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1. Czeizel, Andrew E., et al. "Folate deficiency and folic acid supplementation: the prevention of neural-tube defects and congenital heart defects." *Nutrients* 5.11 (2013): 4760-4775.
2. British National Formulary, Royal Pharmaceutical Society of Great Britain, since 2001
3. 1999年與國家計生委攜手開展「出生缺陷干預工程」，通過懷孕前、出生前的干預措施，預防出生缺陷的發生和嚴重缺陷兒出生為主要目的。

4. 2004 - 2007年，口服「福施福」對預防出生缺陷的療效觀察。
5. 2000年納入為「國家計劃生育委員會科技推薦產品」，亦為同類保健品中唯一推薦產品。
6. 1999年成為「中國優生科學協會」推薦產品。

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- Pharmacy Education & Practice
- OTC & Health
- Medication Safety
- Society Activities
- Drugs & Therapeutics
- Pharmaceutical Techniques & Technology
- Herbal Medicines & Nutraceuticals
- 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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Pilot Programme on Drug Refill Services in Public Hospitals



The Hospital Authority announced on December 14, 2018 the launching of a pilot programme on Drug Refills in Prince of Wales Hospital and Tuen Muen Hospital (page 126). Ms. Anna Lee, Chief Pharmacist (HA) explained that the programme aims to enhance medication safety as elderly patients with chronic diseases are

given prolonged period of drugs in the HA hospitals & clinics. If these elderly patients are admitted to hospitals resulting in change of medications, the bulk of the old medications would be wasted and the remaining drugs can cause a lot of confusion to these elderly patients. Whereas this is a bold step forward for HA to address the drug wastage issue, this seems to contradict the Public Private Partnership direction advocated by the Health Food Bureau and the strengthening of primary healthcare as announced by Chief Executive in her maiden speech. The patients again go back to the hospitals for the refill drugs instead of having their drugs filled in the community pharmacies. The pilot programme will be launched in January 2018, around 20,000 high-risk Medical SOPC patients aged 60 or above have been identified to join the pilot programme. Through this pilot programme, HA will learn about the essential elements required for drug refill prescription and further extend the scope and coverage of the programme after gathering the feedback from patients and professional. I hope that in the near future, the drug refill programme can be extended to the community pharmacies for the benefit of patients and better utilization of community pharmacists.

Pharmacists play an important role in the healthcare system, the education and training programme enable them to take up roles in many different sectors. Most pharmacy graduates in Hong Kong work in the hospitals and community pharmacies. Increasingly, more pharmacy graduates are working in multinational pharmaceutical companies or local manufacturers. In the article on page 127, Fion Cheng, Cherie Chung and Donald Chong wrote about “Students Exposure-Industrial Placements in Multi-National Pharmaceutical Company” and described the scope of work in RA department the multinational pharmaceutical company.

Mandy Chan and Donald Chong wrote an article on “Update on the Safety of Paracetamol” on page 130. Paracetamol – containing products have a long history of use and it is currently the most widely used analgesic and antipyretic for mild to moderate pain control. However its safety has been under considerable debate from time to time. Despite being on the market for about 60 years, it wasn’t until 2009 that FDA required

manufacturers of OTC Tylenol and the generic equivalents to post a warning label for liver damage. Since overdose is very common, the FDA limits the strength of paracetamol in prescription drug products to 325mg per dosage unit. For US OTC products, the Joint Advisory Committee voted to reduce the maximum daily adult OTC dose from 4000mg to 3000mg. Doctors, pharmacists and health workers need to be aware that administration of paracetamol in doses that are thought traditionally to be safe might lead to different toxicities.

On page 137, Tsai Jui Ling, Vincent Wong, Terrence Lau and Cheung Hon Yeung wrote about “Comparison of the constituents and Functions of White and Red Ginseng prepared from *Panax ginseng*”. Ginseng is a medicinal plant widely used for various purposes. It has been used for promoting immunity, neurological function, relief stress, and for prevention of cancer based on its antioxidant activities. The biological effects of ginseng have been observed in people with cancers, diabetes or cardiovascular diseases. *Panax ginseng* C. A. Meyer, is a valuable and important source for both white and red ginseng. The major bioactive components of this herb are ginsenosides, of which about 80 ginsenosides have been identified and isolated. However, the ginseng roots, which are white in nature, could be changed into red whenever it is steam-heated. It has been claimed that they have different effects on human health. In this article, the chemical components and structures, biological effects and pharmacological properties of both white and red ginseng are reviewed.

On page 145, To Ka Wing, Terrence Lau and Cheung Hon Yeung wrote about “*Atractylodes Rhizoma*- Its Phytochemistry, Biological Activities and Medicinal Uses”. *Atractylodes* is a dampness-dispelling medicinal. It is used for indigestion, stomachache, bloating, fluid retention, diarrhea, loss of appetite, weight loss due to cancer, allergies to dust mites, and joint pain (rheumatism).

When combine with other herbs in Traditional Chinese Medicine, it is used for treating lung cancer and complications of dialysis, a mechanical method for “cleaning the blood” when the kidneys have failed.

It is encouraging to read about the activities of the Society of Hospital Pharmacists and the Public Engagement of the pharmacists of the Pharmaceutical Society of Hong Kong from page 149 to 151. Keep up with the Good Work.

Cheng Mary Catherine
Managing Editor
2 January 2018

Prepared by Brian Kan, Tommy Lee

Romosozumab Superior to Alendronate for Fracture Prevention in Postmenopausal Women

Date: October 12, 2017

Bone fracture accompanying osteoporosis is common for the elderly and postmenopausal women. The current first-line therapy for osteoporosis is alendronate. Among the newly developed drugs, romosozumab is a monoclonal antibody against sclerostin. It increases bone formation and reduce resorption.

A phase 3, multicentre, randomized, double-blind trial was carried out to compare the effectiveness of romosozumab and alendronate. 4093 postmenopausal women with osteoporosis and fracture were enrolled and randomly assigned monthly subcutaneous injection of romosozumab (210 mg) and weekly oral alendronate (70 mg) in 1:1 ratio, followed by alendronate treatment for both groups. The primary end points were the cumulative incidences of new vertebral fracture and clinical fracture while secondary end points included the incidences of nonvertebral and hip fracture.

Regarding the primary outcomes, the romosozumab group had 48% and 27% risk reduction in new vertebral and clinical fracture over 24 months than the alendronate group ($P < 0.001$) respectively. For secondary outcomes, the romosozumab group had 19% ($P = 0.04$) and 38% ($P = 0.02$) risk of nonvertebral and hip fracture respectively. Overall adverse events and serious adverse events were balanced between the two groups.

In postmenopausal women with high risk of fracture, romosozumab treatment for 12 months followed by alendronate resulted in a significant risk reduction in fracture than alendronate alone.

Source: www.nejm.org

The Use of Tofacitinib for Psoriatic Arthritis

Date: October 19, 2017

Tofacitinib is an oral Janus kinase inhibitor that is under investigation for the treatment of psoriatic arthritis. This 12-month, double-blind, active-controlled and placebo-controlled, phase 3 trial evaluated tofacitinib in patients with active psoriatic arthritis who previously had an inadequate response to conventional synthetic disease-modifying antirheumatic drugs (DMARDs).

The patients were randomly assigned to the tofacitinib group, adalimumab group and the placebo with a blinded switch to the tofacitinib dose at 3 months. Primary end points were the proportion of patients who had an American College of Rheumatology 20 (ACR20) response ($\geq 20\%$ improvement from baseline in the number of tender and swollen joints and at least three of five other important domains) at month 3 and the change from baseline in the Health Assessment

Questionnaire–Disability Index (HAQ-DI) score (scores range from 0 to 3, with higher scores indicating greater disability) at month 3.

ACR20 response rates at month 3 were 61% in the tofacitinib group, as compared with 33% in the placebo group ($P < 0.001$). The mean change in the HAQ-DI score -0.40 in the tofacitinib group, as compared with -0.18 in the placebo group ($P < 0.001$). The rate of adverse events through month 12 was 71% in the tofacitinib group and 69% in the placebo group. The efficacy of tofacitinib was superior to that of placebo at month 3 in patients with psoriatic arthritis who had previously had an inadequate response to conventional synthetic DMARDs. Adverse events were more frequent with tofacitinib than with placebo.

Source: www.nejm.org

UK MHRA: Severe Respiration Depression Risk with Gabapentin

Date: October 27, 2017

The UK Medicines and Healthcare products Regulatory Agency (MHRA) warned the public about the risk of severe respiratory depression of gabapentin. Gabapentin is used to treat epilepsy and neuropathic pain. The risk of severe depression of gabapentin is now recognized with or without concomitant use with opioids.

The agency recommended amendment of the product information for gabapentin to include warning about breathing problems. Meanwhile, healthcare professionals are advised to be aware of the depressing effect of the gabapentin to the CNS, as well as to consider dose adjustment in high risk patients. Elderly

patients, patients with neurological diseases, renal or respiratory impairment, and patients with concomitant use of CNS depressants are examples of the high-risk patients. Patients are advised to seek medical help in case they experience breathing difficulties.

According to the Drug Office, there are 24 registered pharmaceutical products containing gabapentin, which are all prescription-only. No case of adverse drug reaction related to gabapentin was received locally.

Source: www.drugoffice.gov.hk

The Use of ACEI Inhibitor and Statins in Adolescents with Type 1 Diabetes

Date: November 2, 2017

There is a rapid increase in albumin excretion during puberty among adolescents with type 1 diabetes, which may increase the risk of microalbuminuria and macroalbuminuria, long-term renal and cardiovascular disease. The study hypothesized that adolescents with high levels of albumin excretion might benefit from angiotensin-converting-enzyme (ACE) inhibitors and statins, drugs that have not been fully evaluated in adolescents.

The adolescents with type 1 diabetes were randomly assigned in a placebo-controlled trial of an ACE inhibitor and a statin. The primary outcome was the change in albumin excretion, assessed according to the albumin-to-creatinine ratio (ACR) calculated from three early-morning urine samples obtained every 6 months over

2 to 4 years. Secondary outcomes included the development of microalbuminuria, progression of retinopathy, changes in the glomerular filtration rate, lipid levels, and measures of cardiovascular risk.

The primary outcome was not affected by ACE inhibitor and statin. The use of an ACE inhibitor was associated with a lower incidence of microalbuminuria than the use of placebo; in the context of negative findings for the primary outcome and statistical analysis plan, this lower incidence was not considered significant (hazard ratio, 0.57; 95% confidence interval, 0.35 to 0.94). therefore, the use of ACE inhibitor and statin did not change the ACR over time.

Source: www.nejm.org

The Efficacy of Osimertinib in Untreated EGFR-Mutated Advanced Non-Small-Cell Lung Cancer

Date: November 18, 2017

Osimertinib is an oral and third-generation medication. It is an irreversible epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) that selectively inhibits both EGFR-TKI-sensitizing and EGFR T790M resistance mutations. The

trial compared osimertinib with standard EGFR-TKIs in patients with previously untreated, EGFR mutation-positive advanced non-small-cell lung cancer (NSCLC).

This double-blind, phase 3 trial randomly assigned 556 patients with previously untreated, EGFR mutation-positive advanced NSCLC in a 1:1 ratio to receive either osimertinib (at a dose of 80 mg once daily) or a standard EGFR-TKI (gefitinib at a dose of 250 mg once daily or erlotinib at a dose of 150 mg once daily). The primary end point was investigator-assessed progression-free survival.

The median progression-free survival was significantly longer with osimertinib (18.9 months) than with standard EGFR-TKIs (10.2 months) (hazard ratio for

disease progression or death, 0.46; 95% confidence interval [CI], 0.37 to 0.57; $P < 0.001$). The median duration of response was 17.2 months (95% CI, 13.8 to 22.0) with osimertinib versus 8.5 months (95% CI, 7.3 to 9.8) with standard EGFR-TKIs. Osimertinib showed efficacy superior to that of standard EGFR-TKIs in the first-line treatment of EGFR mutation-positive advanced NSCLC, with a similar safety profile and lower rates of serious adverse events.

Source: www.nejm.org

Fremanezumab as new preventive treatment for chronic migraine

Date: November 30, 2017

Migraine is characterized by recurrent attacks of pulsating headache pain. It can be broadly classified as episodic or chronic. Chronic migraine refers to occurrence of headache of ≥ 15 days each month for ≥ 3 months.

Fremanezumab was recently developed for chronic migraine. It is a humanized IgG2a monoclonal antibody that selectively binds to CGRP. A randomized, double-blind, placebo-controlled, parallel-group trial was conducted to evaluate its effectiveness. 1130 patients with chronic migraine were randomly assigned in a 1:1:1 ratio to receive fremanezumab quarterly (675 mg), fremanezumab monthly (675 mg once plus 225 mg twice), or placebo. The primary end-point was the mean change in the number of headache days per month while secondary end-point included percentage of patients with reduction of $\geq 50\%$ in the number of headache days per month.

