes. According to a study conducted by WHO, it was found that more than 50% of the world population have used botanical based medicines for their primary health care (Fig. 1). Amongst all the herbs, Ginseng is one of the most popular and bestselling herbal products.

Ginseng is referred to species within the genus *Panax* (Araliaceae family), comprising of approximately 14 species of slow-growing perennial plants with fleshy roots.⁽¹⁾ The English word ginseng is derived from the Chinese term *rénshēn* in reference to the root's characteristic human-like forked shape. The most widely used species of *Panax* are *Panax ginseng* (Korean or Asian ginseng), *Panax quinquefolium* (American ginseng), *Panax japonicus* (Japanese ginseng), *Panax notoginseng* (Sanchi ginseng), and *Panax*

vietnamensis (Vietnamese ginseng)⁽²⁾ (Table 1). Ginsenosides showing various pharmacological effects have been isolated from roots, leaves/stems, fruits, and/or flower heads of *Panax* species.⁽³⁾ Of all *Panax* species, both *P. ginseng* C.A. Meyer and *P. notoginseng* (Burk) are native to China and Korea and have been used for centuries. The former is one of several types of true ginseng; another is American ginseng (*Panax quinquefolius*). Notoginseng, although looks very similar to Asian ginseng when it comes to their main bioactive compounds, is not a true ginseng. When the dried root and rhizome of *P. ginseng* is used as Chinese medicine, its Chinese name is renshen; when the dried leaf of *P. ginseng* is used, its Chinese name is renshenye. In most cases, when it comes to *P. ginseng*, it refers to its dried root.

Recommended uses for Asian ginseng are numerous, including the use of the herb to support overall health and boost the immune system. Traditional and folk uses of ginseng include improving

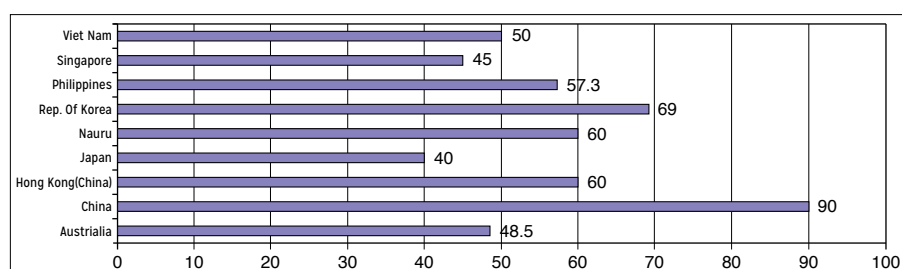


Figure 1. Percentage of population using traditional medicine, selected countries in the Western Pacific Region. [Adapted from Haq et al.⁽⁴⁾]

Table 1. Medicinally used ginseng species

Common name	Botanical name
Asian ginseng (Chinese or Korean ginseng) ^a	<i>Panax ginseng</i> C.A.Meyer
American ginseng ^a	<i>Panax quinquefolium</i> L.
Japanese ginseng	<i>Panax japonicus</i> C.A. Meyer
San-chi or Tien-chan ginseng ^a	<i>Panax notoginseng</i> (Burk)
Siberian or Russian or Eleuthero ginseng	<i>Eleutherococcus senticosus</i>
Vietnamese ginseng	<i>Panax vietnamensis</i>

^a Most commonly used

the health of people recovering from illness; increasing a sense of well-being and stamina; improving both mental and physical performance; treating erectile dysfunction, hepatitis C, and symptoms related to menopause; and lowering blood glucose and controlling blood pressure. Despite those benefits mentioned above, adverse issues have been reported. Further indepth and systematic studies of ginseng are still required to reveal their full potential uses as a medicinal herb.

DESCRIPTION AND IDENTIFICATION

Morphological and macroscopic features

Ginseng is a perennial umbel herb with weight of 10–15 g. The plant has white and fleshy roots and its primary root with several stout rootlets is about 7–10 cm in length and 3 cm in diameter. Numerous distinct “rings” (transverse wrinkles) are on the surface of the root because of the shrinking of the root, which is utilized for establishing the age of the plant. Ginseng is originally a self-pollination plant which starts to bloom at its third-year growth stage with flower buds removed for seeds and root growth. The stalk is straight and slender with cluttered red berries on the top of it where pale yellow seeds can be obtained. In general, its seeds are obtained from the red berries at its fourth year, each having 2 pale yellow seeds in it (Fig. 2).

Microscopic description

The transverse section illustrates cork comprising of several rows of cells; cortex is narrow. Phloem shows clefs in the outer part, and parenchymatous cells densely arranged and scattered with resin canals which contain yellow secretions in the inner part; cambium is in a rin and xylem rays are broad (2–26 rows). Vessels are singly scattered or grouped in an interrupted radial arrangement, occasionally accompanied by non-lignified fibers; parenchyma cells containing abundant starch grains as well as clusters of calcium oxalate (Fig. 3).

BIOACTIVE COMPOUNDS

Polysaccharides

A lot of researches have been conducted on the purification, structural analysis and bioactivities of polysaccharides from *P. ginseng*. Polysaccharides as biological response modifiers (BRMs)

have attracted more and more attention by researchers due to their various biological activities used in food and medicine. Many biological active polysaccharides have been isolated from the leaves, roots or fruits of *P. ginseng*. Since the first research on *P. ginseng* polysaccharide reported, there were total 35 polysaccharides identified from the leaves, roots and fruits of *P. ginseng* up to date, including 16 ones came from the leaves, 18 ones from the roots and one from the fruits of *P. ginseng*. Kiyohara *et al.* investigated an anti-ulcer polysaccharide (GL-BIII, Rha, Ara, Man, Gal, Glc, GalA, GlcA in the ratio of 3:4:2:10:1:7:4) isolated from leaves of *P. ginseng*.⁽⁶⁾ Gao *et al*

identified GL-3, GL-4, GL-5, GLA-3, GLA-4 and GLA-5, with molecular mass weight from 5000 to 8000, from the leaves of *P. ginseng* for the first time in 1989.⁽⁷⁾ After 2 years, Gao *et al.* reported another four poly saccharides from the leaves of *P. ginseng*, including GL-NIa, GL-NIb, GL-AIa and GL-AIb.⁽⁸⁾ A complex pectic polysaccharide (GL-4IIb2) from the leaves of *P. ginseng*, which was believed to be a macrophage Fc receptor expression-enhancing polysaccharide was reported by Shin *et al.*⁽⁹⁾ Two acidic polysaccharides, named PA and PB, were isolated from the roots of *P. ginseng* by Tomoda *et al.*⁽¹⁰⁾ Recently, Zhang *et al.* adopted a combination method of ethanol precipitation, ion-exchange and gel

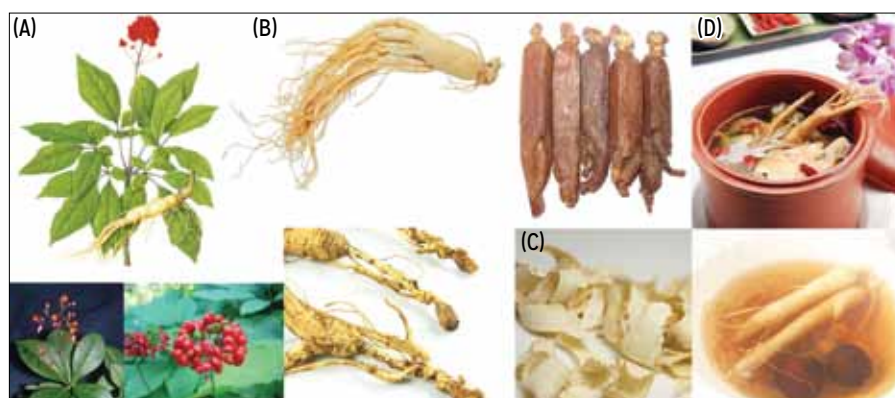


Figure 2. Morphological features of *P. ginseng*. (A) Whole plant photo and its fruits; (B) Fresh root and dried root of *P. ginseng*; (C) Decoction pieces of *P. ginseng*; (D) *P. ginseng* based dishes.

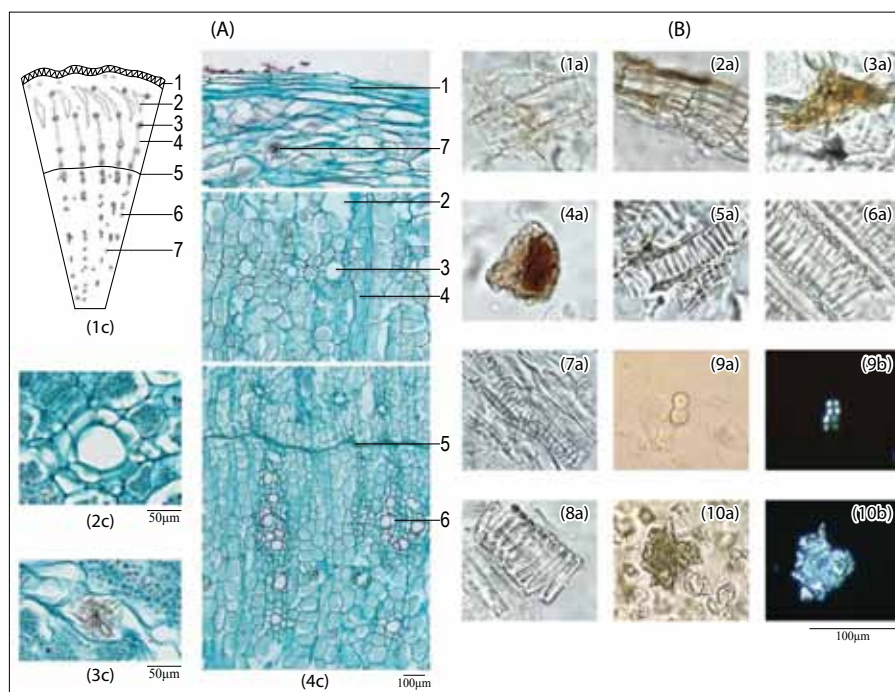


Figure 3. Microscopic features of transverse section of *Radix Ginseng* (A). (1c) Sketch; (2c) Section illustration; (3c) Resin canal; (4c) Cluster of calcium oxalate. Microscopic features of powder of *Radix Ginseng* (B). 1. Cork cells (surface view); 2. Cork cells (lateral view); 3. Resin canal; 4. Resin canal with yellowish-brown secretion; 5. Single scalariform vessel; 6. Reticulated vessels in a group; 7. Single scalariform vessel with parenchymatous cells; 8. Single reticulated vessel; 9. Starch grains; 10. Cluster of calcium oxalate. a. Features under a light microscope, b. Features under a polarizing microscope. [Adopted from HKCMMS.⁽⁵⁾]

permeation chromatography to fraction water-soluble polysaccharides from the roots of *P. ginseng* into two groups, namely neutral (WGPN and WGPA-N) and acidic polysaccharides (WGPA-1-RG, WGPA-2-RG, WGPA-1-HG, WGPA-2-HG, WGPA-3-HG and WGPA-4-HG).⁽¹¹⁾