The reduction in the number of headache days per month was 4.3 with fremanezumab quarterly, 4.6 with fremanezumab monthly, and 2.5 with placebo ($P < 0.001$ for both vs. placebo). The percentage of patients with a reduction of $\geq 50\%$ in the number of headache days per month was 38% in the fremanezumab-quarterly group, 41% in the fremanezumab-monthly group, and 18% in the placebo group ($P < 0.001$ for both vs. placebo).

Fremanezumab significantly reduces the frequency of headache for patients with chronic migraine. However, long-term durability and safety of fremanezumab require further study.

Source: www.nejm.org

Erenumab as new ways in preventing episodic migraine

Date: November 30, 2017

Migraine is highly impairing and can be classified as episodic and chronic. Episodic migraine is defined as < 15 migraine days or headache days per month. It accounts for $\geq 90\%$ of persons with migraine.

Erenumab was recently developed for episodic migraine. It is a fully humanized monoclonal antibody that inhibits the CGRP receptor. A randomized, double-blind, placebo-controlled, parallel-group trial was conducted to evaluate its effectiveness. 955 migraine patients were enrolled and assigned in 1:1:1 ratio to receive 70 and 140 mg erenumab, and matching placebo. The primary end-point was the mean number of migraine days per month while secondary end-point included the percentage of patients with $\geq 50\%$ in the number of headache days per month.

The number of migraine days was reduced by 3.2 and 3.7 with 70 and 140 mg of erenumab respectively, as compared with 1.8 days for placebo ($P < 0.001$ for each dose vs. placebo). A reduction of $\geq 50\%$ in the number of migraine days per month was achieved for 43.3% and 50.0% of patients with 70 and 140 mg erenumab respectively, as compared with 26.6% for placebo ($P < 0.001$ for each dose vs. placebo).

Erenumab significantly reduces frequency and effect of episodic migraines. However, long-term safety and durability of the effect of erenumab require further study.

Source: www.nejm.org

The Combination Use of Sotagliflozin and Insulin in Type 1 Diabetic Patients

Date: December 14, 2017

In patients with type 1 diabetes, the first line treatment is the use of insulin. In most of the patients, adequate glycemic control is not achieved with monotherapy of insulin. This study investigated the safety and efficacy of sotagliflozin, which is an oral sodium-glucose cotransporter inhibitor, in combination with the insulin therapy for type 1 diabetic patients.

This phase 3, double-blind trial randomly assigned selected patients to receive sotagliflozin (400 mg daily) or placebo for 24 weeks. The primary end point was a glycated hemoglobin level (HbA1c) lower than 7% by week 24, without episodes of severe hypoglycemia or diabetic ketoacidosis. Secondary end point was the change from baseline in weight, systolic blood pressure, and mean daily bolus dose of insulin.

A significantly larger proportion of patients in the sotagliflozin group than in the placebo group achieved the primary end point (28.6% vs. 15.2%, $P < 0.001$). The rate of severe hypoglycemia was similar in the sotagliflozin group and the placebo group (3.0% and 2.4% respectively). The rate of diabetic ketoacidosis was higher in the sotagliflozin group than in the placebo group (3.0% and 0.6% respectively). To conclude, the patients with type 1 diabetes who were receiving insulin, the proportion of patients who achieved a HbA1c lower than 7.0% with no severe hypoglycemia or diabetic ketoacidosis was larger in the group that received sotagliflozin than in the placebo group.

Source: www.nejm.org

Drug Refill Services Launched to Enhance Patient Safety

Date: December 14, 2017

The Hospital Authority announced on Dec 14 the launching of a pilot programme on Drug Refill Services in Prince of Wales Hospital (PWH) and Tuen Mun Hospital (TMH). Ms. Anna Lee, Chief Pharmacist (HA) said that with an ageing population and increase in patients with chronic illnesses, there is the need to address the drug compliance and safety issues associated with polypharmacy. Elderly patients with multiple drugs prescribed for a prolonged period could easily confuse the drugs and the dosage, besides having problems in storing the large quantity of drugs. Elderly patients may also be admitted to hospitals resulting in change of medications. The newly introduced Drug Refill Services, "E-Fill", split prescriptions into smaller and manageable quantities for patients, with pharmacist reviewing and reaffirming the latest condition of the patient before each refill. "Special telephone or face-to-face counselling sessions will also be arranged for patients with complex situations, such as hospital readmission, cross-specialty consultations or when there is a need to adjust the prescriptions," Anna Lee said.

Patients will be reminded by telephone calls or Short Message Service (SMS) three to five days prior to the scheduled refill date, while the medications will be prearranged for the patients to expedite the collection process. Refill medications can be collected by patients or their carers with the "Refill Prescription Coupons" in designated counters of the two hospitals' 24-hour pharmacy department. The pilot programme will be launched in PWH and TMH in January 2018. "Around 20,000 high-risk Medical SOPC patients aged 60 or above have been identified to join the pilot programme. They are typically prescribed with more drug items for an extended period, such as over 16 weeks, until the next refill schedules during their upcoming SOPC consultation sessions.

Anna Lee remarked that the operation workflow and scope of the programme will be refined during the pilot stage taking into account patient and professional feedbacks, with a view to further extending the scope and coverage of the programme to benefit more high-risk patients.

Source www.ha.org.hk/haho

Students' Exposure - Industrial Placements in Multi-National Pharmaceutical Company

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Pharmacists play an important role in the health care system. Pharmacy practice covers a wide range of sectors – hospital, community pharmacy and pharmaceutical industry. As pharmacy students, we would like to explore more in different settings and choose the most suitable field to work on. Among all sectors, industry seems to be more irrelevant to our study because pharmacists can hardly apply their clinical knowledge learnt in school. Despite the misconception, we are still eager to learn from working in industry. This summer, we are very lucky to have a chance working in GSK, a multi-national pharmaceutical company as industrial placement for 6 months. **(Picture 1)**



Picture 1. Left: Fion Cheng; Right: Cherie Chung
We are guided by the mission in GSK: to help people do more, feel better, live longer.

GSK (GlaxoSmithKline) is a science-led global healthcare company. There are two legal entities in Hong Kong. GSK Limited is responsible for the sales of prescription products and vaccines, while GSK Consumer Health (HK) Limited focuses on a series of over-the-counter, skin care, oral care and nutritional products. There are several departments in the company, namely Sales and Marketing, Supply Chain, Regulatory Affairs (RA), Medical Affairs and Quality Assurance.

We are currently working in the RA department of GSK Consumer Health. RA is involved all along in a product life cycle, including but not limited to artwork review, drug registration, promotional material review, handling enquiry from customers or healthcare professionals, risk management and incident handling.

RA also works with different stakeholders in the process. Drug office from the Department of Health (DoH) is the most important external party that RA interacts with. Internally, we collaborate with all the departments mentioned above. During the placement, we have various exposures to understand the functions of RA and even the roles of pharmacist in a pharmaceutical company.

Patients safety must always come first:

One of the core values in GSK is “patient focus”. To do what is right and safe for patients, GSK improves individual well-being through providing new medicines and vaccines to cater for patients' needs. Apart from providing medications with high quality, it is also important to promote safe use of products. Hence, one of the RA roles is to review and ensure precise materials are published, especially the product information and their claims.

As we worked in RA, we experienced the reviewing process within and across teams. Artworks of products such as cartons, labels, blisters and package inserts are often updated and they therefore require RA review. We once checked the original artwork, amended artwork or the final artwork of the package insert. We also examined their consistency, accuracy and legal requirements of the texts and words used. This exposure not only strengthened our knowledge on pharmacy law with respect to the labelling requirements, but also allowed us to gain a practical experience on reviewing and checking. Apart from proofreading the insert, we also need to translate the text from English to Chinese in order to fulfil the legal requirement of bilingual statements shown on OTC products. This enhances our translation skills and reminds us to work with carefulness. **(Picture 2)**



Picture 2. *We experienced how the package insert is created, checked, finalized and submitted.*

Besides artwork management, RA also collaborates with external parties to provide online health information. One of the useful resources accessed by the healthcare professionals is MIMS. To ensure all the product information displayed on is clear and correct, we check and review the content of our products published in MIMS periodically. We have been helping for the reviews and checking for several times, we know more about the direction of use of OTC products and how to present the information in a more precise and simpler way.

Nowadays, there are more educated people who are concerned about their health. They would search and ask healthcare professionals about the medical information. We feel satisfied when our work is published in MIMS because we contributed to deliver the right information to the healthcare professionals. In turn, they can help to give proper advice to patients in selecting and using the products appropriately.

In short, the printed text on the products or promotional materials should be checked carefully. The content should be clear and easy for the public to understand, so it can prevent misuse of products by consumers and reduce the chance of having any harmful consequences. Pharmacist in the RA team is like a gatekeeper. We ensure our products safety and information accuracy before the product is launched in the market. This exposure allowed us to reflect how our work in each step impacts public health as an industrial pharmacist.

Standard operating procedures and risk management to improve efficiency and protect company's property:

Being a multi-national company, it is essential to ensure communication and smooth co-operation between different departments and even with the global team. To facilitate effective communication across countries, local sectors should always follow the standard operating procedures (SOP) published by the company. The SOP does not only schedule some periodic work or checking, it also encourages employees to document their work clearly.

Record keeping and documentation should be performed after each process or procedure. **(Picture 3)** RA team records the submission to DoH, artwork changes and the market status of each product. It is essential to keep updating the product status as it promotes effective discussion on supply and marketing issues during the product meeting. It also allows us to prepare for the product license renewal in advance. Although this action might be just a trivial step, it could allow the tracing of errors when any deficiencies are observed.



Picture 3. Apart from keeping electronic records, we also file the hardcopies of product information, submissions, letters from DoH and artworks.

Moreover, conformance check is one of the risk management performed by RA. It aims to prevent business loss and infringement of regulations. We followed the SOP and helped with self-inspection on actual sales pack. We must be careful in checking with the DoH approved artwork and the existing sales pack and complete the checklist. If there are any discrepancies, we have to document and take corrective and preventive actions (CAPA). **(Picture 4)**



Picture 4. All the products have to do conformance check periodically.

All the record keeping and self-inspection are the tools of risk management. It is crucial to take these actions in order to protect both the employees and the company. We understand that these steps do not only apply in a company but we could also make it as our habit which helps to improve our work performance and prevent mistakes.

Effective communication is a fundamental to success:

Besides communicating with DoH, RA also has to collaborate with many internal parties. In particular, we work closely with marketing since the sales of OTC products count on advertising and marketing campaigns. Sometimes they might want to use some fancy slogans to promote the product. However, there are certain laws and regulations on the advertising of pharmaceutical products that restrict the use of these slogans and claims. RA has an important function to ensure the wordings are appropriate. In view of this, we would hold some workshops for marketing colleagues to acquire basic knowledge of *Undesirable Medical Advertisements Ordinance* (UMAO). Not only did it provide deeper understanding of the law to our colleagues, but it also refresh and strengthen our knowledge learnt in pharmacy law.

Whenever there are global projects or local regulatory changes that require amendments in packaging information of the products, RA and marketing need to approve for the artwork changes mutually. We had a chance to work with marketing colleagues as we had to initiate artwork change of an insert with some update of information. Within the company, we always use email for communication. How can we convey the messages clearly and precisely? How can we express our gratitude towards others? It is more than just a word. Our email writing skills had been improved since we learnt to write in a more humble and polite way. It is also a good experience for us since business etiquette is something we cannot learn in school.

Furthermore, there are monthly meetings for different departments to align their work. We participated in a monthly meeting. As a team player, colleagues have to foresee the regulatory, marketing and supply issues at the same time. This gives us a perspective on how a product is launched with the co-operation of different teams.

The structure of multi-national company:

Working in a multi-national company, there is always a close working relationship between the global and local sectors. When global RA despatches some updates on product information or initiate projects, local RA needs to act accordingly to meet the local regulatory requirements. For example, if global has an update on shelf life of a product, we have to submit change of registered particulars form to DoH. Such submission requires global to provide valid stability data as evidence for the changes. This gives us a holistic view on the structure of a multi-national company and how the global, area and local companies work hand in hand.

Global RA also provides a lot of e-learning resources for local RA to familiar with the regulatory policies. As GSK upholds its core values, it also assigns various legal and ethical learning programmes, such as Anti-bribery and corruption and

Code of Conduct to ensure employees are acting and working with integrity. We are impressed by such practice. Company's core values can serve as a guide for the employees to work accordingly. As a result, the culture of the company is well-established.

Interview with Mr. Deacon Leung:

Apart from our first-hand experience in GSK, we also invited one of the colleagues who is also a pharmacist in GSK, Mr. Deacon Leung, to share his views on being an industrial pharmacist.

Mr. Deacon Leung is a pharmacy graduate from The University of Hong Kong. He had his internship in GSK for 6 months and after being qualified with a pharmacist certification, he has been working as a regulatory affairs associate in GSK for 1 year.

DL: Mr. Deacon Leung **I:** Interviewer

I: What is your main role in the RA team?

DL: I am a regulatory affairs associate. I work with different stakeholders. For example, I usually liaise with DoH, Hospital Authority externally and communicate with GSK global internally. I would also need to co-operate and communicate internally with other teams such as Medical Affairs, Supply Chain and even Quality Assurance.

I: Why did you choose to work in the pharmaceutical industry? What attracts you to work in here instead of working in the hospital or community settings?

DL: During my internship, I had a great experience in GSK. The company culture and working environment made me enjoy working here. That's why I would like to continue my career in this company.

Hospital settings are more stressful and busy due to excessive demand for the public medical system. Hospital pharmacists are also needed to work shift which may affect the work-life balance. Personally, it may not suit my lifestyle so I would still opt for working in pharmaceutical company. As for community pharmacist, I have never had such experience, therefore, I did not consider it after graduation.

I: What major challenges or problems did you face? How did you cope with it?

DL: When I first had my internship at GSK, I was too shy and always afraid of asking questions. However, I have overcome the obstacles as my colleagues are very nice and do give me a lot of help.

Also, I think we can develop problem-solving skills when we have worked for a period of time and gained more experience. When I just started working in GSK, I received an urgent order of a huge number of vaccines by the Hospital Authority (HA) during the flu season. However, there was not enough stock in Hong Kong. Therefore, I tried different ways and eventually fulfilled the order by requesting stock from other GSK companies in different countries.

I: Do you agree that working in industry might not require the pharmacy knowledge learnt from the degree?

DL: Many students may think that pharmacists working in industry is a bit of 'waste' because we cannot fully utilize our clinical knowledge. However, there are a lot of positions which require our professional judgement. For example, Medical Affairs need to read the journals and research studies thoroughly in order to ensure there is valid evidence to support the claims on the products. Evidence-based medicine is an important practice. As a pharmacy student, we would have advantage over others since we know how to analyse and evaluate journals. As for RA, we are more familiar with pharmacy law and the product licensing. Actually, being a successful salesperson also requires certain clinical knowledge. Salespersons need to be equipped with the latest guidelines so that they can persuade the healthcare professionals to use their company's newly developed products.

Although we may not be able to apply as much clinical knowledge as we learnt in school when working in pharmaceutical company, there are still many opportunities that we can demonstrate our added values in those positions.

I: Do you have any tips for pharmacy students who want to work in pharmaceutical industry?

DL: When I was a pharmacy student, I did not have many placement opportunities as you guys have now. So I encourage students who have passion in industry look for these opportunities to gain a comprehensive view of the operation within the company.

Academic results are of importance. Interpersonal skills, good attitude and passion towards your job are also crucial elements you need in a workplace. Even if you may not have a good result, but do not underestimate yourself. Just go to grab every opportunity.

CONCLUSION

In conclusion, it has been a fruitful experience for us to work as a placement in GSK. The exposure in RA show us the value and position of a pharmacist in the pharmaceutical company. It does give us a new perspective on the job nature of an industrial pharmacist. Everything deserves a chance and do not constrain yourself. Grab the opportunity to work in the pharmaceutical industry. You will definitely find that you receive a lot more than you can ever imagine!

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Update on the Safety of Paracetamol

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ABSTRACT

Paracetamol-containing products have a long history and it is currently the most widely used analgesic and antipyretic drug worldwide. However, from the history of paracetamol, the safety has been under considerable debate from time to time. Nowadays, safety concerns also draw the attention of regulatory authorities. Since overdose is very common, the FDA limits the strength of paracetamol in prescription drug products to 325 mg per dosage unit. Healthcare professionals and patients need to be aware that administration of paracetamol in doses that are thought traditionally to be safe might lead to different toxicities. It is important to carefully weigh the benefits and risks of using prescription and OTC pain medicines. Healthcare professionals have the responsibility to counsel the patients and recommend appropriately.

Keywords: safety, overdose, acetaminophen, paracetamol

INTRODUCTION

Paracetamol is one of the most widely used antipyretic and analgesic for mild to moderate pain control. Being first used clinically by von Mering in 1893 and commercialized in the United States and Australia in 1950s, it exhibited a relatively consistent safety profile for normal use. Currently, paracetamol is the first line treatment for pain management and antipyresis in a variety of patients, including children, pregnant women and the elderly. In most countries, it is available both over-the-counter and as a prescribed medicine. However, a major overdose which was complicated by severe liver toxicity has compromised its safety profile despite the fact that early treatment with N-acetylcysteine prevents liver toxicity. Concerns about the safety of paracetamol draw the attention of various parties in relation to the development of liver toxicities and possible effect in the development of asthma and psychiatric disorders. This article provides an overview about efficacy and safety of paracetamol, pathophysiology or rationales of toxicities, the controversies of paracetamol regarding its safety and the role of pharmacists to safeguard the use of paracetamol.

History of paracetamol

Different safety concerns arose in the history of paracetamol starting from the nineteenth century. Paracetamol is the short form of para-acetylamino phenol. In early nineteenth century, German chemists isolated indigo dye from coal tar. The dye was named aniline dye. Like the development of many medicines, acetanilide was found to possess analgesic and antipyretic properties by trial and error process. It became a medicine with the name of Antifebrin in 1886. However, some reports of toxicity, such as cyanosis made scientists search for alternative. A clinical pharmacologist, called Joseph von Mering at University of Strabourg experimentally found paracetamol might be a good alternative to Antifebrin. However, it caused methemoglobinemia in some patients, leading to the disappearance of paracetamol for the next 60 years.⁽¹⁾ In 1947, two researchers at Yale University called David Lester and Leon Greenberg found that large doses of paracetamol given to rats did not result in methemoglobinemia as what Joseph believed. They also found that paracetamol was the breakdown product of acetanilide in human bodies. Finally, paracetamol was marketed in the USA in 1953 and it became the most popular drug by 1980s because of its efficacy and safety profile.⁽²⁾

Role in pain management

Since 1953 when it was marketed in the US, the consumption increased dramatically. Over 3000 million tablets of paracetamol of 500 mg were consumed every year in 1970s.⁽³⁾ Paracetamol is effective when taken at the recommended doses with a better safety profile than non-steroidal anti-inflammatory (NSAID) drugs. Several Cochrane reviews have shown that paracetamol is effective to treat acute pain, such as postoperative pain following the surgical removal of wisdom teeth.⁽⁴⁾

Paracetamol has been placed on all three steps of pain treatment intensity in the WHO analgesic ladder. Being a basic non-opioid analgesic, paracetamol is a weak analgesic together with NSAID or coanalgesics in pains of moderate intensity.⁽⁵⁾ When pain intensity increases, paracetamol is used as an additional analgesic with opioids. It is the first drug of choice to be used for chronic pain, such as osteoarthritis or musculoskeletal pain or when NSAID drugs are contraindicated.

Mechanism of action

Paracetamol was discovered long time ago, but its mechanism of action has not been fully understood. It is thought to mediate the actions via activation of descending serotonergic pathways centrally. Similar to NSAIDs, paracetamol is thought to increase the pain threshold and achieve antipyretic effect by inhibiting prostaglandin synthesis, but paracetamol does not have significant anti-inflammatory or antiplatelet actions. Paracetamol may potentially inhibit nitric oxide pathway mediated by a variety of neurotransmitter receptors and indirect activation of cannabinoid receptors.⁽⁶⁾

Safety concerns of paracetamol

Despite being on the market for about 60 years, it wasn't until 2009 that the FDA required manufacturers of OTC Tylenol and its generic equivalents to post a warning label for liver damage. These labels are often glossed over by consumers who assume OTC medications are safer than prescription drugs.

The FDA is concerned because most people aren't aware that there are more than 600 medicines on the US market that contain the popular painkiller, and it is the leading cause of acute liver failure in the U.S.

Overdose

Worldwide prevalence

Rajanayagam et al have highlighted the large number of children that developed acute liver failure following medication errors with paracetamol.⁽⁷⁾ Doctors will rarely take a full history of medicines that includes OTC medicines and exact dose, frequency of administration and formulation. Parents who have deliberately given their children medicine for symptomatic relief are unlikely to give this information in the history. Researchers identified all cases of acute liver failure from liver transplant registries in France, Greece, Ireland, Italy, the Netherlands, Portugal, and the United Kingdom over a three year period from January 2005 to December 2007.⁽⁸⁾ The results, reported in the British Journal of Clinical Pharmacology, showed that a total of 663 patients were admitted with paracetamol-induced severe liver injury between 1992 and 2008. Over one-sixth (114) were the result of overdoses, 72 of which were intentional, 10 were non-intentional, and 32 were uncertain.⁽⁹⁾

Prevalence in HK

Paracetamol is readily available both in OTC and prescribed preparations. According to the Department of Health, there are 891 registered pharmaceutical products containing paracetamol in 2016. Therefore, overdose is commonly seen. According to the Hong Kong Poison Information Centre, paracetamol is the most commonly overdosed therapeutic agent in Hong Kong in 2014, which accounts for 340 cases and about one-third of the cases required antidote management.⁽¹⁰⁾

Symptoms of overdose

Commonly, patients are asymptomatic for the first 24 hours or have nonspecific abdominal symptoms, such as nausea and

vomiting. Hepatic necrosis begins to develop after 24 hours. Presentations include elevated transaminases, right upper quadrant pain and jaundice. It can progress to acute liver failure. Patients may also develop encephalopathy, oliguria, hypoglycaemia, renal failure after two to three days. Although people who have taken an overdose of paracetamol may not feel unwell in the early stages, it is recommended that anyone who suspects that they have taken an excessive dose, either deliberately or by mistake, should contact a healthcare professional immediately, even if they feel well.

Mechanism of action of liver toxicities

When supratherapeutic or repeated doses of paracetamol are consumed, hepatic storage of glucuronide and sulphate will be depleted, leading to increased formation of N-acetyl-para-benzoquinoneimine (NAPQI), which is usually detoxified by glutathione. Due to the insufficiency of glutathione, NAPQI binds to cytosol proteins, causing liver necrosis.⁽¹¹⁾ Kidney is also susceptible to toxicity when glutathione is depleted. However, studies found that hepatic necrosis after acute overdose may be less common in young children than adults, due to reduced rates of metabolism by CYP450 system and increasing ability to synthesize glutathione.⁽¹²⁾

Threshold for paracetamol toxicity

In adults, ingestion of less than 125 mg/kg is unlikely to lead to hepatotoxicity.⁽¹³⁾ The risk of hepatotoxicity is associated with a sharp dose-dependent rise for higher doses. The threshold for toxicity after acute ingestion may be higher in children, which may relate to different metabolic pathways or their larger relative liver size. The threshold for paracetamol toxicity in children is unclear but is likely to be 150 mg/kg – 200 mg/kg.⁽¹⁴⁾ There is, however, substantial individual variability. In addition, the level of toxicity following repeated doses or chronic administration is even less clear.

Risk factors for paracetamol toxicity

Risk factors for paracetamol toxicity may include protein malnutrition or starvation (particularly in combination with repeated paracetamol dosing), and pre-existing liver diseases. There is little evidence to confirm or refute these risk factors for hepatotoxicity. However there is sufficient doubt to strongly advocate the administration of the lowest possible effective dose of paracetamol for children (10 mg/kg), especially when febrile children with poor intake of food may be administered paracetamol over a period of several days.

Factors that may contribute to unintentional overdose

Factors contributing to unintentional overdose are listed as follows:

1. There are a large number and wide array of OTC and prescription paracetamol products.
2. Patients may take more than the recommended dose because they are seeking additional therapeutic benefit.
3. A specific threshold dose for toxicity has not been established and may not be the same for all people.

4. Victims of unintentional overdose may not be treated within the required timeframe because symptoms of liver damage can take several days to emerge.
5. Patients are not well educated regarding the risk of liver injury with paracetamol.

Treatment of overdose

An overdose of paracetamol can lead to liver failure. However, unlike some other pain relievers, paracetamol has an effective antidote (N-acetylcysteine) which can protect the liver if given within 10-12 hours of overdose and may be effective up to and possibly beyond 24 hours.