Ginsenosides

Generally, ginsenosides (Fig. 4) are commonly considered to be the main active components in *P. ginseng*. Most ginseng ginsenosides belong to a family of steroids with a four trans-ring rigid steroid skeleton. They are also referred to as ginsenosides, triterpenoid saponins or dammarane derivatives. More than 200 ginsenosides have been isolated from ginseng plants. Based on their aglycone moieties, ginsenosides can be divided into 20(S)-protopanaxadiol (e.g., Rb₁, Rb₂, Rb₃, Rc, Rd, Rg₃) and 20(S) protopanaxatriol (e.g. Re, Rg₁, Rg₂, Rh) types. Ginsenosides can also be classified into polar (e.g. Rg₁, Re, Rb₁, Rc, Rb, Rd) and less polar (e.g. Rg₆, F₄, Rk₃, Rh₄, Rg₃, Rk₁, Rg₅ compounds.

ISOLATION AND ANALYSIS OF GINSENG

Sample preparation techniques

Extraction is the essential step for purification and recovery of various bioactive compounds from plant materials. Ginseng saponins have been extracted from ginseng based on the choice of solvents and use of heat and/or mixing to increase the solubility of materials and the rate of mass transfer.⁽¹²⁾ The conventional method includes heat-reflux, Soxhlet, ultrasound-assisted extraction (UAE) and microwave-assisted extraction (MAE). Heat reflux extraction is a solid-liquid extraction, accomplished by allowing hot solvent to leach out the compounds from the solid tissue. This technique allows extraction of the solid at an elevated temperature without loss of solvent under evaporation. Kim *et al.* optimized the parameters of heat reflux method and applied it to extract panaxatriol (Rg group) and panaxadiols (Rb group) ginsenosides from fresh; air dried and powdered adventitious roots

of ginseng (*P. ginseng*).⁽¹³⁾ Ultrasound-assisted extraction improves both solvent penetration into plant materials and the release of intracellular product by disruption of the cell walls at lower temperatures, avoiding thermal damage to extracts and loss of volatile components in boiling. Wu *et al.* successfully extracted the ginseng saponins from ginseng roots and cultured ginseng cells.⁽¹⁴⁾ Microwave-assisted extraction (MAE), as a relatively new extraction method, has been shown to enhance the extraction efficiency of interested components from a wide variety of sample matrices. It has been used as an alternative sample preparation technique for various applications.⁽¹⁵⁾ Shu *et al.* used focused microwave-assisted technique to extract ginsenosides Rg₁ and Rb₁ from ginseng root under atmosphere pressure.⁽¹⁶⁾

Methods of analysis

Determination of ginseng saponins could be achieved by TLC or HPTLC; HPLC, HILIC or UPLC; gas chromatography (GC); multidimensional chromatography; or electrophoresis (CE). Among these techniques, liquid chromatography is used most frequently.

Thin-layer chromatography (TLC)

Versatility, speed, flexibility and low cost are the characteristic of TLC being used for tests of purity, quick qualification or species identification in pharmacopoeias and the pharmaceutical industry (Fig. 5). Vanhaelen-Fastré *et al.* optimized a densitometric determination of six major ginsenosides in *P. ginseng*, separated by high-performance thin-layer chromatography (HPTLC).⁽¹⁷⁾ A fingerprint pattern with HPTLC discriminates white and red *P. ginseng*, *P. quinquefolius* and *P. notoginseng*. Xie *et al.* used high performance thin-layer chromatography (HPTLC) fingerprint analysis for species authentication of a wide range of species of ginseng (*P. ginseng*, *P. quinquefolium*, *P. notoginseng*) and stability of ginseng preparations.⁽¹⁸⁾ However, the application of thin-layer chromatography (TLC) or high-performance thin-layer chromatography (HPTLC) is limited by the poor sensitivity and specificity of the detection of ginsenosides whose electronic spectra shows no characteristic absorption above 215 nm.

Gas chromatography (GC)

GC is a sensitive technique for detecting volatile chemical compounds or non-volatile compounds readily derivatized.

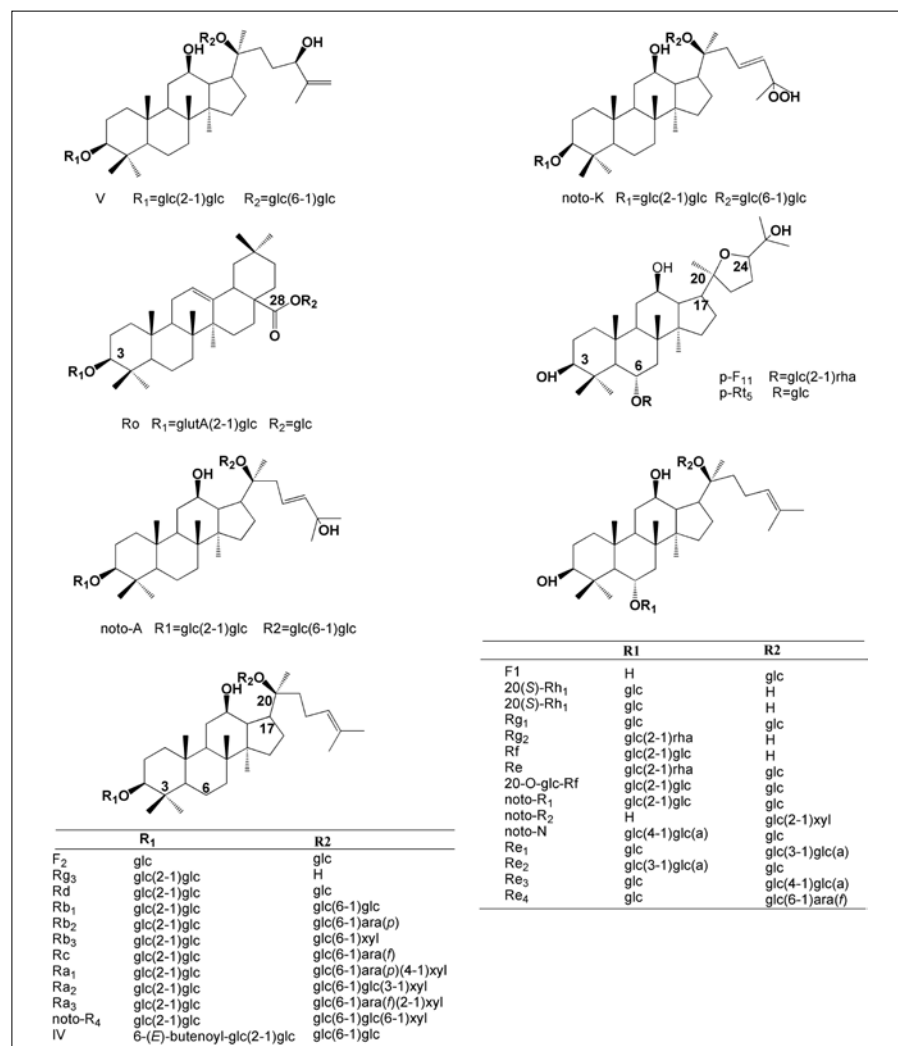


Figure 4. Chemical structures of saponins in *P. ginseng*.

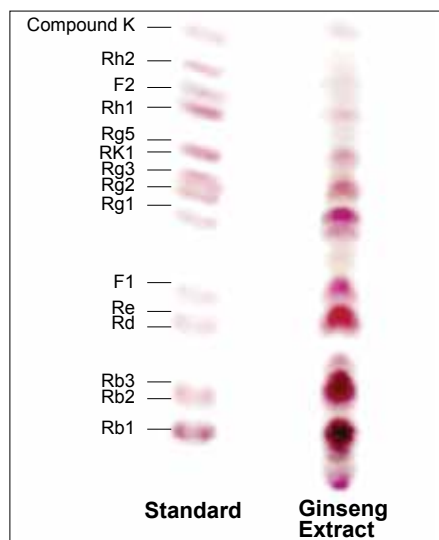


Figure 5. TLC results of extracts from *Panax Ginseng*. The plates were placed in a 20×20 cm TLC tank containing about 110 mL of the mobile phase prepared by mixing 1,2-dichloroethane–100% ethanol–methanol–water, 56.8:19.2:19.2:4.80 (v/v %) and developed at 4°C over a path of 10 cm for 30 min. The ginsenosides were quantified by UV absorbance at 275 nm in the reflectance mode using a densitometer. [Adapted from <http://www.ginbiotic.com/en/product-information/ginsenosides/ginsenosides-analysis>]

The main constituents of ginseng are the non-volatile saponins, and much of the work in identifying and determining ginseng extracts has focused on the non-volatile fraction. Semi-volatile component of ginseng root, however, has proved to contain a number of sesquiterpenes, which may comprise a characteristic fingerprint containing sufficient chemical information to allow species differentiation.⁽¹⁹⁾ Shellie *et al.* used comprehensive two-dimensional gas chromatography with flame ionisation detection (GC-GC) and with quadrupole mass spectrometry detection GC-GC-qMS to analyze the semi-volatile oils of three ginseng species; *P. ginseng*, *P. notoginseng* and *P. quinquefolium*.⁽²⁰⁾

Liquid chromatography (LC)

High-performance liquid chromatography (HPLC) is the most used technique for the analysis of ginsenosides because it is low-cost, readily available, and easy to use.⁽²¹⁾ Zhu *et al.* has developed and validated a HPLC method for the simultaneous determination of 11 triterpene saponins with four-type aglycones (protopanaxadiol, protopanaxatriol, ocotillol and oleanolic acid types) in Ginseng drugs.⁽²²⁾ Fuzzati *et al.* created a high-performance liquid chromatographic method for electrospray mass spectrometric analysis of ginsenosides in *P. ginseng* roots (Fig. 6).⁽²³⁾ Li *et al.* determined saponins in