Severe Cutaneous Adverse Reactions

A review on medical literature and the FDA Adverse Event Reporting System (FAERS) uncovered 107 cases of Severe Cutaneous Adverse Reactions (SCARs) from 1969 to 2012, resulting in 67 hospitalizations and 12 deaths. Most cases involved single-ingredient acetaminophen products; the cases were categorized as either probable or possible cases associated with acetaminophen. A small number of cases, just over two dozens, are documented in medical literature, with cases involving people of various ages.⁽¹⁵⁾

SCARs include Stevens Johnson Syndrome, toxic epidermal necrolysis, acute generalised exanthematous pustulosis, and erythema multiforme, which can be fatal and include symptoms such as flu-like symptoms, blindness, organ damage, rash and scarring.⁽¹⁶⁾ These reactions can occur when using paracetamol for the first time or at any time during administration, and can be fatal. It is likely that these reactions occur rarely. The risk of all of these side effects increases when people take acetaminophen with alcohol.⁽¹⁷⁾

The Centre for Adverse Reactions Monitoring (CARM) of the New Zealand Medicines and Medical Devices Safety Authority has received four reports of serious skin reactions causally associated with paracetamol in 2012.⁽¹⁸⁾ These included two reports of erythema multiforme, one of toxic epidermal necrolysis and one of Stevens Johnson Syndrome.

Risk of use in infant

Exposure to paracetamol in pregnancy or infancy has been linked with an increased risk of developing asthma. The meta-analysis by Cheelo et al⁽¹⁹⁾ however suggests that this is likely to be due to the effect of respiratory infections, rather than the paracetamol itself. The odds ratio of developing asthma after exposure to paracetamol in infancy, after adjusting for respiratory infections was only 1.06. This suggests that the effect of paracetamol is likely to be minimal.

Risk of use in pregnancy

Severe and persistent pain that is not effectively treated during pregnancy can result in depression, anxiety, and high blood pressure in the mother.⁽²⁰⁾ Medicines including nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, and paracetamol can help treat severe and persistent pain. However, it is important to carefully weigh the benefits and risks of using prescription and OTC pain medicines during pregnancy.

Increased risk of hyperkinetic disorder (HKD) and Attention Deficit and / Hyperactivity Disorder (ADHD)

Paracetamol can cross the placenta barrier. A study conducted in Denmark in 2014 suggests that paracetamol is a hormone disruptor, and abnormal hormonal exposures in pregnancy may influence fetal brain development, increasing the risk for hyperkinetic disorder and ADHD-like behaviors in children.⁽²¹⁾ Children whose mothers used paracetamol during pregnancy were at higher risk for receiving a hospital diagnosis of hyperkinetic disorder, use of ADHD medications, or having ADHD-like behaviors at age 7 years. When women reported having used paracetamol for 20 or more weeks during pregnancy, the risk for hyperkinetic disorder diagnosis in children almost doubled (hazard ratio, 1.84; 95% CI, 1.39-2.45) and the risk for receiving ADHD medication increased by 50% (hazard ratio, 1.53; 95%CI, 1.21-1.94). Stronger associations were observed with use in more than 1 trimester during pregnancy, and exposure response trends were found with increasing frequency of paracetamol use during gestation for all outcomes (i.e., HKD diagnosis, ADHD medication use, and ADHD-like behaviors).

Increased risk of autism

Maternal hormones, such as sex hormones and thyroid hormones, play critical roles in regulating fetal brain development, and it is possible that paracetamol may interrupt brain development by interfering with maternal hormones or via neurotoxicity such as the induction of oxidative stress that can cause neuronal death.^(22,23) Others reported that paracetamol may increase the rate of autism by direct effects on immunological pathways or secondary effects such as impact on blood serotonin, glutathione, or transsulfuration. Antipyretics may suppress normal immunological reaction in the brain, causing autism in some children.⁽²⁴⁾

Increased risk of cryptorchidism

Recent studies suggested that maternal use of paracetamol increases the risk for cryptorchidism (undescended testis) in boys due to its endocrine-disrupting properties.⁽²⁵⁾ Jensen et al found that maternal intake of acetaminophen for more than 4 weeks during pregnancy, especially during the first and second trimesters, may moderately increase the occurrence of cryptorchidism. Exposure to acetaminophen during both the first and second trimesters was associated with increased occurrence of cryptorchidism (HR = 1.33 [95% confidence interval = 1.00-1.77]). Exposure for more than 4 weeks within the postulated time-window of programming testicular descent (gestational weeks 8-14) was associated with a HR of 1.38 (1.05-1.83) for cryptorchidism.⁽²⁶⁾

The views of different regulatory authorities on adult use of paracetamol

Different regulatory authorities reviewed the safety of paracetamol and expressed their concerns from time to time. The considerations of the US, Europe, Australia and England regulatory authorities will be discussed below.

FDA considerations

Regarding the safety concerns of paracetamol, the US Food and Drug Administration (FDA) held a Joint Advisory Committees meeting in 2009. As a result of this meeting, the Advisory Committees made a number of recommendations to the FDA.⁽²⁷⁾ These recommendations are summarized in **Table 1** below.

Table 1. Recommendations of Joint Advisory Committees meeting
For US OTC products, the Joint Advisory Committees voted to: <ul style="list-style-type: none">• Reduce the maximum daily adult OTC dose from 4000 mg to 3,000 mg• Reduce the maximum single adult OTC dose from 1000 mg to 650 mg• Switch the maximum single adult dose (i.e. 2 x 500 mg) from OTC to Rx only• Not limit pack sizes• Maintain the availability of OTC paracetamol combination products
For US Rx products, the Joint Advisory Committees voted to: <ul style="list-style-type: none">• Eliminate Rx paracetamol narcotic combinations• Require "unit-of-use" packages – if Rx combinations continue to be marketed• Implement boxed warnings for Rx paracetamol combination drugs – if Rx combinations continue to be marketed

After considering the recommendations from the Joint Advisory Committees, the FDA mandated drug manufacturers to limit the strength of acetaminophen in prescription drug products, which are predominantly combinations of acetaminophen and opioids in January 2011. This action will limit the amount of acetaminophen in these products to 325 mg per tablet, capsule, or other dosage unit, making these products safer for patients.

In July 2011, McNeil Consumer Healthcare announced that it will voluntarily change dosing instructions for its single-ingredient Extra Strength **TYLENOL®** products (500 mg/tablet) sold in the US. In 2011, the maximum daily dose will be reduced from 4,000 mg to 3,000 mg. Also, the frequency of administration will be every 6 hours instead of every 4-6 hours. McNeil has also stated that these actions are being taken in an attempt to decrease the large number of accidental paracetamol overdosing cases that occur in the US.⁽²⁸⁾

In addition, a boxed warning highlighting the potential for severe liver injury and a warning highlighting the potential for allergic reactions (e.g., swelling of the face, mouth, and throat, difficulty breathing, itching, or rash) are required to be added to the labels of all prescription drug products that contain acetaminophen.

The recommendations of the FDA can help to reduce the risk of severe liver injury and allergic reactions associated with acetaminophen.

OTC products containing acetaminophen are not affected by the above action. However, the regulation requires that acetaminophen-containing OTC products include a warning on the labeling stating that exceeding the maximum daily amount of acetaminophen (currently 4,000 mg) is associated with severe liver damage. This language can be used instead of specifying the maximum number of tablets or dosage units for the product, as has been required. Example of approved statement is: "Liver warning: This product contains acetaminophen. Severe liver damage may occur if you take • more than 4,000 mg of acetaminophen in 24 hours • with other

drugs containing acetaminophen • 3 or more alcoholic drinks every day while using this product."⁽²⁹⁾

EMA considerations

In July 2016, with a request from the Swedish medicines regulator, the Medical Products Agency, the EMA's Pharmacovigilance Risk Assessment Committee will review the benefits and risks of paracetamol modified- and prolonged-release tablets, which are available in several EU Member States.⁽³⁰⁾ The PRAC will evaluate available evidence to determine the risk of overdose with modified- and prolonged-release paracetamol, and whether any additional measures need to be taken. The preliminary result of review will be available in 2017.

TGA considerations

In August 2011, the Therapeutic Goods Administration (TGA) made an announcement in response to the recommended dosage changes to paracetamol-containing products in the US and UK. The TGA has considered these changes and recommends that there should be no change to recommended paracetamol dosing regimens in Australia. Therefore, the recommended paracetamol dosing for adults and children 12 years and over will be kept 500 to 1000 mg every four to six hours as necessary, with a maximum of 4000 mg in any 24 hour period. However, medicines containing paracetamol have the following registration requirements:⁽³¹⁾

- contain clear dosing instructions
- contain warnings for safe use
 - a warning not to take with any other medicine containing paracetamol
 - instructions to patients on what to do in the event of overdose
- stress the risk of paracetamol overdose with clear advice
 - not to take more than eight tablets or capsules per day
 - not to take for longer than a few days without medical advice
- be in child-resistant containers
- be in packs of limited quantity
 - packs containing 21 or more tablets or capsules can only be sold by pharmacies as from 1 September 2013 (previously 26 or more)

The severity of overdose appears to have decreased since the maximum permitted packet size was reduced, with five studies reporting a reduction in the number of severe overdoses (measured by numbers of tablets ingested, serum paracetamol concentrations and usage of antidotes).⁽³²⁾

MHRA considerations

The Medicines and Healthcare products Regulatory Agency mainly concerns about the safe use of paracetamol in pediatric patients. And this will be discussed later in this article.

The views of different regulatory authorities on the pediatric use of paracetamol

Due to different pharmacokinetics and pharmacodynamics properties in pediatric patients, extra caution should be exercised when administering paracetamol to this patient group. The FDA and MHRA both provide clear recommendation on this issue.

Table 2. Past and current regulation regarding OTC paracetamol products		
	Past	Current recommendations
Weight-based dosing for children	Voluntarily made available by some manufacturers	Weight-based dosing is mandatory for all manufacturers
Pediatric indication (fever)	Indicated for fever in children ages 2 years and above (at 10-15 mg/kg dose)	Add fever indication for children 6 months to 2 years of age
Pediatric indication (pain)	Indicated for pain in children ages 2 years and above (at 10-15 mg/kg dose)	
Dosing directions	No specific requirements	The dosing directions in the Drugs Facts label should be provided only in milliliters
Administration	No specific requirements	The product package should include an appropriate dosage delivery device, such as a calibrated and labeled oral syringe or dosing cup
Strengths	Liquid oral dose forms available in multiple strengths	All single-ingredient paracetamol oral liquids should have a concentration of 160mg/5ml The concentrated infant drops will no longer be sold.

FDA recommendations

FDA issued guidance to address ongoing concerns about the potential for acetaminophen overdose associated with these products and to promote their safe use in pediatric patients in 2015. The recommendations are summarized in **table 2**.⁽³³⁾

MHRA recommendations

According to MHRA UK Public Assessment Report, the new dosing recommendations for children's liquid paracetamol products are as follows:⁽³⁴⁾

Infant paracetamol suspension (120 mg/5 ml):

Age	Conditions for treatment	How much to give?	How often (in 24 hours)?
2 – 3 months	1. post-vaccination fever 2 – 3 months 2. Other causes of pain and fever if your baby weighs over 4 kg and was born after 37 weeks	2.5 mL	Usually once. However, if necessary, after 4–6 hours a second 2.5 mL dose may be given
3 – 6 months	Pain and/or fever	2.5ml	4 times
6 – 24 months		5ml	
2 – 4 years		7.5ml	
4 – 6 years		10ml	

Do not give more than four doses in any 24-hour period
Leave at least 4 hours between doses
Do not give this medicine to your child for more than 3 days without speaking to your doctor or pharmacist

Important points relating to pharmacy practice

The relative ease with which paracetamol can be obtained as a nonprescription medicine is believed to be a major factor that accounts for the relatively high incidence of accidental and deliberate overdosage.^(35,36)

Several measures can be taken to reduce incidents of paracetamol poisoning.

1. Paracetamol-containing products are generally classified as OTC preparations to be dispensed at the discretion of the pharmacist unless compounded with active ingredients that have prescription status. Avoid dispensing large quantities unless justified.
2. Paracetamol is considered to be a safe and effective drug only if taken for its intended use and at the recommended therapeutic doses for children and adults. Advise patients never to exceed the stated doses unless under the supervision of a physician.
3. There are several multi-ingredient preparations, such as cold and flu products and compound analgesics that contain paracetamol. Advise patients not to take more

than one product containing paracetamol at any time to avoid the risk of exceeding the recommended daily dose.

4. Paracetamol is also known by the name acetaminophen. This terminology is primarily used in products originating from the United States and Canada. Always inform patients that paracetamol is the same as acetaminophen when dispensing such products.
5. The liver and the kidneys are the major organs in the body that are susceptible to the toxic effects of paracetamol. Products containing paracetamol should be used with caution in patients with impaired hepatic or renal function, dependent on alcohol, or taking medicines that are potentially hepatotoxic.
6. Clinical manifestations of paracetamol toxicity are seen several hours after an accidental or intentional overdose but treatment is more successful if the antidote is administered as soon as possible after ingestion. Always refer a patient with suspected or confirmed paracetamol overdose to hospital for emergency examination and treatment even in the absence of symptoms.

CONCLUSION

Paracetamol products have a long history and are used by billions of consumers each year. After decades of study and over half a century after paracetamol was first made available to the public as an OTC medicine, it remains a safe and critical OTC medicine when used as directed. In most countries, paracetamol can be purchased in retail stores, and it is currently the most widely used analgesic and antipyretic drug worldwide.

However, from the history of paracetamol, the safety has been under considerable debate from time to time. Paracetamol was once disappeared due to safety issues in 18th century. In the 21st century, safety concerns also draw the attention of regulatory authorities. Since overdose is very common due to its relatively high accessibility, the FDA limits the strength of paracetamol in prescription drug products to 325 mg per dosage unit. Some drug makers voluntarily reduced the maximum daily dose from 4,000 mg to 3,000 mg afterwards. Doctors, health workers, pharmacists, and patients need to be aware that administration of paracetamol in doses that are thought traditionally to be safe might lead to different toxicities. Such awareness is particularly important for people who are likely to be at high risk of unintentional paracetamol hepatotoxicity, such as alcoholics. Consumers should be encouraged to carefully read all instructions before using any paracetamol products and consult their healthcare providers if in doubt.

Apart from hepatotoxicity, some safety issues are less well-known. The FDA mandated the addition of a warning highlighting the potential for allergic reactions on the label. It is important to carefully weigh the benefits and risks of using prescription and OTC pain medicines in some vulnerable patients, such as infant and pregnant women. Healthcare professionals have the responsibility to counsel the patients and recommend appropriately after assessing the benefits and risks.

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Questions for Pharmacy Central Continuing Education Committee Program

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

1. FDA limits the strength of paracetamol in prescription drug products to _____ per dosage unit.

- a. 300 mg
- b. 500 mg
- c. 325 mg
- d. 425 mg

2. What are the symptoms of overdose of paracetamol?

- a. Abdominal symptoms
- b. Jaundice
- c. Right upper quadrant pain
- d. All of the above

3. Which organ is susceptible to the damage by paracetamol overdose?

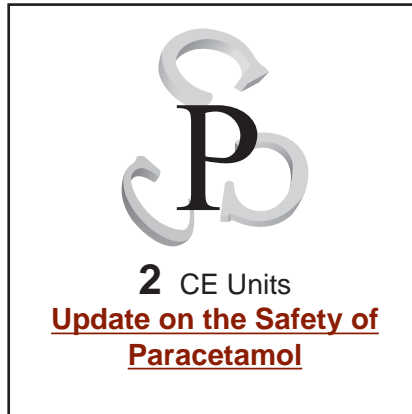
- i. Liver
- ii. Kidney
- iii. Heart
- a. i & ii
- b. i & iii
- c. ii & iii
- d. i & ii & iii

4. What is the threshold for paracetamol toxicity for adult?

- a. 150 mg/kg
- b. 125 mg/kg
- c. 100 mg/kg
- d. No threshold

5. Which of the following is true?

- i. Victims of unintentional overdose may not be treated within the required timeframe because symptoms of liver damage can take several days to emerge
- ii. Paracetamol can cross the placenta barrier
- iii. Patients may take more than the recommended dose because they are seeking additional therapeutic benefit.
- a. iii
- b. ii
- c. i & ii
- d. i & ii & iii



6. What are the risks of use of paracetamol in pregnancy?

- i. Increased risk of hyperkinetic disorder (HKD) and Attention Deficit and / Hyperactivity Disorder (ADHD)
- ii. Increased risk of autism
- iii. Increased risk of cryptorchidism
- a. iii
- b. ii
- c. i & ii
- d. i & ii & iii

7. In 2011, McNeil Consumer Healthcare voluntarily change dosing instructions for its single-ingredient Extra Strength **TYLENOL®** products:

- a. Maximum daily dose was reduced from 4,000 mg to 3,000 mg
- b. Frequency of administration was every 8 hours instead of every 4-6 hours
- c. A boxed warning highlighting the potential for severe kidney injury was added
- d. OTC products containing acetaminophen were affected

8. The maximum dose of paracetamol for infant aged 3 – 6 months for pain or fever is

- a. 60mg BD
- b. 60mg QID
- c. 80mg QID
- d. 80mg BD

9. Joint Advisory Committees meeting voted to

- i. Reduce the maximum daily adult OTC dose from 4000 mg to 3,000 mg
- ii. Reduce the maximum single adult OTC dose from 1000 mg to 650 mg
- iii. Maintain the availability of OTC paracetamol combination products
- a. iii
- b. ii
- c. i & ii
- d. i & ii & iii

10. What are the MHRA new recommendations for children's liquid paracetamol products?

- a. Do not give this medicine to your child for more than 4 days without speaking to your doctor or pharmacist.
- b. Leave at least 6 hours between doses
- c. Do not give more than four doses in any 24-hour period.
- d. 500mg QID paracetamol can be given to children aged 6 year-old

Answers will be released in the next issue of HKPJ.

CE Questions Answer for 243(D&T)

Refresher on Vaccines: Six Facts You Need to Know

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

Comparison of the Constituents and Functions of White and Red Ginseng Prepared from *Panax ginseng*

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ABSTRACT

Ginseng is a medicinal plant widely used for various purposes. It has been used for promoting immunity, neurological function, relief stress, and for prevention of cancer based on its antioxidant activities. The biological effects of ginseng have been observed in people with cancers, diabetes or cardiovascular diseases. *Panax ginseng* C. A. Meyer, also known as Asian ginseng, is a valuable and important source for both white and red ginseng. The major bioactive components of this herb are ginsenosides, of which about 80 ginsenosides have been identified and isolated. However, the ginseng roots, which are white in nature, could be changed into red whenever it is steam-heated. It has been claimed that they have different effects on human health. In this article, the chemical components and structures, biological effects and pharmacological properties of both white and red ginseng are reviewed. Bioactive constituents, such as polysaccharides, ginsenosides, peptides, polyacetylenic alcohols, fatty acids and mineral oils of the white ginseng and red ginseng were compared. Biological activities, including anti-aging activities, anti-diabetic activities, immunoregulatory activities, anti-cancer activities and neuroregulation activities were described and contrasted. Based on the current available data and information, it is concluded that further research studies are necessary in order to fully unveil the differences between these two types of ginseng.

Keywords: *Panax ginseng*, white ginseng, red ginseng, steaming ginseng, ginsenosides, ginseng saponins, polysaccharides, polyacetylenic alcohols, chemical components, biological effects

GENERAL INFORMATION OF THE HERB

Botanical Name: *Panax ginseng* C. A. Meyer;

Family: Araliaceae

Common Names/other Names: (1) White Ginseng; Ginseng Radix; Bai Shen; (2) Red Ginseng; Ginseng Radix et Rhizoma Rubra; Hung Shen; Hunseng; Kao-li-seng. **Other synonyms:** Jenseng; Jenshen; Jinpi, Yuan Shen, Shan Shen, Senti, Lutou, Luwan, Senpian, Senwei, Shenshiu, Minjin, Nhan Sam, Korean ginseng, Yakuyo Ninzin, Five-fingers, Seng, Sang, Tartar root.

Chinese Name: (1) Báisè shēn (白參); (2) hóng shēn (紅參)

Source: Ginseng Radix et Rhizoma Rubra is the steamed, dried root and rhizome of the cultivar of *Panax ginseng* C.A.Meyer (Araliaceae). The root and rhizome are collected in autumn, washed clean, steamed and then dried in the shaded area to obtain Ginseng Radix et Rhizoma Rubra

Part Usually Used: root and rhizoma

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

INTRODUCTION

Ginseng has been known for thousands of years as a cure-all miracle herb. Its multiple health benefits as naturally-occurring adaptogen continues to attract people's daily consumption and scientist's exploratory interest in order to validate its value through various investigating methodologies and instrumental analysis. There have been over 3,000 scientific studies published on Ginseng. Studies have indicated its activities against tumor, infection, neurological disorders, lipid deposition, and fatigue.⁽¹⁻⁴⁾ Experimental studies revealed that ginseng helps the body adapt to stress, protects the body against radiation, and stabilizes blood sugar levels and favorably promote metabolism, neuron functions and the endocrine secretion.⁽⁵⁻⁶⁾ Hence, the Chinese name of ginseng, Ren Shen, which verbally means "Man-Root" because of its human alike shape may imply it's important to health.

Ginseng root is the dried root of *Panax ginseng* C.A. Meyer. If it is a cultivated one, it is called "Yuan Shen" (garden ginseng) and if it is derived from the wild, it is named as "Shan Shen", which means wild ginseng. The main cylindrical part of a ginseng root is called Senti, the rhizomes region is called Lutou, the thin roots and rootlets are called Senwei and Senshiu, respectively, while slide piece of ginseng is known as Senpain.

It has been a long practice in trade whenever cultivated ginseng is sold as native form, it is commonly known as white ginseng (Bai Shen) while steam processed ginseng is called red ginseng (Hung Shen) (**Figure 1**). It is not only that the price of these two form of ginseng is significantly different but also the biological effects were claimed to be vary as well.

The biological effects of ginseng can be different depending upon the species, the way it is prepared, and of course the dose administered. There are two main kinds of

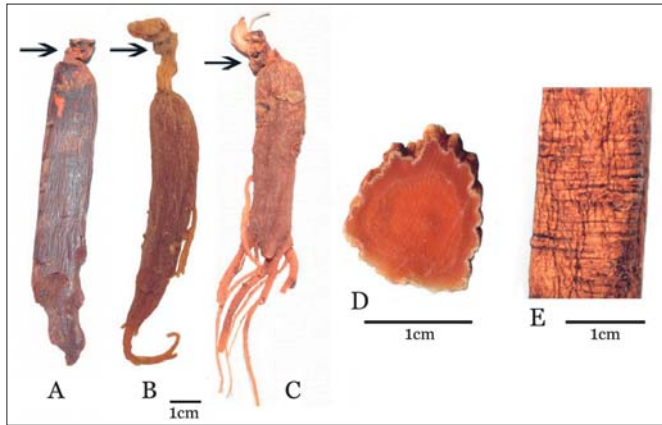


Figure 1. A photograph of Ginseng Radix et Rhizoma Rubra. (A) Ginseng Radix et Rhizoma Rubra (Flat square-columnar root) (B) Ginseng Radix et Rhizoma Rubra (fusiform root) (C) Ginseng Radix et Rhizoma Rubra (cylindrical root) (D) Magnified image of cut surface of root (E) Magnified image of upper part of root (adopted from HKCMMS, Vol.9)⁽⁶³⁾

ginseng commonly available on the market; namely American and Asian ginseng; i.e. *Panax quinquefolius* L. and *P. ginseng* C.A. Meyer, respectively. According to folk medicine, American ginseng has diaphoretic, anti-pyretic and reproduction-facilitating actions while Asian ginseng restores the pulse, reinforces prostration, invigorates the spleen, benefits the lung, promotes the production of body fluid and calms the mind. From a traditional Chinese medical doctor's point of view, it means the former replenishes qi, nourishes yin, clears heat and promotes the production of body fluid; while the later toxifies qi, benefits the lung, dispels summer heat and promotes the production of body fluids. In other words, each of it has different effects but overall speaking, ginseng is frequently labeled to act like steroids for human health.

Ginseng has been characterized by the presence of ginsenosides and gintonin⁽⁷⁻⁹⁾ The ginseng root, in particular, is packed with the most powerful medicinal punch. The roots, which are white in nature, are sometimes treated with steam at about 100°C for two to three hours to preserve them from microbiological spoilage. The result is reddening of the root, producing the so-called "red ginseng". Hence, red ginseng is simply white ginseng modified by heat treatment. The red colour comes about from the caramelization of the sugars in the root due to the heat.^(8,12,13)

Herein, we review the bioactive constituents, structural and pharmacological properties of these two type of ginseng, namely WG and RG, based on the processing conditions of the *P. ginseng* roots.

DESCRIPTION OF WHITE AND RED GINSENG⁽¹⁴⁾

Ginseng is a perennial herb with characteristic branched roots extending from the middle of the main root in the form of a human figure. Stem erect, simple and not branching. Leave verticillate, compound, digitate, leaflets 5, with the 3 terminal leaflets larger than the lateral ones, elliptical or slightly obovate, 4-15 cm long by 2-6.5 cm wide; apex acuminate; base cuneate; margin serrulate or finely bidentate. In general, 1 leaf in the first year with 1 leaflet added annually until the sixth year. Inflorescence a small terminal umbel, hemispherical in early summer. Flowers polygamous, pink. Calyx vaguely 5-toothed. Petals, stamens 5. Fruit a small berry, nearly drupaceous, and

red when ripe in autumn. This product results in two different processing methods, upon the processing method, divide into two different kinds of ginsengs. White ginseng with sun-dried or dried by heat and red ginseng with steaming and drying.^(4, 10)

White Ginseng

White ginseng is the fresh ginseng which has been dried without being heated. It is peeled and dried to reduce the water content to 12 % or less. Drying in the sun may bleach the root to a yellowish-white color. The main root of a WG could be 3-10 cm in length, externally khaki, with blackish brown transverse striations and longitudinal wrinkles, lateral roots thin, fibrous scars. Texture fragile, light, fracture even, white with radial fissures. Odor is fragrant and has a bitter taste.