P. notoginseng using high-performance liquid chromatography with evaporative light-scattering detection.⁽²⁴⁾ It had been showed that PLE combined with rocket column HPLC analysis could provide a rapid method for analysis of compounds in traditional Chinese medicines.⁽²⁵⁾ Pressurized liquid extraction (PLE) has been tested as a fast and high efficiency extraction method for Chinese herbs. On the other hand, the rocket column with large internal diameter, short column length and smaller silica particle size, has been successfully applied in rapid analysis.^(26, 27) Thus, PLE and rocket column HPLC analysis may provide a rapid quality control method for CMs on conventional HPLC system. Qian *et al.* successfully simultaneously determined flavonoid, saponins and polyacetylenes in Folium Ginseng and Radix Ginseng by pressurized liquid extraction and high-performance liquid chromatography coupled with diode array detection and mass spectrometry.⁽²⁵⁾

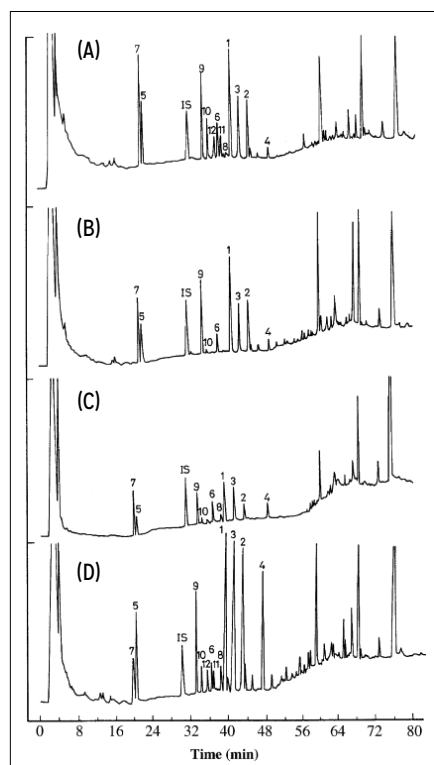


Figure 6. HPLC chromatograms of ginseng extracts. (A) Asian white ginseng; (B) Asian red ginseng; (C) Chinese Shih-Chu ginseng; (D) Asian ginseng hairy roots. The peaks from (1) to (12) were Rb1, Rb2, Rc, Rd, Re, Rf, Rg₁, Rg2, Ro, mRb₁, mRb₂ and mRc, respectively. [Adapted from Fuzzati.⁽²⁸⁾]

Micellar electrokinetic chromatography (MEKC) and microemulsion EKC (MEEKC)

Micellar electrokinetic chromatography (MEKC) and microemulsion electrokinetic

chromatography (MEEKC) are put into the use of separating neutral ginseng saponins.⁽²⁹⁾ Wang *et al.* utilized a field-enhanced sample injection with reverse migrating micelles to separate and concentrate ten ginseng saponins in *P. notoginseng* on-line.⁽³⁰⁾ Sensitivity was one magnitude higher than with the method by Glockl *et al.*⁽³¹⁾ making it possible to determine two minor ginsenosides, Rh₁ and Rg₂. Cao *et al.*⁽³²⁾ used on-line dual sweeping based on borate complexation and enhancement of the organic solvent field enhancement for the preconcentration of ginsenosides Rf, Rg₁, and Re in MEKC with nonionic Brij-35 micelles.

Matrix assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF/MS)

MALDI is a soft ionization technique used in mass spectrometry, allowing the analysis of biomolecules (biopolymers such as DNA, proteins, peptides and sugars) and large organic molecules (such as polymers, dendrimers and other macromolecules), which tend to be fragile and fragment when ionized by more conventional ionization methods. Taira *et al.* used mass spectrometric imaging (MSI) to localize ginsenosides (Rb₁, Rb₂ or Rc, and Rf) in cross-sections of the *P. ginseng* root at a resolution of 100 μm and confirmed that ginsenosides were located more in the cortex and the periderm than that in the medulla of a lateral root, besides, it revealed that localization of ginsenosides in a root tip (diameter, 2.7 mm) is higher than that in the center of the root (diameter, 7.3 mm).⁽³³⁾ Nagappan *et al.* utilized MALDI-TOF/MS to reveal the protein profile in the roots of both Asian ginseng (*P. ginseng*) and Indian ginseng (*W. somnifera*), with the aim of clarifying similarly- and differentially-expressed proteins.⁽³⁴⁾ Lai *et al.* acquired MALDI-MS spectra and showed different patterns of ginsenosides and small chemical molecules between *P. ginseng* and *P. quinquefolius* (Fig. 7), thus allowing unambiguous differentiation between the two *Panax* species based on the specific ions, intensity ratios of characteristic ions or principal component analysis.⁽³⁵⁾

Two-dimensional gel electrophoresis

Two-dimensional gel electrophoresis, abbreviated as 2-DE or 2-D electrophoresis (Fig. 8), is a form of gel electrophoresis commonly used to analyze proteins. Mixtures of proteins could be separated by two properties in two dimensions on 2D gels. Ma *et al.*

for the first time employed proteomics and biochemical variables to unravel the growth strategies for the different root growth periods of *P. Ginseng* by 2-DE, showed 83 differentially expressed

spots, and explained the interaction of metabolic proteins associated with the growth strategies of ginseng.⁽³⁶⁾ Kim *et al.* Detected the most abundant root proteins of ginseng (*P. ginseng*) and

identified them by comparative proteome analysis with cultured hairy root of ginseng.⁽³⁷⁾ Kim *et al.* also detected more than 300 protein spots on silver stained two-dimensional (2-D) gels using pH 3–10, 4–7, and 4.5–5.5 gradients. Major protein spots were analyzed by peptide fingerprinting or *de novo* sequencing and the functions of 91 of these proteins were identified.⁽³⁸⁾

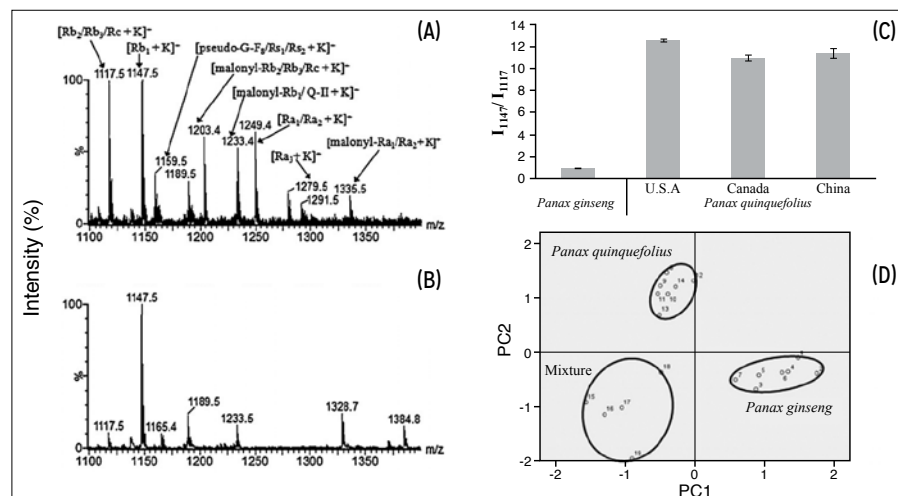


Figure 7. MALDI-TOF/MS spectrum in mass region of 1100–1400 for *P. ginseng* (A) and *P. quinquefolius* (B) respectively; (C) The intensity ratio of *m/z* 1147 to *m/z* 1117, which was regarded as a marker for authentication of *P. ginseng*, in the MALDI-TOF/MS spectra obtained for *P. ginseng* and *P. quinquefolius*; (D) PCA plot of the MALDI-TOF/MS results for *P. ginseng*, *P. quinquefolius* and mixed ginseng samples. [Adapted from Lai *et al.* ⁽³⁵⁾]

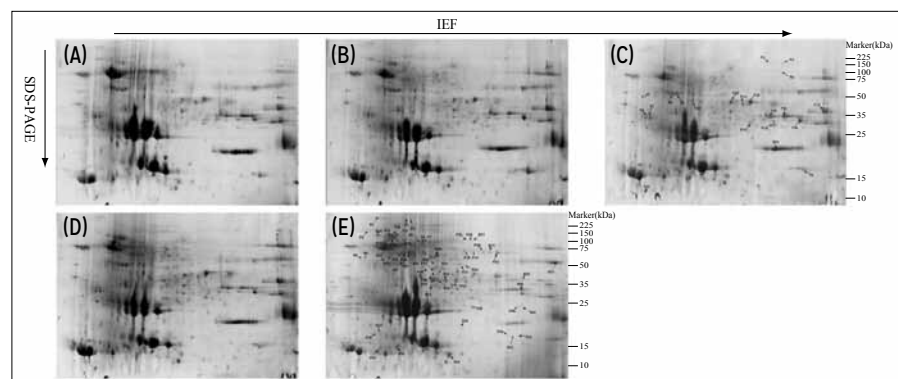


Figure 8. Ginseng proteomic patterns with different ages, from one to five years old for (A) to (E), respectively. [Adapted from Ma *et al.* ⁽³⁶⁾]

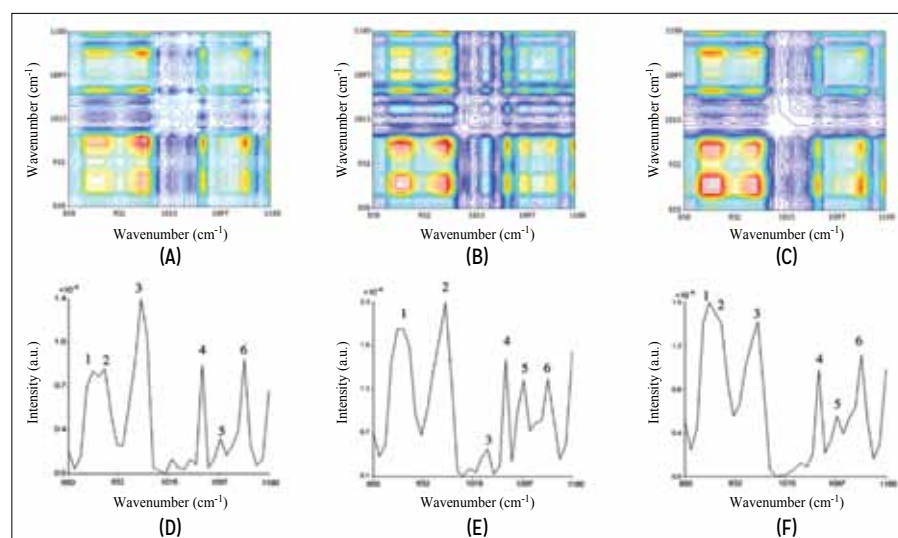


Figure 9. Synchronous 2D-FTIR correlation spectra of (A) *P. ginseng*; (B) *P. quinquefolius*; (C) *P. notoginseng* in the region of 850–1180 cm^{-1} with their curves of auto-peaks in the 2D-FTIR spectra for: (D) *P. ginseng*; (E) *P. quinquefolius*; (F) *P. notoginseng*. [Adapted from Lu *et al.* ⁽³⁹⁾]

Fourier transform infrared spectroscopy

The herbal materials of Asian ginseng (the root of *P. ginseng*), American ginseng (the root of *P. quinquefolius*) and Notoginseng (the root of *P. notoginseng*) had been differentiated by conventional Fourier transform infrared spectroscopy (1D-FTIR), when two-dimensional (2D) correlation FTIR applying a thermal perturbation is used, it is a powerful analytical method, as shown in Fig. 9, each species could be well differentiated.⁽³⁹⁾

BIOLOGICAL EFFECTS

Preventing cancer and activate antitumor immunity

In vitro, ginsenosides stimulated the apoptosis of human hepatocarcinoma SK-HEP-1 cells, rat glioma C6Bu-1 cells, SK-N-BE human neuroblastoma cell, human melanoma A375-S2 cells and prostate carcinoma LNCaP cells. Ginsenosides also induced the differentiation of Morris hepatocarcinoma, B16 melanoma and F9 teratocarcinoma, and inhibited the angiogenesis and metastasis of 12-O-tetradecanoylphorbol-13-acetate and H_2O_2 in WB-F344 rats and reduced the carcinogenic activity of methycolanthrene.^(40, 41) The polysaccharides and panaxynol inhibited the proliferation of promyelocytic leukemia HL-60 cells. Results of epidemiological studies of *P. ginseng* intake and cancer cases (4600 patients) indicated that those who took *P. ginseng* were less likely to contract various cancers such as stomach, liver and lung cancers. Increased intake leads to a lesser ratio of danger, demonstrating its value for primary prevention.^(42, 43) Suh *et al.*⁽⁴⁴⁾ monitored cancer recurrence in people diagnosed with stage III gastric cancer by giving 4.5 g/day of red ginseng for 6 months. People were followed up for 4.5 years after treatment, and there was a significant reduction in cancer recurrence (RR 0.49 [0.25, 0.98]). Yun *et al.* monitored incidence of cancer in people with chronic atrophic gastritis

who were given 1 g/week of red ginseng for 3 years. Participants were followed up for 8 years after treatment, and there was a notable reduction in incidences of cancer (RR 0.49 [0.21, 1.13]).⁽⁴⁵⁾ Histological monitoring revealed that ginseng can increase apoptosis and reduce proliferation of tumors from mice, as shown in Fig. 10.⁽⁴⁶⁾ The possible cellular and molecular mechanisms of ginsenosides against cancer were illustrated in Fig. 11.⁽⁴⁷⁾

Increasing immunization functions

Ginsenosides promoted the cytophagic

activity of blood colloid carbon particles, and increased the production of antibodies in several animals. The polysaccharides raised the serum anti-IgH Level in mice treated with sheep red blood cells. Scaglione *et al.*⁽⁴⁸⁾ conducted two studies that followed the same protocol, using 200 mg G115 or PKC for 8 weeks. Immune cell activity and numbers were measured at the end of treatment. Significance for G115 and PKC was observed, chemotaxis (G115, MD 0.53 [0.19, 0.87]; and PKC, MD 0.52 [0.19, 0.85]) and total lymphocytes (PKC, MD 5.82 [0.89, 10.75]). Jung *et al.*⁽⁴⁹⁾ investigated post-exercise

muscle damage and inflammation after administration of 60 g of red ginseng to healthy people for 10 days. In that time, creatine kinase significantly decreased (MD 39.50 [65.98, 13.02]), indicating reduced muscle damage. Insulin sensitivity also improved (MD 1.40 [0.52, 2.28]) possibly because of reduced muscle damage.⁽⁵⁰⁾

A water-soluble ginseng marc polysaccharide (GMP) was examined for immunomodulatory effects in murine peritoneal macrophages by Lim *et al.*⁽⁵¹⁾ Results suggested that GMP was an effective nonspecific immunomodulatory agent, and its immuno-stimulating effects may be due to its ability to stimulate the production of reactive oxygen intermediates.

Improving blood circulation

The root produced a biphasic effect on the heart, excitatory at low doses and inhibitory at high doses. Ginsenosides reduced the heart rate of dogs and rats, prolonged contraction time in guinea pig isolated atria under hypoxia, decreased the lactic level in ischemic coronary sinus, increased tolerance to hypoxia, prevented arrhythmias caused by barium chloride, and reversed tachycardia. Reports have showed ginseng's inhibitory effects on platelet aggregation⁽⁵²⁾ and endotoxin-induced disseminated intravascular coagulation.⁽⁵³⁾ The role of ginsenoside Rg₃ in the inhibition of platelet aggregation has been described.⁽⁵⁴⁾ The role of ginsenosides in protecting human erythrocytes against hemin-induced hemolysis has been described.⁽⁵⁵⁾

Antioxidant function

Kim and Lee studied the results of healthy smokers taking 1.8 g of red ginseng or placebo for 4 weeks, but no significant effect was reported.⁽⁵⁶⁾ Kim *et al.*⁽⁵⁷⁾ investigated the effect of *P. ginseng* at 1 or 2 g/day on healthy people for 4 weeks. Lipid peroxidation decreased with low and high doses, MD 1.50 [2.97, 0.03] and MD 1.80 [3.20, 0.40], respectively. These studies showed evidence of *P. ginseng*'s antioxidant effect; however, other measured components, including total reactive oxygen species and antioxidant capacity, were not significant. Voces *et al.*⁽⁵⁸⁾ investigated the effect of prolonged treatment with the standardized *P. ginseng* extract G115 on the antioxidant capacity of the liver. The results demonstrated that the administration of G115 significantly improves the hepatic glutathione

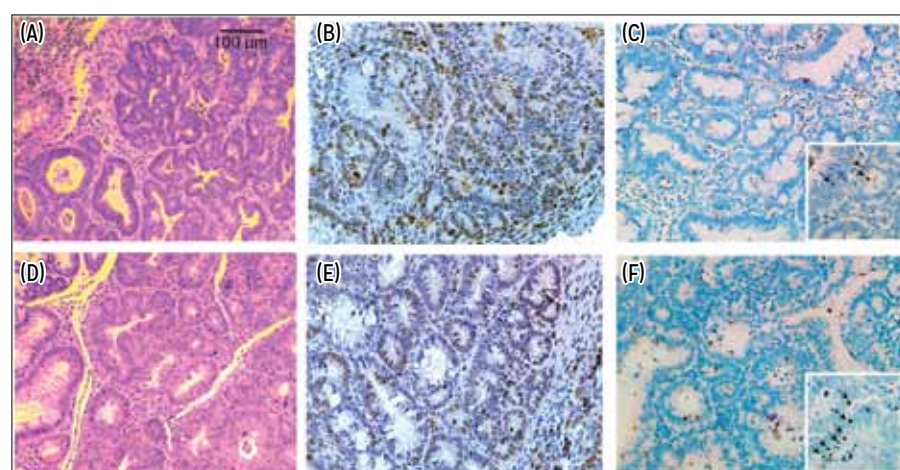


Figure 10. Ginseng can increase apoptosis and reduce proliferation in AOM/DSS-induced tumors from mice. (A) HE stained tumor from mouse on normal diet (20x); (B) HE stained tumor from mouse on normal diet supplemented with 250 ppm *P. ginseng* extract (20x); (C) Ki67 in tumor from normal diet fed mouse (20x); (D) Ki67 in tumor from mouse on normal diet plus ginseng (20x); (E) TUNEL staining in tumor from normal diet fed mouse (20x); (F) TUNEL staining in tumor from mouse on normal diet with *P. ginseng* (20x). Inset 40x magnifications. [Adapted from Dougherty *et al.*⁽⁴⁶⁾]

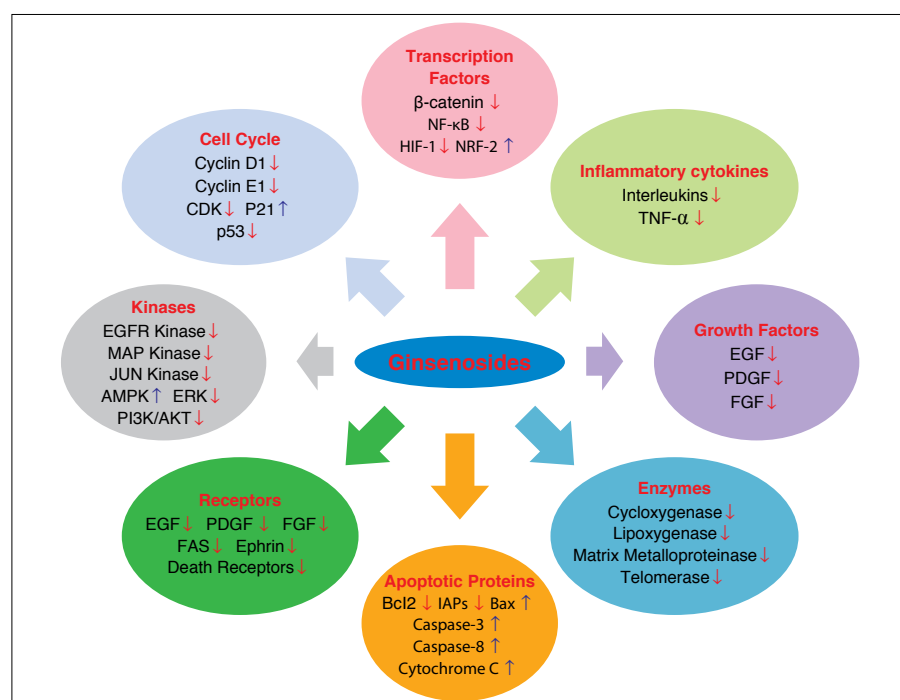


Figure 11. Possible cellular and molecular mechanisms of ginsenosides against cancer. [Adapted from Nag *et al.*⁽⁴⁷⁾]

peroxidase activity (GPX) and the reduced glutathione (GSH) levels in the liver, with a dose-dependent reduction of the thiobarbituric acid reactant substances (TBARS).