White ginseng air-dried in the sun may contain less of the therapeutic constituents. Enzymes contained in the root may break down these constituents in the process of drying.

Red Ginseng

Red ginseng, as mentioned above, has been peeled, heated through steaming at standard boiling temperatures of 100°C (212°F), and then dried or sun-dried (**Figure 2**). It is frequently marinated in an herbal brew which turns the roots to extremely brittle.

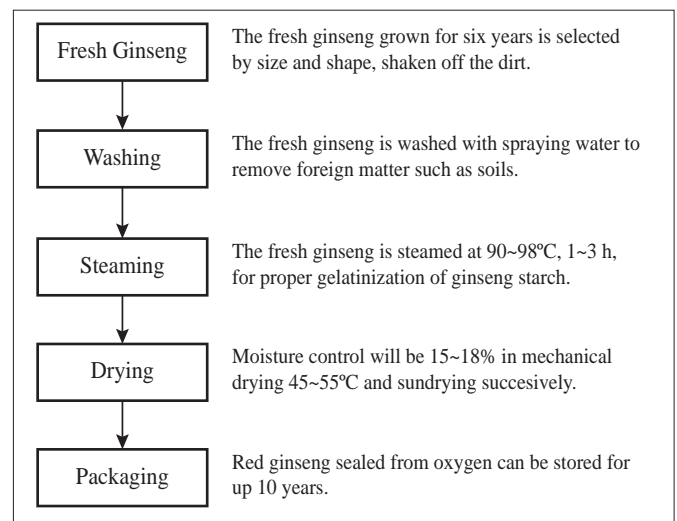


Figure 2. Schematic flow chart of the manufacturing process of red ginseng.

Main roots of a RG is about 5-20 cm in length, 0.7-2 cm in width, externally reddish-brown, translucent, with large transverse striations, indistinct annulations and scars of lateral roots. Rhizomes externally khaki, with circular stem scars 4-6. Texture is hard and fragile, fracture even, horny, reddish-brown, with a pale colored center of the circle. Odor of RG is fragrant and it is slightly bitter.

GENERAL APPEARANCE OF RED GINSENG⁽¹⁴⁾

Main roots fusiform, cylindrical or flat square-columnar, 2-12 cm long, 10-20 mm in diameter. Externally reddish-brown to yellowish-brown, occasionally exhibiting a few dark yellowish-brown patches, with longitudinal fissures, wrinkles and rootlet scars; the upper part sometimes exhibiting interrupted indistinct annulations, the lower part sometimes bearing 2-3 twisted and

intersected branch roots and curved rootlets or just showing remnants of rootlets. Rhizomes 1-2 cm long, showing several impressed-circular stem scars, some bearing 1-2 entire or broken adventitious roots. Texture hard and fragile, fracture flat, cutinized. Odour delicately aromatic; taste sweet at first, then slightly bitter (**Figure 1**).

IDENTIFICATION⁽¹⁴⁾

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 (**Figure 3**).

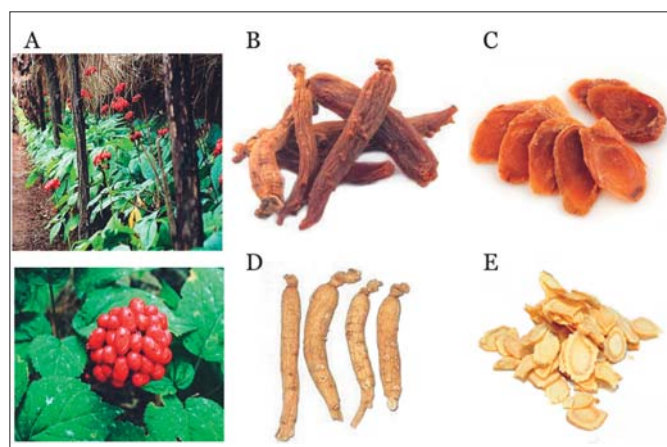


Figure 3. Morphological features of *P. ginseng*. (A) Whole plant photo and its fruits; (B) Red ginseng-fresh root and steaming root; (C) red ginseng slices of *P. ginseng* (D) White ginseng- fresh root and dried root; (E) White ginseng slices of *P. ginseng*.

Microscopic Description⁽¹⁴⁾

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 grain as well as clusters of calcium oxalate (**Figure 4**). The powder is colour yellowish-white. Fragments of resin canals contain yellow or yellowish-brown secretions. Cluster of calcium oxalate numerous, in rosette aggregate, 14-69 μ m in diameter; polychromatic under the polarized microscope. Reticulate vessels and scalariform vessels visible, 15-71 μ m in diameter. Gelatinization starch granules irregular; outline indistinct. Cork cells polygonal in surface view, narrow-rectangular in lateral view, walls thickened (**Figure 5**).

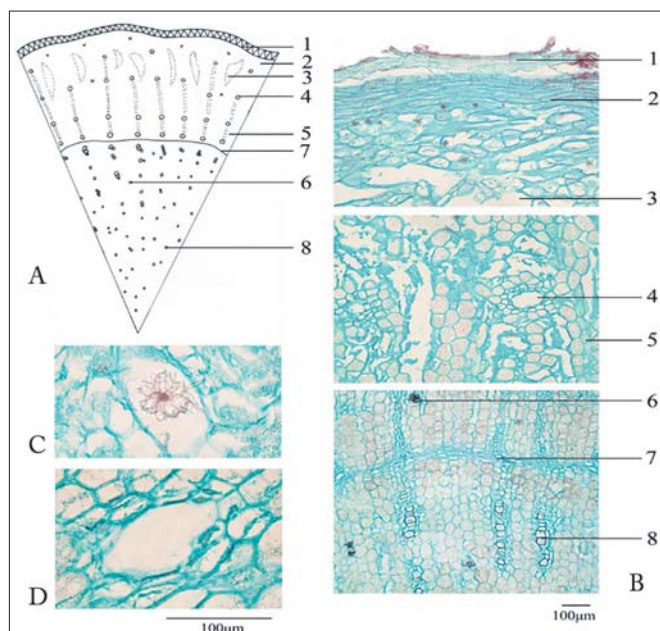


Figure 4. Microscopic features of transverse section of *Ginseng Radix et Rhizoma Rubra*. A = Sketch; B = Section illustration; C = Cluster of calcium oxalate; D = Resin canal; 1. Cork; 2. Cortex; 3. Cleft; 4. Resin canal; 5. Phloem; 6. Cluster of calcium oxalate; 7. Cambium; 8. Xylem (adopted form HKCMMS, Vol.9)⁽⁵³⁾

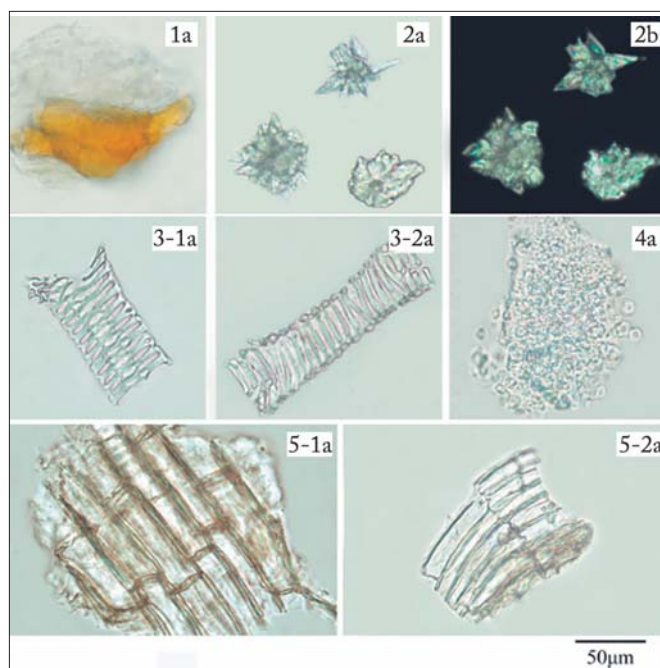


Figure 5. Microscopic features of powder of *Ginseng Radix et Rhizoma Rubra*. 1. Resin canal; 2. Clusters of calcium oxalate; 3. Vessel (3-1a reticulate vessel, 3-2a scalariform vessel); 4. Gelatinized starch granules; 5. Cork cells (5-1a = surface view, 5-2a = lateral view); a: Features under the light microscope; b: Features under the polarized microscope (adopted form HKCMMS, Vol.9)⁽⁵³⁾

CHEMICAL CONSTITUENTS

Scientists in Western countries are still unable to isolate physiologically active constituents from ginseng. Only relatively inert compounds such as oleanolic acid and β -sitosterol, have been identified. Most ginseng saponins are believed to be biosynthesized from 2,3-oxidosqualene, which is also the precursor of β -sitosterol, a steroid commonly found in plants.⁽¹⁴⁾ It has been suggested that the action of three different enzymes

on 2,3-oxidosqualene leads to the formation of cycloartenol, dammarenediol-II, and β -amyrin, the latter two of which are eventually biotransformed into ginseng saponins.^(14,15) Chinese and Russian studies reported a large amount of physiologically active compounds, mostly glycosides are present; unfortunately most of them are not structurally characterized.⁽¹⁴⁾ These include: panaquilon, a glycoside said to stimulate endocrine secretion; panaxin, a reported brain stimulant and cardiovascular tonic; panaxic acid, an "aid" to heart and blood vessels; panacen, an analgetic and tranqumzer; ginsenin, an antidiabetic substance. The identity and physiologic activity of these compounds require verification.^(6,16-18)

However, the major chemical constituents of ginseng are triterpene saponins. More than 30 of them are based on the dammarane structure, and one (ginsenoside Ro) which is derived from oleanolic acid. The dammarane saponins are derivatives of either protopanaxadiol or protopanaxatriol. Members of the former group include ginsenosides Ra1-3, Rb1-3, Rc, Rc2, Rd, Rd2 and Rh2. The main bioactive constituents in white ginseng include ginsenoside Rb1, ginsenoside Ro and ginsenoside Re; while the main bioactive constituents in red ginseng are ginsenoside Rb3 and ginsenoside Rg3 (Figure 6).

On the other hand, apart from common essential primary metabolites, various secondary metabolites related to a variety of biological activities have been identified and isolated from *P. ginseng*. Up till now, more than 80 phytochemicals have been identified from ginseng herbs, which can be divided into phenylethanoid glycosides, flavonoids, iridoids, triterpenoids, polysaccharides, phenolic acids and some other compounds.

Native untreated ginseng, which is produced merely by drying of the fresh ginseng in the sun, contains numerous ginseng saponins and ginsenosides whereas red ginseng (RG) which is a processed product has its ginsenosides partially chemically modified and/or destroyed. Colour is an important index for grading red ginseng. With respect to the color of the red ginseng, its colour formation was found to be influenced by steaming time and drying temperature.⁽¹⁹⁾ It has been reported that after steaming for several hours, the total ginseng saponins were decreased; some ginsenosides (Rg2, 20R—Rg2, Rg3, Rh1 and Rh2) were increased, while others (Rb1, Rb2, Rb3, Rc, Rd, Re, and Rg1) were decreased (Table 1). Overall speaking, the processed red ginseng has been identified to contain more main non-saponin compounds, phenol compounds, acid polysaccharides and polyethylene compounds than the native ginseng.^(20,21)