The memory enhancing effects

The roots of *P. ginseng* contain several triterpene glycosides named ginsenosides (or panaxosides), which are believed to serve to the adaptogenic and physical performance enhancing properties of the ginseng extracts.⁽⁵⁹⁾ Published trials indicated beneficial effects of ginseng include those of D'Angelo *et al.*⁽⁶⁰⁾ demonstrating improvements on motor performance, and Rosenfeld *et al.*⁽⁶¹⁾ and showing benefits on neuro-psychological measures. Beneficial effects on memory have also been reported in animals⁽⁶²⁾ there have also been indications of benefits for cognitive functioning from ginseng in both humans⁽⁶³⁾ and animals. Wesnes *et al.*⁽⁶⁴⁾ conducted an experiment on healthy middle-aged volunteers to test the memory enhancing effects of a Ginkgo biloba/*P. ginseng* combination, and the results showed the Ginkgo/ginseng combination significantly improves an Index of Memory Quality.

Anti-radiation activity

Kim *et al.*⁽⁶⁵⁾ previously reported that an acidic polysaccharide from *P. ginseng*, namely ginsan. Ginsan was found to significantly increase the number of bone marrow cells, spleen cells, granulocyte-macrophage colony-forming cells (GM-CFC), circulating neutrophils, lymphocytes and platelets in irradiated mice. Moreover, ginsan induced the endogenous production of cytokines such as IL-1, IL-6, IL-12 and TNF- α , which are required for hematopoietic recovery.⁽⁶⁶⁾ Kim *et al.* also identified ginsan alter the phenotype of bone marrow cells, and increased the viability and alloreactivity of bone marrow cells after gamma radiation both *in vitro* and *in vivo*.⁽⁶⁷⁾ In addition, ginsan modulates the radiation-induced disturbance of antioxidant enzymes such as superoxide dismutase (SOD), catalase and glutathione peroxidase (GPx).⁽⁶⁸⁾ Recently, Park *et al.*⁽⁶⁹⁾ draw a conclusion that ginsan protected mice from radiation-induced damage of the small intestine via the lengthening of villi and a numerical increase of crypt cells in the small intestine at 3.5 days after 7Gy irradiation compared to irradiated, non-treated controls. Additionally ginsan significantly decreased the amount of proapoptotic p53 and Bax to inhibit

irradiation-induced apoptosis; on the other hand, it increased that of anti-apoptotic Bcl-2 at 24 h after irradiation. Therefore, these results indicated that ginsan might be a useful candidate radio protective adjunct for cancer patients.

Hepatoprotective activity

The effects of polysaccharide ginsan from *P. ginseng* on liver function were analyzed by Song *et al.*⁽⁷⁰⁾ The data illustrated that ginsan treatment did not seem to cause hepatic injury, since serum aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP) activities as well as levels of total bilirubin and albumin were not changed. In order to make a good recognition for ginsan as a hepatoprotective formulations as well as combined application with other drugs, ginsan on carbon tetrachloride (CCl₄)-induced liver injury was examined in their next research.⁽⁷¹⁾ BALB/c mice were injected intraperitoneal (i.p.) with ginsan 24 h prior to CCl₄ administration. Serum liver enzyme levels, histology, expression of antioxidant enzymes, and several cytokines/chemokines were subsequently estimated. The results suggested that ginsan effectively prevented liver injury, mainly through down regulation of oxidative stress and inflammatory response.

CLINICAL APPLICATIONS

Enhancing cognitive performance in Alzheimer disease

Protective and trophic effects of ginseng in the memory function of Alzheimer disease (AD) have been showed in several experimental evidences. Lee *et al.* investigated the clinical efficacy of *P. ginseng* in the cognitive performance of AD patients in an open-label study. Consecutive AD patients were assigned to the ginseng (n=58) or the control group (n=39) at random, with the ginseng group ingesting *P. ginseng* powder (4.5 g/d) for 12 weeks. Mini-mental state examination (MMSE) and Alzheimer disease assessment scale (ADAS) were employed to monitor cognitive performances during 12 weeks of the ginseng treatment and 12 weeks after the ginseng discontinuation respectively. MMSE and ADAS scales showed no baseline difference between the groups. After ginseng treatment, the cognitive subscale of ADAS and the MMSE score began to show improvements and continued up to 12 weeks (P=0.029 and P=0.009 vs. baseline, respectively).

After cease of ginseng, the improved ADAS and MMSE scores decreased to the levels of the control group. These results demonstrated that *P. ginseng* is clinically effective in the cognitive performance of AD patients (Clinical Trials.gov Identifier: NCT00391833).⁽⁷²⁾

Improving myocardial protection

Myocardial disease is the leading cause of mortality in industrialized nations. Ginseng has been utilized to treat heart failure and protect tissues from damage when an organism is under stress.⁽⁷³⁾ In 2010, Vuksan *et al.* developed and initiated the *P. Ginseng* Clinical Testing Program for vascular function which is an efficacy and safety-based clinical screening model for ginseng. The most efficacious sources, ginsenoside profiles, doses, and modes of administration were examined in sequential, acute, followed by long term, randomized-controlled trials to investigate the efficacy and safety profiles.⁽⁷⁴⁾ Total ginsenosides inhibit right ventricular hypertrophy in rats⁽⁷⁵⁾ and nitric oxide functions in ginsenoside Rg₁-induced protection against left ventricular hypertrophy in rats.⁽⁷⁶⁾ Wang *et al.* reported that Ginsenoside Rb₁ preconditioning protects against myocardial infarction after regional ischemia and reperfusion by activation of phosphatidylinositol-3-kinase signal transduction.⁽⁷⁷⁾ Ginsenoside Re activates cardiac potassium channels via a nongenomic pathway of sex hormones⁽⁷⁸⁾ and ginsenoside Rb₁ preconditioning protects against myocardial infarction after regional ischemia and reperfusion.⁽⁷⁹⁾ Wang *et al.* and Yook *et al.* suggested that *P. ginseng* suppresses apoptosis by regulation of Bcl-2 and caspase-3 during hypoxia/reoxygenation in neonatal rat cardiomyocytes.^(80, 81) Besides, ginsenoside Rg₁ protects rat cardiomyocyte from hypoxia/reoxygenation oxidative injury via antioxidant and intracellular calcium homeostasis⁽⁸²⁾ and enhances angiogenesis and ameliorates ventricular remodeling in a rat model of myocardial infarction.⁽⁸³⁾ Moreover, compound K, a metabolite of ginsenosides, bestows nitric oxide-mediated cardiac protection via the Akt/phosphoinositol-3-kinase (PI3K) pathway.⁽⁸⁴⁾ Ginseng also protects from cardiac injury by acute myocardial ischemia-reperfusion in rodents through Gr/Er-activated risk pathway in an endothelial nitric oxide synthase (eNOS)-dependent mechanism.⁽⁸⁵⁾ Guo *et al.* reported ginseng inhibits cardiomyocyte hypertrophy and heart failure via NHE-1 inhibition and attenuation of calcineurin

activation⁽²⁾ (Fig 12). The collective data conclusively showed that ginseng protects the heart from myocardial damage.

Adjusting blood lipid profile

It is well known that high blood cholesterol level is one of the three major risk factors of coronary heart disease, which is one of the leading causes of death in the world. Given the fact that people who have metabolic syndrome are susceptible to atherosclerotic myocardial diseases,⁽⁶⁷⁾ effective and feasible therapeutic strategies are urgently needed for the treatment of complications of metabolic syndrome. In recent years, more attention has been paid to bioactive components from *P. ginseng*. Particularly, it was reported that *P. ginseng* saponin reduces weight

gain in mice.⁽⁶⁸⁾ Kim *et al.* examined the effects of *P. ginseng* extract on lipid metabolism in humans by measuring cholesterol, malondialdehyde, superoxide dismutase, and catalase and found that the hypolipidemic effect of *P. ginseng* extract is associated with a decrease in serum total cholesterol, triglyceride, low density lipoprotein, malondialdehyde levels and an increase in high density lipoprotein, which support scientific claims that ginseng has the hypolipidemic potential.⁽⁶⁹⁾ *P. notoginseng* saponins attenuate atherosclerosis by regulating the lipid profile and have an antiinflammatory action in rats,⁽⁹⁰⁾ and atherosclerosis is inhibited by total ginsenosides in apolipoprotein E-knockout mice.⁽⁹¹⁾ *P. notoginseng* attenuates hypercholesterolemia enhanced platelet aggregation by suppressing diacylglycerol liberation in

rabbits fed a diet high in cholesterol.⁽⁹²⁾ Jia *et al.* reported that ginseng saponins could significantly decrease the level of cholesterol ester in foam cells at middle and high dosages, the expression of ABCA1 was up-regulated by PNS in a dose-dependent manner, and the cholesterol ester level was negatively correlated with ABCA1 expression.⁽⁹³⁾ The antihyperlipidemic effects of acidic polysaccharide from *P. notoginseng* were reported.⁽⁹⁴⁾ *P. notoginseng* saponins attenuate atherosclerosis in rabbits,⁽⁹⁵⁾ and radix notoginseng has hypolipidemic and antioxidant activities in rats fed a high fat diet.⁽⁹⁶⁾ Ginsenoside-Rd prevents atherosclerosis in ApoE-knockout mice.⁽⁹⁷⁾

Adjusting blood circulation

Reports have showed ginseng's, especially Rg₃, inhibitory effects on platelet aggregation^(98, 99) and endotoxin-induced disseminated intravascular coagulation.⁽¹⁰⁰⁾ The *P. ginseng* significantly prevented rat carotid arterial thrombosis *in vivo* in a dose-dependent manner and inhibited adenosine diphosphate (ADP)- and collagen-induced platelet aggregation *ex vivo*.⁽¹⁰¹⁾ The role of ginsenosides in protecting human erythrocytes against hemin-induced hemolysis has been noticed.⁽¹⁰²⁾ Screening of antiplatelet aggregation agents from *P. notoginseng* can be done using human platelet extraction.⁽¹⁰³⁾ *P. notoginseng* saponins improve the post-treatment effects on lipopolysaccharide induced microcirculatory disturbance in rat mesentery.⁽¹⁰⁴⁾ Anti-platelet and anticoagulant effects of *P. notoginseng* were described in a comparison of raw and steamed *P. notoginseng* with *P. ginseng* and *P. quinquefolium*.⁽¹⁰⁵⁾ Ginsenoside Rk1 and Rg5 inhibited arachidonic acid and U46619 induced platelet aggregation in a dose dependent manner, while ginsenoside 20(S)-Rg₃ and 20(R)-Rg₃ showed mild inhibitory activity against arachidonic acid and U46619-induced aggregation.^(106, 107) Another study documented the interaction between warfarin and Asian red ginseng in patients with cardiac valve replacement.⁽¹⁰⁸⁾ Total ginsenosides dose-dependently and significantly increased coronary perfusion flow and improved systolic and diastolic function of the ischemia/reperfused rat heart, while inhibitors of NO synthase, soluble guanylate cyclase, heme oxygenase, cyclooxygenase, and potassium channel abolished the vasodilation effect of total ginsenosides.⁽¹⁰⁹⁾ Red ginseng extract improves coronary flow reserve and increases absolute numbers of various circulating angiogenic cells in patients with acute myocardial infarction.⁽¹¹⁰⁾

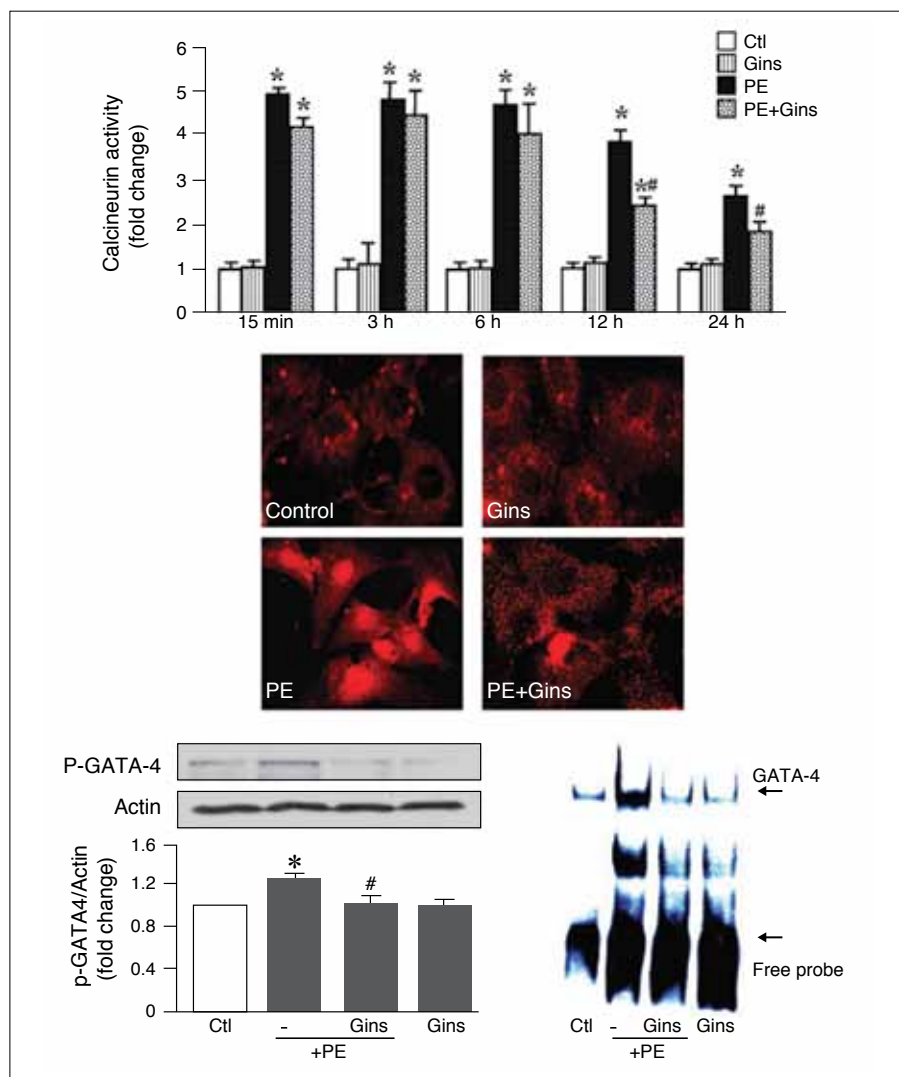


Figure 12. Phenylephrine (10 $\mu\text{mol/L}$) treatment on calcineurin activity, NFAT3 translocation, and the DNA-binding activity of GATA-4 with/without of 10 $\mu\text{g/mL}$ ginsenosides. (A) Calcineurin activity of PE treated cells with/without ginsenosides for 0.15 to 24 hours: (B) Immunofluorescent images of NFAT3 translocation into nucleus in PE treated cells with/without ginsenosides for 24 hours: (C) Western blots and quantification of GATA-4 phosphorylation. D, GATA-4/DNA-binding activity in the PE treated cells with/without ginsenosides. Data are shown as means \pm SEM. * $P < 0.05$ versus control; # $P < 0.05$ versus PE, $n = 3$ to 5. Ctl, control; Gins, ginsenosides; PE, phenylephrine. [Adapted from Guo *et al.*⁽⁸⁶⁾]

Overall, these results indicate that ginseng may improve blood circulation by inhibiting platelet aggregation and coagulation activity.

Adjusting blood pressure

Ginseng use was once misunderstood to increase blood pressure to unhealthy levels. Actually, it can elevate blood pressure, and this generally occurs with low blood pressure, which helps restore blood pressure to normal level; ginseng also lowers high blood pressure.⁽¹¹¹⁾ Biochemical and pharmacological activities of ginseng related to blood pressure control are being clarified with continued research. The vasodilation action of *P. ginseng* improves blood circulation.⁽¹¹²⁾ Panaxa ginseng has an antihypertensive effect, which appears to be related to lower rather than higher doses of ginsenosides.⁽¹¹³⁾ Furthermore, the capacity of lowering the blood pressure of *P. ginseng* is due to promotion of vascular endothelial cell-derived nitric oxide (NO) secretion.⁽¹¹⁴⁾ In addition, a mixed aqueous extract of salvia miltiorrhiza and *P. notoginseng* demonstrated anti-hypertensive effects by inhibition of arterial myogenic responses.⁽¹¹⁵⁾ The collective observations indicate that ginseng normalizes blood pressure and improves blood circulation.

Regulating intracellular ion channels

Jeon *et al.* investigated the effect of crude saponin and non-saponin fraction of Asian red ginseng on the blood pressure and nitric oxide production in the conscious rats and cultured endothelial cell line, ECV 304 cells, and the results showed the hypotensive effect induced by crude saponin reached maximum at 2–4 min and slowly recovered after 20 min to the initial level.⁽¹¹⁶⁾ Rb₁ treatment can inhibit the right ventricular hypertrophy induced by monocrotaline, which may be involved in its inhibitory effects on calcineurin signal transduction pathway.⁽¹¹⁷⁾ Ginsenoside Rd reverses basilar hypertrophic remodeling in stroke-prone renovascular hypertensive rats as a new voltage-independent Ca²⁺ entry blocker.⁽¹¹⁸⁾ The cardiac therapeutic effects of ginseng and sanqi was reported to be partly attributed to the effective inhibition of Na⁺/K⁺-ATPase by their metabolized ginsenosides with sugar moieties attached only to the C-3 position of the steroid-like structure.⁽¹¹⁹⁾ Another study reported that Rg₃ inhibition of L-type Ca²⁺ channel currents is attenuated by mutations of Leu427, Asn428 and

Leu431 in transmembrane domain-I-segment 6 residues.⁽¹²⁰⁾ The data indicate that ginsenosides inhibit Ca²⁺ entry, and so may ameliorate cardiac function.

Regulating vascular endothelial cells

Ginsenoside Rb₁ has protective effects on human oxidized low-density lipoprotein injuring cells *in vitro* and can reverse the effects of oxidized low-density lipoprotein on nitric oxide, tissue-type plasminogen activator, and plasminogen activator inhibitor-1.⁽¹²¹⁾ Water extract of *P. ginseng* exhibits angiogenesis by activating the PI3K/Akt-dependent extracellular signal-regulated kinase 1/2 and eNOS pathways in human umbilical vein endothelial cells.⁽¹²²⁾ Ginsenosides also exhibit angiomodulatory and neurological effects.⁽¹²³⁾ Besides, ginsenoside Re releases nitric oxide via membrane sex steroid receptors, resulting in Kca channel activation in vascular smooth muscle cells, promoting vasodilation and preventing severe arterial contraction.⁽¹²⁴⁾ Ginsenoside Rb₁ may attenuate capillary morphogenesis by the action of oestrogen receptor beta agonist and induces the signaling pathway of NO production in human aortic endothelial cells.⁽¹²⁵⁾ Moreover, experiments using fluorescent transgenic mice established the angiogenic effect of ginsenoside Rg₁ from *P. ginseng*.^(126, 127) Compound K inhibits basic fibroblast growth factor-induced angiogenesis through regulation of p38 mitogen-activated protein kinase and Akt in human umbilical vein endothelial cells.⁽¹²⁸⁾ Ginsenoside Rg₁ induces angiogenesis via non-genomic crosstalk of glucocorticoid receptor and fibroblast growth factor receptor-1⁽¹²⁹⁾ and mediates the microenvironment-dependent endothelial differentiation of human mesenchymal stem cells *in vitro*. Furthermore, ginsenoside Rb₁ protects endothelial cell from damage and stimulates ghrelin expression caused by hyperhomocysteine.⁽¹³⁰⁾ These collective observations indicate that ginseng saponin protects vascular endothelial cells via cellular signaling pathway.