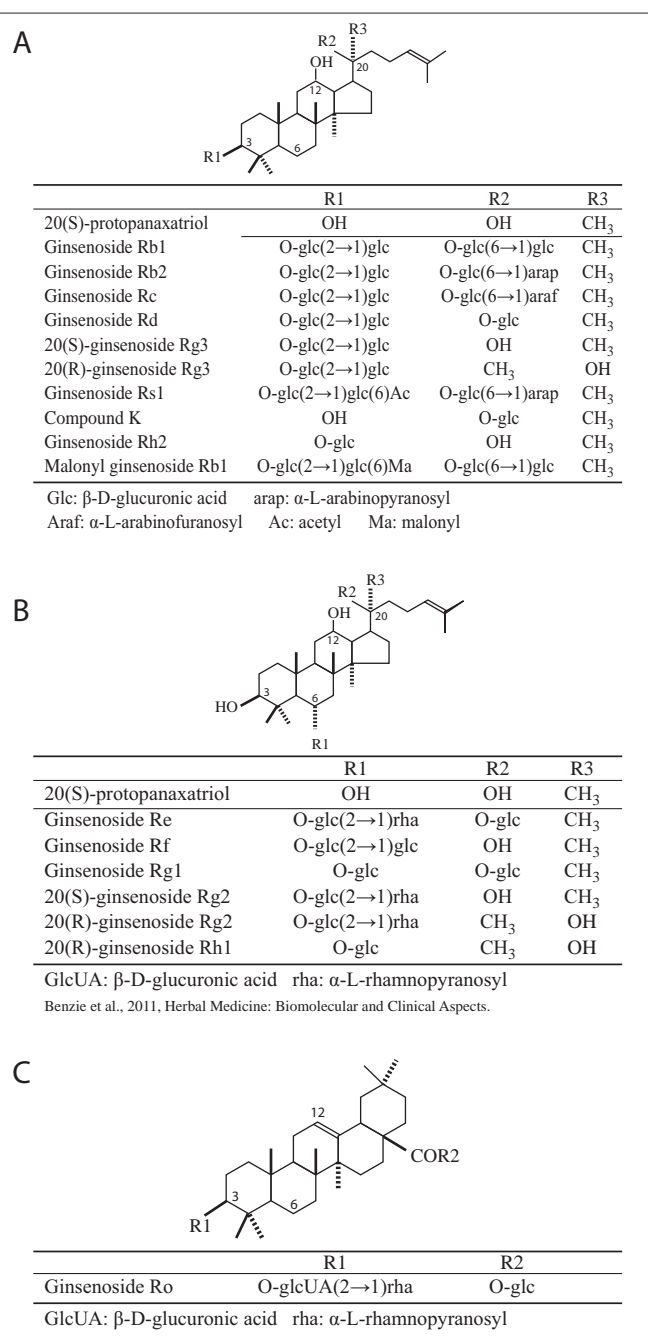


Figure 6. Chemical structure of (a) Protopanaxadiol-type ginsenoside. (b) Protopanaxatriol-type ginsenoside. (c) Oleanane-type ginsenoside

Sample	PPTs (mg/g, RSD%)						PPDs (mg/g, RSD%)					
	Rg1	Re	Rf	Rh1	Rg2(S)	Rg2(R)	Rb1	Rc	Rb2	Rd	Rg3(S)	Rg3(R)
White ginseng ^{a)}	2.01±0.65 (32.5)	1.75±0.75 (42.9)	0.54±0.26 (47.8)	ND	0.13±0.07 (50.5)	ND	2.02±0.72 (35.5)	0.66±0.20 (30.6)	0.63±0.21 (33.3)	0.15±0.08 (53.8)	ND	ND
Red ginseng ^{b)}	3.341±0.98 (29.3)	2.02±0.63 (31.3)	0.78±0.25 (32.3)	0.24±0.12 (50.9)	0.24±0.07 (29.5)	ND	5.80±1.85 (31.9)	1.78±0.56 (31.5)	2.31±1.04 (45.1)	0.44±0.19 (48.8)	0.16±0.04 (25.5)	0.06±0.02 (27.8)
EX of Red ginseng ^{c)}	1.31±1.01 (75.9)	1.35±0.45 (33.5)	0.97±0.14 (14.5)	0.99±0.21 (21.3)	1.09±0.33 (29.8)	0.52±0.19 (36.8)	6.43±1.36 (21.1)	2.58±0.64 (24.9)	2.37±0.57 (24.1)	0.94±0.34 (35.8)	1.87±0.79 (42.2)	0.74±0.30 (40.3)

a) The whole roots of white ginsengs are 6-y-old cultivated in Korea

b) The whole roots of red ginseng are made by traditional manufacturing methods from 6-y-old fresh ginseng cultivated in Korea

c) Red ginseng extracts are collected from several ginseng markets as the products of major ginseng product in Korea. Analyses were performed on HPLC/UV (203 nm) from general analytical method of ginsenosides from KFDA. RSDs are relative standard deviation (n=40)

EX = Extracts; ND = Not Detected

BIOLOGICAL EFFECTS

The WG is said to be less warm than the RG.⁽¹⁰⁻¹²⁾ Many researchers have reported that the steaming process increases the bioactivity of ginseng.^(8,12-13)

Ginseng is a medicinal plant widely used for treatment of various conditions. The pharmacological effects of ginseng have been demonstrated in cancers, diabetes, cardiovascular diseases. Ginseng has been used for promoting immunity, central nervous system (CNS) function, stress relief, and for antioxidant activities.^(22,23) *Panax* is derived from the word "panacea," which means a cure for all diseases and a source of longevity as well as physical strength and resistance. As the use of traditional Chinese herbs for medicinal and dietary purposes becomes increasingly popular in Western countries, sales of *P. ginseng* are increasing in North America and Europe as well as in other parts of the world. The major bioactive components of *P. ginseng* are the ginsenosides, a group of saponins with dammarane triterpenoid structure.^(8-10,19,24-27) The pharmacological and clinical usages of ginseng, particularly ginsenosides, are discussed in relation to its anticancers, antidiabetes, immunomodulatory functions, and improving CNS functions including learning, memory, and neurodegenerative diseases.^(8,18,28)

Antineoplastic and Immunomodulatory Effects

Shibata *et al* demonstrated that production of partially deglycosylated ginsenosides was attributed to the steaming process and metabolic transformation by human intestinal bacteria. The modified compounds have enhanced biological activity, particularly anti-carcinogenic.^(29,30) This is likely attributed to increased bioavailability of the structurally modified ginsenosides as prominent amount of ginsenosides has been detected in red ginseng, such as Rh1, Rh2, Rg3, and Rg5. Rh1 is derived from protopanaxatriol (PPT) ginsenosides, such as Rg1, while Rh2, Rg3, and Rg5 are derived from protopanaxadiol (PPD) ginsenosides.⁽³¹⁾

Other degraded raw ginseng ginsenosides, produced by hydrolysis, isomerization at C-20, and dehydration, are present in relatively minute quantities. Other researchers had indicated that Rg3 inhibits *in vitro* cancer cell invasion and metastasis; Rh2 inhibited human cancer cell growth in nude mice. Rh1, Rh2, Rg3, and Rg5 as the major saponin components in red ginseng. Rg3 and Rg5 were shown to significantly reduce lung tumor incidence, while Rh2 has a tendency to prevent non-organ-specific cancer in humans.⁽³²⁾ Ginsenosides have been shown to exert anti-carcinogenic effects *in vitro* through different mechanisms. Several ginsenosides were reported to cytotoxicity and growth inhibitory of tumor cells²⁰.

Tumor cell growth inhibition and apoptosis

Ginsenoside Rh2 inhibited growth and stimulated melanogenesis,⁽¹⁰⁾ and arrested cell cycle progression at the G₁ stage^(33,34) in B16-BL6 melanoma cells. In association with G₁ arrest, there was a suppression of cyclin-dependent-kinase-2 activity. After oral administration, ginsenosides Rb₁, Rb₂, and Rc are metabolized by intestinal bacteria to a modified

ginsenoside named M1.⁽⁹⁾ Wakabayashi *et al.* reported that M1 inhibited the proliferation of B16-BL6 mouse melanoma cells, and at a higher concentration induced cell death within 24 hours by regulating apoptosis-related proteins.⁽³⁵⁾

It has been reported that Rh₂ either administered orally or injected subcutaneously inhibited the growth of ovarian cancer cells transplanted into nude mice and significantly prolonged the survival times of the mice. Rg₃, whenever administered intravenously or orally, led to a decrease in lung metastasis of B16-BL6 melanoma cells.⁽³⁶⁾ Several studies utilizing medium-term and long-term anti-carcinogenesis models in mice showed that ginseng extracts have a tumor inhibitory effect in mice exposed to chemical carcinogens. Results of a cohort study showed that ginseng consumers had a lower risk for gastric and lung cancer, suggesting that ginseng may have a non-organ-specific anti-carcinogenic effect.⁽²⁹⁾ In order to confirm and validate all these reports, a large-scale, controlled clinical study is necessary.

Antimitogenic activity

Sister chromatids exchange is regarded as a sensitive indicator of DNA damage and significantly correlates with the mutagenic activities of many chemicals.⁽³⁷⁾ Rh₂ significantly suppressed both baseline and induced sister chromatid exchanges in human lymphocytes.⁽³⁸⁾ In addition, ginseng may enhance the proofreading activity of eukaryotic DNA polymerase. Cho *et al.* showed that total ginseng extracts activated both polymerase and exonuclease activities of DNA polymerase δ .⁽³⁹⁾

Differentiation and inhibition of metastasis

In vitro studies demonstrated that Rh₂ and Rh₃ induced differentiation of promyelocytic leukemia HL-60 cells into granulocytes, possibly by modulating PKC isoforms. Total ginseng extract was shown to induce differentiation of cultured Morris hepatoma cells. In addition, Mochizuki *et al.* showed that Rg₃ significantly inhibited the adhesion and invasion of B16-BL6 cells into reconstituted basement membranes, and inhibited pulmonary metastasis.⁽⁴⁰⁾

Immunomodulatory Effects

Immunomodulatory and anticarcinogenic activities of ginsenosides are discussed here. Yun *et al.* following the NK cell activity and the incidence of lung adenoma in mice treated with urethane or benzopyrenes, found that the NK activity of mice once administered ginseng, was depressed for 4–24 weeks and then returned to control levels. Concurrently, in animals treated with ginseng, a lower chance of having lung adenoma was reported.⁽⁴¹⁾

Ginsenoside Rg₁ was shown to increase both humoral and cell-mediated immune responses.^(42,43) The paper reported that spleen cells recovered from ginsenoside-treated mice injected with sheep red cells as an antigen showed a significantly higher plaque-forming response and some hemagglutinating antibody titers.⁽³²⁾ In addition, Rg₁ increased the number of antigen-reactive T helper cells, T lymphocytes, and NK cells.

Reduction of Blood Glucose Level in Diabetes Treatment

There are numerous reports about improvement of diabetic conditions by ginseng root in both humans as well as animal. In animal studies, orally administered ginseng root was found to counteract the effects of high-fructose induced insulin resistance in rats after 4 weeks, to decrease glucose concentrations, as well as to inhibit insulin resistance.⁽⁴⁴⁾ Ethanol extract of ginseng root prevented weight gain, fasting blood glucose, triglyceride and high free fatty acid levels in a high-fat induced hyperglycemia mouse model.^(39,45) Ginsenoside Re reduced blood glucose levels, cholesterol and triglyceride levels as well as reduced oxidative stress in the eye and kidney of diabetic rats.⁽⁴⁶⁾

Clinical studies have revealed that ginseng has the ability to lower blood glucose in diabetic patients.⁽⁴⁷⁾ In some cases, both type II diabetic patients and non-diabetic subjects were reported to be benefited by taking ginseng for stabilizing post-prandial glycemia after meals, suggesting that ginseng may be beneficial to human health. In subjects with gestational diabetes, significant reductions in blood sugar were observed when ginseng was taken 40 minutes before the glucose challenge.⁽⁴⁷⁾ In both clinical and animal studies, ginseng root has been shown to have the ability to improve hyperglycemia in diabetic conditions.

Effects of Ginseng on Neurological Functions and Protection

Ginseng has both stimulatory and inhibitory effects on the CNS, and many modulate neurotransmission. Ginsenosides

Rb1 and Rg1 play a major role in these effects. Results of several animal studies show that Rb₁, Rg₁, and Re prevent scopolamine-induced memory deficits.⁽³⁹⁾ Central cholinergic systems have been implicated in mediating learning and memory processes.⁽⁴⁸⁾ Rb₁ was shown to increase the uptake of choline in central cholinergic nerve endings, and to facilitate the release of acetylcholine from hippocampal slices. Both Rb₁ and Rg₁ appear to partially reverse scopolamine-induced amnesia by increasing cholinergic activity.⁽⁴⁸⁾ Results from these investigations suggest that ginsenosides may facilitate learning and memory and are able to enhance nerve growth. Ginsenosides may also possess the ability to protect neurons from ischemic damage. Rb₁ was shown to rescue hippocampal neurons from lethal ischemic damage and to delay neuronal death from transient forebrain ischemia *in vitro*. In another study, Rg₁ was shown to increase membrane fluidity of cortical cells from 27-month-old rats. Rb₁ increased the fluidity of synaptosomal membranes impaired by FeSO₄-cysteine. Both Rb₁ and Rg₁ significantly decreased the hippocampal [Ca²⁺]_i⁽⁴⁹⁾ level that was found to increase in aged rats.⁽³⁹⁾

As described above, ginseng extracts and several ginsenosides have been shown to possess some anticarcinogenic and immunomodulatory effects.⁽²⁹⁾ It will be interesting to see whether their efficacy can be observed in more double-blind, randomized, placebo-controlled clinical studies. **Table 2** summarizes what have been observed for the differences on the chemical composition, the biological activities and the uses between the white and red ginseng. Based on the currently available data and information, these two types of ginseng are definitely slightly different from each other.