ADVERSE ISSUES

Mastalgia, Vaginal Bleeding and Gynaecomastia

Cell proliferations, induction of estrogen-responsive genes, and isolated cases of adverse reactions such as postmenopausal vaginal bleeding and gynaecomastia have been reported after ginseng treatment. Gray *et al.*

developed estrogen receptor (ER) α and ER β competitive binding assays using recombinant receptors and [³H]-17 β -estradiol to detect phytoestrogens in extracts of Asian ginseng root and the results indicated that root extracts contained substances that bound both receptor isoforms (Fig. 13).⁽¹³¹⁾ A woman developed swollen, tender breasts with diffuse nodularity after taking ginseng powder regularly for 3 weeks, suggest that the preparation may have mild hormonal activity, since small quantities of oestrone, oestradiol and oestriol are present in ginseng root.⁽¹³²⁾ Five women aged between 25 to 40 years who had been taking ginseng for varying periods developed breast symptoms, particularly enlargement of the nipples, they also reported an increase in "sexual responsiveness".⁽¹³³⁾ Ginseng has been reported to raise blood pressure, which may increase bleeding risk. A 72-year-old postmenopausal woman developed vaginal bleeding after administration of 200 mg of ginseng for one month,⁽¹³⁴⁾ and a 44-year-old postmenopausal woman reported vaginal bleeding after using a ginseng face cream.⁽¹³⁵⁾ Therefore, ginseng is best stopped before surgery.

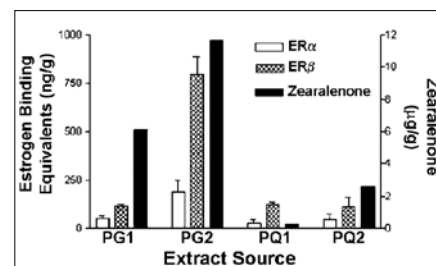


Figure 13. Estrogen binding equivalents of extracts of *P. ginseng* and *P. quinquefolius* from ER α and ER β competitive binding assays and zearalenone concentrations determined by HPLC. [Adapted from Gray *et al.*⁽¹³¹⁾]

Diuretic resistance

It is reported that a 63-year-old man experienced diuretic resistance 10 days after daily administration of 10 to 12 tablets of a germanium-containing ginseng preparation (Uncle Hsu's Korean ginseng). It is concluded that the problem was more likely to be caused by the germanium than the ginseng.⁽¹³⁶⁾

Stevens-Johnson Syndrome

A 27-year-old man experienced typical Stevens-Johnson syndrome (bilateral conjunctivitis, dry cough, a macular rash on his face, painful erosions on his mouth and urogenital mucosa, corneal ulceration and widespread

purpuric macules) 3 days after taking two ginseng tablets a day for 3 days.⁽¹³⁷⁾ The patient stopped aspirin, local antibiotics (amylmetacresol, tyrochricin), and vitamin C 6 days before the onset of Stevens-Johnson syndrome. These drugs have short plasma half-lives or are not absorbed by the intestine; therefore, the authors postulated that ginseng could be responsible for the illness.

Cerebral arteritis

Ryu *et al*, reported that a 28-year-old woman who experienced a severe and explosive headache after ingesting a large quantity of ethanol-extracted ginseng. Cerebral angiograms demonstrated “beading” appearance in the anterior and posterior cerebral and superior cerebellar arteries, consistent with cerebral arteritis. It was concluded that the close temporal association between administration of ginseng and cerebral arteritis indicated a causal relationship.⁽¹³⁸⁾

Psychiatric conditions

A 35-year-old woman with depressive illness who was maintained on lithium carbonate and amitriptyline experienced a manic episode requiring hospital admission 10 days after interrupting her therapy and starting treatment with one tablet of ginseng a day. Her symptoms improved following cessation of ginseng and a return to her previous medication.⁽¹³⁹⁾ It is debatable whether the symptoms were not, at least in part, caused by the cessation of lithium. Five in-patients with diagnoses of schizophrenia were observed to become generally irritable, uncooperative with their treatment programs and overactive with disturbed sleep after smoking ginseng-containing cigarettes. After stopping smoking these cigarettes their behavior was seen to improve.⁽¹⁴⁰⁾

Agranulocytosis

Four non-Chinese patients developed life threatening agranulocytosis while taking Chinese herbal medicines for relief of arthritis and backpain (Long Life Brand Ginseng Hui Sheng Tsaitaowan and Sanlungpai Ginseng Hui Sheng Tsaitaowan; Nan Lien Pharmaceutical Company Ltd. Hong Kong and Taiwan). Subsequent analysis of the herbal preparations revealed the presence of undeclared aminopyrine and phenylbutazone, both of which are known to cause agranulocytosis. The authors conclude that these contaminants were responsible for the observed symptoms in these patients.⁽¹⁴¹⁾

Eye symptoms

Two cases of ginseng adverse effect has been documented that mydriasis and disturbance were noticed on both eyes in accommodation. The systemic symptoms included dizziness and semiconsciousness, which may be related to hyperexcitability of the sympathetic nerves (adrenergic nerves) due to ginseng abuse.⁽¹⁴²⁾

Hypertension

A young man presented to his doctor with hypertension, shortness of breath, dizziness and inability to concentrate. He had been taking ginseng supplements for three years. Following cessation of the ginseng supplements his symptoms improved and did not recur.⁽¹⁴³⁾ A female patient with hypertension, who was receiving no other medication, reported an increase in her blood pressure from between 160/90 and 240/100 to 280/120 mm Hg following treatment with ginseng (Ginzin tablets, Ferrosan) for a few days.⁽¹⁴⁴⁾ Three to four days after cessation of the ginseng product her blood pressure had fallen to 240/100 mm Hg and treatment with a β -blocker was commenced.

Herb-drug Interactions

A 64 year-old woman with depression who ingested *P. ginseng* was reported to experience tremor, insomnia, and headache, which was checked as the results of interactions with phenazine. It was concluded that the ginseng increased cAMP levels, which was mostly responsible for this herb-drug interaction.⁽¹⁴⁵⁾ Another case was documented that a 64-year-old woman with depression developed manic symptoms, hallucinations after taking *P. ginseng* tea and the cause was considered to be same with the previous one, interaction with phenazine.⁽¹⁴⁶⁾

CONCLUSION

P. ginseng is a world-wide popular herbal medicine used for a broad range of indications. Quite a lot of clinical trials and systematic reviews are now available. The obtained conclusions vary but are still encouraging. Future deep clinical research in this area should be concerned with overcoming the methodological limitations of the previous researches.

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A letter to the HK Pharmacy Conference Organizing Committee

Dear Organizing Committee, subcommittee members, performers, singers, musicians, drama crews and helpers,

Every year after the Conference, I often wrote to you saying that it was one of the best Conferences that we had. This year, I have no doubt in saying that it is **the** best Conference I have **ever** had – and trust me, I have seen them all. It is not because I am the Chairman, but because it has been so obviously successful right from the opening until the ending speech, and then everything in between. Its success was evidenced not only by the record participant number of 577, a 34% increase over the last year, but also by the big crowd of people staying right until the end of the second day's plenary session. If it were possible, I would really like to shake everyone's hand and say thank you.

Comfort Zone

About a year ago, I was still struggling whether to take up the Chair of the Conference for 2013. Some of you might not know, I have been declining the job every few years for the past 24 years. Although I used the excuse of being too busy, I was actually afraid to accept the daunting responsibility. I feared that I might ruin the Conference. I would rather stay on back stage to do internal co-ordination, or even stand on the podium as a speaker presenting a topic I felt comfortable with. You see, I was reluctant to leave my comfort zone, just like most of us in daily life and routine work.

But in the end, I said "yes" to the invitation. I was so "brave" because first of all I was going to retire, and indeed I expected myself to be less busy than before. Secondly, I was a little scared that once I left the pharmacy circle, people would forget all about me. But the real driving force was seeing that we now have a large number of young and enthusiastic pharmacists, and students, led by several mature, but still young,

pharmacists doing all the work from planning to execution. I asked myself, "what else should I be worrying about?". So I took advantage of your strength and grab the title of Chairman of the Silver Jubilee Conference. I would be kicking myself today had I not accepted the offer 12 months ago. It is your success that I am capitalizing on. Thank you a whole lot.

Ms Chiang told me a story:

"Come to the edge," we say.

"No, we are afraid,"

"Come to the edge,"

They come. We push. And they fly.

I just realize today that I was the young birds after all these years. The lesson to learn is when you leave your comfort zone, you could really fly, no matter how young or old you are.

The program

The program is the heart of a professional conference, for it is the main purpose for having a conference after all. This year the program subcommittee had tried hard to cater for a diversity of interest. On Day 1 the four speakers gave the audience a sample of innovative services from different countries, ranging from how the pharmacists successfully engaged the government in Singapore, the pioneering Emergency Room (ER) pharmacist service in Australia, the comprehensive pharmacy development in Mainland China, to our own pharmacist's initiatives in helping old age homes locally. The speeches were both informative and inspiring.

The program on Day 2 was literally dazzling. Many felt sorry that they could not hear them all. The therapeutic debates were a new endeavor in Hong Kong. Both the audience and the speakers themselves found it full of fun and flare. Among the nine experts on the stage, they have left no stones unturned with the given therapeutic topics. The

Pediatric series surely quenched the thirst of those interested in clinical pharmacy. The topics were well selected, and so were the speakers.

For those who were interested in technology and pharmacy operation, the sessions on medication reconciliation, e-Drug Management, unit dose dispensing, and decentralized automated system, really opened the eyes of the audience. The lectures on How to Improve Professional Image, and Leadership Lessons were suitable for both the young and the old.

For those who would like to venture out into new services, they have found their interest in the new model for pharmacist's service in China, collaboration between Pharmacist and Dietitian, the contribution of equine hospital pharmacist, case workshop from an ER Pharmacist, advanced primary care service. And to wrap everything up, the workshop on how to plan for a new service has been meaningful.

Lastly, but not the least, the plenary session on pharmacy manpower turned out to be a great success. Although there were no concrete figures coming out on manpower projection for the whole of Hong Kong, the audience were all captivated and deeply moved by the positive and hearty inspiration of the panel and the moderator. It has aptly brought the Conference to a close under a very emotional atmosphere.

The Site Preparation and Performance

People outside of the Organizing Committee (OC) may not be able to imagine the amount of work involved in preparing the non-educational part of the Conference, but certainly we cannot express our appreciation ever enough to the site team, the opening and dinner performance teams, the game and lucky draw teams, and all their helpers. The opening video and the butterfly were

beautifully done. It gave the Conference a good start. Many were glad that the lucky draw was thrilling, especially when the grand prizes were given out. At least everyone went home with something to show their families how fun it was to go to the Conference Dinner this year.

When we first contemplated a musical drama for the Silver Anniversary Conference, some might have doubts. We worried that busy pharmacists like yourselves may have to work very hard to put up a great show, and we know your drama and music directors and producers would not settle for anything less than a grand performance. And our worries were proven to be founded! Indeed you all have been working double, triple hard in planning, practicing and rehearsing for the show. It ached inside me to see some of you looked tired, emaciated, and on the verge of being ill. Paradoxically, despite the exhaustion, you all looked happy and highly energized. In the end the performance was so overwhelming that the audience

felt silent when the sad songs were sung, and excited when the scene was motivating. The loud applause at the end of musical swept away all our earlier doubts that the audience may not be engaged.

The site managers did a wonderful job. Given that their task is to put every bit and piece of the Conference together, and to entertain requests from different organizing teams, speakers and guests, they had to be performing many little miracles that the flow of the Conference was so flawless.

The nuts and bolts, the cogs and wheels

A great team can never be great without a bunch of backend workers who paddle like ducks silently without people noticing them. Our conference secretary, finance manager, treasurer, public relation officers, gimmick coordinator, registration and IT, photographers, our MCs and helpers, you are all the nuts and bolts, the cogs and wheels of

the entire operation. Without you all, everything will fall apart.

When we first started the planning process of the Conference, we met with some operational challenges. Even towards the end of the preparation work, there were many last minute hiccups. Like one of you often said, "The show must go wrong, but the show must go on!" Yes, the show had gone on, and the outcome was marvelous. Like I said in my opening address, I hope this experience of so many people coming together to build such a great conference will not dissipate afterwards, but will meet together in the future to face the challenges we may encounter at work, for the sake of our patients and our profession!

See you all again in the next Conference Organizing Committee!

Michael LING
Chairman
Hong Kong Pharmacy Conference 2013
– Silver Jubilee



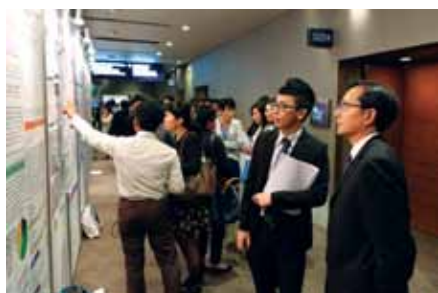
Honourable Guest Dr. KO, Wing Man



Chairman Mr LING, Michael



Workshop conducted by Dr. TAYLOR, Simone



Poster Presentation



Guests were watching the Musical - Pharmtom of the Opera-Action



Dancers on the stage



Opening Ceremony



Hong Kong PharmaCare Orchestra (HKPCO)

[Photos of the Conference are kindly presented and provided by Mr LAU, Michael.]

NEW PRODUCTS

**Brilinta® 90 mg
film-coated tablets**
(AstraZeneca)

Active Ingredient:

Ticagrelor

Presentation:

Each film-coated tablet contains 90 mg ticagrelor.

Pharmacological Properties:

Ticagrelor is a member of the chemical class cyclopentyltriazolopyrimidines (CPTP), which is a selective adenosine diphosphate (ADP) receptor antagonist acting on the P2Y₁₂ ADP-receptor that can prevent ADP-mediated platelet activation and aggregation. Ticagrelor is orally active, and reversibly interacts with the platelet P2Y₁₂ ADP-receptor. Ticagrelor does not interact with the ADP binding site itself, but interacts with platelet P2Y₁₂ ADP-receptor to prevent signal transduction.

Indications:

Ticagrelor, co-administered with acetylsalicylic acid (ASA), is indicated for the prevention of atherothrombotic events in adult patients with Acute Coronary Syndromes (unstable angina, non ST elevation Myocardial Infarction [NSTEMI] or ST elevation Myocardial Infarction [STEMI]); including patients managed medically, and those who are managed with percutaneous coronary intervention (PCI) or coronary artery by-pass grafting (CABG).

Dosage and Administration:

Ticagrelor treatment should be initiated with a single 180 mg loading dose (two tablets of

90 mg) and then continued at 90 mg twice daily. Patients taking ticagrelor should also take ASA daily, unless specifically contraindicated. Following an initial dose of ASA, it should be used with a maintenance dose of ASA of 75-150. Treatment is recommended for up to 12 months unless discontinuation is clinically indicated. In patients with Acute Coronary Syndromes (ACS), premature discontinuation with any antiplatelet therapy, including Ticagrelor, could result in an increased risk of cardiovascular death, or myocardial infarction due to the patient's underlying disease. Therefore, premature discontinuation of treatment should be avoided. Lapses in therapy should also be avoided. A patient who misses a dose should take only one 90 mg tablet (their next dose) at its scheduled time.

Contraindications:

Hypersensitivity to the active substance or to any of the excipients, active pathological bleeding, history of intracranial haemorrhage, moderate to severe hepatic impairment, co-administration of ticagrelor with strong CYP3A4 inhibitors (e.g., ketoconazole, clarithromycin, nefazodone, ritonavir, and atazanavir) is contraindicated, as co-administration may lead to a substantial increase in exposure to ticagrelor.

Precautions:

Patients with a propensity to bleed (e.g. due to recent trauma, recent surgery, coagulation disorders, active or recent gastrointestinal bleeding). The use is contraindicated in patients with active pathological bleeding, in those with a history of

intracranial haemorrhage, and in patients with moderate to severe hepatic impairment.

Patients with concomitant administration of medicinal products that may increase the risk of bleeding (e.g. non-steroidal anti-inflammatory drugs (NSAIDs), oral anticoagulants and/or fibrinolytics) within 24 hours dosing.

Antifibrinolytic therapy (aminocaproic acid or tranexamic acid) and/or recombinant factor VIIa may increase haemostasis.

Patients should be advised to inform physicians and dentists that they are taking this medicine before any surgery is scheduled and before any new medicinal product is taken.

Bradycardic events, more patients had ventricular pauses >3 seconds with ticagrelor than with clopidogrel during the acute phase of their ACS.

Dyspnoea was reported by 13.8% of patients and should be used with caution with history of asthma and/or COPD. If a patient reports new, prolonged or worsened dyspnoea this should be investigated fully and if not tolerated, treatment should be stopped.

Creatinine levels may increase during treatment, renal function should be checked after one month and thereafter according to routine medical practice, paying special attention to patients \geq 75 years, patients with moderate/severe renal impairment and

those receiving concomitant treatment with an ARB.

There is a risk of hyperuricaemia, caution should be exercised when administering in patients with history of hyperuricaemia or gouty arthritis, the use in patients with uric acid nephropathy is discouraged.

Drug Interactions:

Ticagrelor is primarily a CYP3A4 substrate and a mild inhibitor of CYP3A4. Ticagrelor is also a P-gp substrate and a weak P-gp inhibitor and may increase the exposure of P-gp substrates. Co-administration with strong CYP3A4 inhibitors (e.g., ketoconazole, clarithromycin, nefazodone, ritonavir, and atazanavir) is contraindicated. Co-administration with strong CYP3A4 inducers (e.g. rifampicin, dexamethasone, phenytoin, carbamazepine and phenobarbital) is discouraged, as co-administration may lead to a decrease in exposure and efficacy. Co-administration with CYP3A4 substrates with narrow therapeutic indices (i.e., cisapride and ergot alkaloids) is not recommended, as ticagrelor may increase the exposure to these medicinal products. The concomitant use with doses of simvastatin or lovastatin greater than 40 mg is not recommended.

Side Effects:

Dyspnoea, epistaxis, gastrointestinal haemorrhage, dermal bleeding and bruising, intracranial haemorrhage, dizziness, headache, eye haemorrhage, rash, bleeding, vaginal bleeding and others.

Forensic Classification:

P1S1S3

Hong Kong Pharmaceutical Journal: For Detailed Instructions for Authors

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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), μM , 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, μm , mm, cm, m
Literature: lit.
Mass spectrometry: m/z $[\text{M}]^+$ (molecular ion, parent ion)
Melting points: uncorr. (uncorrected)
Molecular mass: Da (daltons), kDa
Molecular weight: M,
Nuclear magnetic resonance: ^1H NMR, ^{13}C 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_1 (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), μl , ml
Weight: wt, pg, ng, μg , mg, g, kg

Inorganics, e.g. AlCl_3 (aluminum chloride), BF_3 (boron trifluoride), Cl, CO_3 , H_2 , HCl, HClO_4 (perchloric acid), HNO_3 , H_2O , H_2O_2 , H_2SO_4 , H_3BO_3 (boric acid), He, KHCO_3 (potassium bicarbonate), KMnO_4 (potassium permanganate), KOH, K-Pi buffer (potassium phosphate buffer), LiAlH_4 (lithium aluminium hydride), Mg^{2+} , MgCl_2 , N_2 , NH_3 , $(\text{NH}_4)_2\text{SO}_4$, Na^+ , NaBH_4

(sodium borohydride), NaCl, NaIO_4 (sodium periodate), NaOH, Na_2SO_3 (sodium sulphite), Na_2SO_4 (sodium sulphate), $\text{Na}_2\text{S}_2\text{O}_3$ (sodium thiosulphate), O_3 , PPI (inorganic phosphate), SO_4^{2-} , Tris (buffer).

Organics, e.g. Ac_2O (acetic anhydride), n-BuOH (butanol), C_6H_6 (benzene), CCl_4 (carbon tetrachloride), CH_2Cl_2 (methylene chloride), CHCl_3 (chloroform), CH_2N_2 (diazomethane), CM (carboxymethyl), DEAE (diethylaminoethyl), DMF (dimethylformamide), DMSO (dimethyl sulphoxide), EDTA (ethylene-diaminetetraacetic acid), Et₂O (diethyl ether), EtOAc (ethyl acetate), EtOH (ethanol), HCO_2H (formic acid), HOAc (acetic acid), iso-PrOH (iso-propanol), Me_2CO (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: CDCl_3 (deutero-chloroform), D_2O , $\text{DMSO-}d_6$ [deuterodimethylsulphoxide not $(\text{CD}_3)_2\text{SO}$], pyridine- d_5 (deuteropyridine), TMS (tetramethylsilane).

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**Proven Evidence in BP Reduction
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Reference 1: Dahlöf B, Sever P, Poulter M, et al. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendidumefibrate as required: in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomized controlled trial. *Lancet*. 2005;365:895-906.

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