Table 2. Differences on chemical components, biological effects and clinical applications of white and red ginseng

Category	Parameter	Types of Ginseng		References
		White	Red	
Chemical Aspects	Total ginsenosides identified	53	43	58
	Contents of Ginseng saponins	+++	+	
	Contents of Rb1, Rb2, Rb3, Rc, Rd, Re, Rg1	less	increased	59
	Content of Rg2, Rg3, Rh1, Rh2	more	decreased	59
	Malonyl ginsenosides	++	+	
	Decarboxyl malonyl ginsenosides	+	++	
	Glycosylation	++	+	
Biological Effects	Immunomodulatory	+	++	
	Neuroprotective	++	++	
	Antioxidative	+	++	
	Antitumor activities	+	++	
	Hepatoprotective activities	ND	ND	
	Bioavailability / Absorption	±	enhanced	
	Improvement of Spatial and Place - learning	+	++	
Clinical Applications	Production of inflammatory proteins, e.g. NF, iNOs, COX-2, Cytokines	+	+++	54
	Promotion of fatty acid oxidation by activation of AMPK	+	++	55
	Reduction in steroid	uncertain	++	56
	Anti-melanogenesis	+	uncertain	57
	Reduction of stress	++	+	
	Promotion of qi	++	++	
	Anti-aging	++	+++	

ND: Not Determined

CLINICAL APPLICATIONS

Tonifying and replenishing medicinal (Qi-tonifying medicinal)

DOSAGE

Dosages vary with the health stage and duration of administration; usually, 3~10 gm per day on short term use. For improved well-being in debilitated elderly patients, 0.4~0.8 gm of root daily on a continual basis.

ADVERSE ISSUES

Short-term use of red ginseng is considered safe for most people. Side effects do not occur in everyone who takes ginseng but over a long period of administration, the herb may affect human body. The most common side effects of gross overdose with *P. ginseng* may be nausea, vomit, irritability, restlessness, urinary and bowel incontinence and fever. Less common side effects include: menstrual issues, increased heart rate, elevated blood pressure, headache, diarrhea, dizziness and rash.^(24,50)

SAFETY EVALUATIONS / CONTRAINDICATIONS

Being a herbal medicine with a long application history, there are few incident reports relating to the safety of *P. ginseng*. A few undesirable effects relating to individual allergic response have also been described. Hence, some countries restrict the use for both pregnant and breastfeeding women. However, there is no any proven scientific evidences to support this restriction. To date there appears very few contraindications associated with the use of this herb.⁽⁴⁹⁻⁵¹⁾

CONCLUSIONS

Both white and red preparations of *P. ginseng*, are the most commonly used traditional medicine, but there are some differences between them in their ginsenoside contents and pharmacological effects as described above. RG is manufactured when WG is produced by additional steaming and sun drying, and during this process, ginsenosides in native ginseng undergo chemical changes during the manufacturing. Although *P. ginseng*, is widely used as a functional health food for revitalization and eliminating chronic fatigue, and has been used extensively as a dietary supplement in Asia for over 2000 years, further investigations of *P. Ginseng* for accurate comparison of WG and RG on various constituents and functions are still inadequate. Based on the limited data and literature we have found so far, more works are required in order to fully unveil a complete picture of these two different preparation of ginseng.^(39,52,53)

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Author's background

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Atractylodis Rhizoma - Its Phytochemistry, Biological Activities and Medicinal Uses

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Abstract

Atractylodis Rhizoma, also known as Cangzhu, is the dried rhizome of *Atractylodes lancea* (Thunb.) DC. or *Atractylodes chinensis* (DC.) Koidz of the Asteraceae family. The former is a plant indigenous to central China, Japan and Korea while the later to northern China. The knotty-lumpy rhizome of these two plants are used as a medicine. They are dug in spring or autumn and dried. When use the herb is sliced after soaked with water. Due to its high content of atractylodin, which is one of the major volatile oil, atractylodes is used for strengthen digestion, treatment of stomachache, bloating, fluid retention, diarrhea, loss of appetite and weight loss due to cancer, allergies to dust mites and swelling joint pain. When combined with other herbs, it also has anti-lung cancer effect.

Keywords: *Atractylodis Rhizoma*, *Atractylodes lancea* (Thunb.) DC; *Atractylodes chinensis* (DC); phytochemistry, ethnopharmacology, atractylodin, indigestion, anti-diabetes, swelling pain.

GENERAL INFORMATION OF THE HERB

Official Name: *Atractylodes Rhizoma*

Botanical Name: (1) *Atractylodes lancea* (Thunb.) DC; (2) *Atractylodes chinensis* (DC.) Koidz

Family: Compositae

Common Names/Other Names: Maozhu (茅朮), Maocangzhu (茅蒼朮), Nancangzhu (南蒼朮), Beicangzhu (北蒼朮), Red Atractylodes, Swordlike Atractylodes, AMK, ATR, Atractylodis, Atractylenolide, Sojutsu (Japanese)

Chinese Name: 蒼朮 (Cangzhu)

Part Usually Used: rhizome / roots

Common uses: Dampness-dispelling medicinal

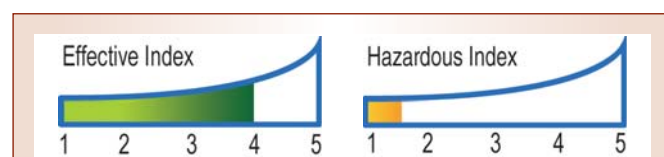
INTRODUCTION

Atractylodis Rhizoma, which is commonly called Cangzhu in Chinese, is a traditional Chinese medicinal herb (Figure 1). It is the root section of the *Atractylodes* species (Figure 1, bottom photos). It was first documented in the book "Shen Long Ben Cao Jing" in around 1 A.D. and was classified as an upper class of herbal medicine. It is a frequently used herb and regarded as a safe, effective and harmless herbal medicine. This herb is the dried rhizome of lance-leafed atractylodis, a plant indigenous grown in northern China. According to the

latest edition of the Chinese Pharmacopoeia, the dried rhizome of two species of atractylodes, namely, *Atractylodes lancea* (Thunb.) DC. (南蒼朮) or *Atractylodes chinensis* (DC.) Koidz (北蒼朮) could be used as the medicine.⁽¹⁾ These two plants are belongs to the same Compositae (Asteraceae) family,⁽¹⁻³⁾ and are commonly found in Eastern Asia.



Figure 1. Photographs of plants of *Atractylode* herbs. *Atractylodes chinensis* Koidz (top left), sketch of *A. lancea* (Thunb.) DC. (top central), magnified flowers of *A. lancea* (top right). **Photos in the bottom row show the appearance of *Atractylode* rhizomes.** The lumpy or nodular-cylindrical rhizome with hairy roots removed of *Atractylodes lancea* (bottom left) and *Atractylodes chinensis* (bottom central left) and slices of the rhizoma (bottom right). 1 = whole plant; 2 = flower; 3 = the rhizome.



Contraindications

It should be avoided by those with internal heat due to yin deficiency and excessive sweating caused by qi deficiency. It may cause an allergic reaction in people who are sensitive to the Asteraceae/Compositae family

Undesirable Effect

The main effective components in atractylodes root is essential oil, which obvious side effects can cause nausea, dry mouth and leave a bad taste in the mouth if it is over used.

Interaction with Conventional Drugs

No report has been identified

The rhizome is collected in spring and autumn with aerial part discarded. It is dried in the sun followed by removal of fibrous roots to obtain medicinal *Atractylodes Rhizoma*. In the past, the root part was not used but it was shown recently that the bioactive components in the root of these plants are basically similar to that in the rhizome. Hence, it may be advisable to use both the root and the rhizome as medicine in order to maximal use of the natural resources and be environmentally friendly.⁽³⁾

DESCRIPTION AND IDENTIFICATION

The two species of *Atractylodes* officially adopted for the source of rhizome are *Atractylodes lancea* (Thunb.) DC. (南蒼朮) or *Atractylodes chinensis* (DC.) Koidz (北蒼朮).^(1,2) Both are dicotyledon plants and grown in the Eastern Asia.

The plant of the *A. lancea* could be found in central China such as Henan, Anhui and Hubei.^(3,4) It usually grows in semi-shaded grass and bushy field. The height of an *A. lancea* plant is about 30-80 cm. Flower of the plant is white in color.⁽⁴⁾ Flowering normally takes place during August to October and the fruiting period is between October and November. Roots and stems of the plant are growing horizontally and the growing pattern is thick and irregular.^(3,4) They have many branches which are about 3-10 cm long and their diameters are about 1-2 cm. Surface of the fresh roots of *A. lancea* is greyish-brown to dark-brown, marked with wrinkle and remains of rootlets or stem scars. Texture of the roots is compact, fracture fibrous-like, pale yellow or greyish-white and scattered with many reddish-brown oil spots. Dried roots may have white fine needle crystals on their surface. The smell is aromatic and quite concentrated but the taste is bitter along with little sweet and pungent.

Growing condition

Atractylodes lancea is usually present in the south of the China. It mainly grows in the shred area, grassland and near the trees. For example, *Liquidambar formosana*, *Platycaryastrobilacea* and *Albizia kolkora*.⁽³⁾ Besides, the growing conditions for *Atractylodes chinensis* are quite similar to those for *Atractylodes lancea*. The major difference is that *Atractylodes chinensis* grows in the north of China.⁽⁵⁾

Morphological Description of *Atractylodes lancea* and *Atractylodes chinensis*

Atractylodes lancea is either irregularly moniliform or nodular-cylindrical. The branches of the plants are about 3-10 cm long and 1-2 cm in diameter. It is externally greyish-brown, wrinkled, and transversely twisted-lined, with remains of rootlets and stem scars or remains of stem attached on apex. It has a compact texture, fracture yellowish-white or greyish-white appearance scattered with many orange-yellow or brownish-red oil cavities and crystallized out as white fine raphides of calcium oxalate after exposure to air for a long time. Besides, the smell and taste are pungent and bitter respectively.⁽¹⁾

Atractylodes chinensis is Knotty-lumpy or nodular-cylindrical. The branches of the plants are 4-9 cm long and 1-4 cm in diameter. It is externally blackish-brown and yellowish-brown when peeled. It has lax texture, fracture scattered with

yellow oil cavities. Besides, the smell and taste are pungent and bitter respectively.⁽¹⁾

Microscopic Identification of *Atractylodes lancea* and *Atractylodes chinensis*

The rhizome of both *Atractylodes lancea* and *Atractylodes chinensis* contains cork, cortex, phloem, Xylem fibers and Xylem.^(5,6) They have the similar microscopic features (**Figure 2**). In *Atractylodes lancea*, the cork has 10-40 layers of cells and it contains 1 or more stone cells bands. It also has one band composed of 2-3 layers of stone cells. *Atractylodes lancea* contains a broad cortex with a few oil ducts. Besides, the phloem is narrow in shape. The phloem pattern of the cell is relatively thin-walled. The oil ducts of phloem are relatively abundant and arranged in several rings. Besides, the xylem is a vessel standing singly or in group pattern but it also has xylem fibers inside.⁽⁶⁾ They are large in portion inside the xylem but the alternate arrangement with vessels can be observed.

In *Atractylodes chinensis*, the cork has 10-40 layers of cells and it contains 1 or more stone cells bands. It also has one band composed of 2-3 layers of stone cells. It contains a broad cortex with a few oil ducts. Besides, the phloem is narrow in shape. The phloem pattern of the cell is relatively thin-walled. The oil ducts of phloem are relatively abundant and arranged in several rings.

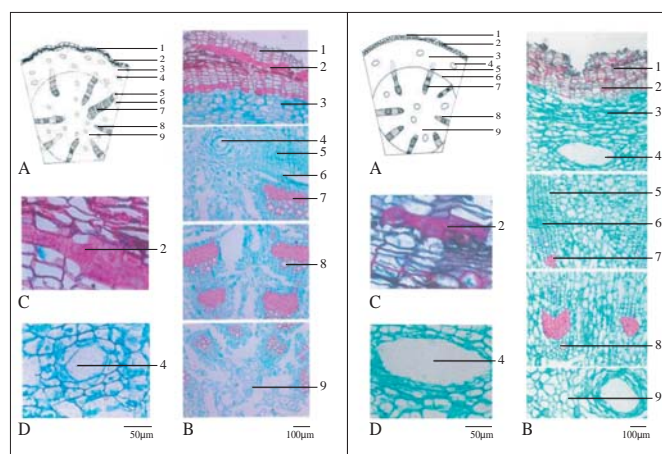


Figure 2. Microscopic features of transverse section of dried rhizome of *Atractylodes lancea* (Thunb.) DC (left photo) and *A. chinensis* DC. (right photo). A: Sketch; B: Section illustration; C: Stone cell band; D: Oil cavity. 1 = cork; 2 = stone cell band; 3 = cortex; 4 = oil cavity; 5 = phloem; 6 = cambium; 7 = fibres; 8 = xylem; 9 = pith.⁽⁶⁾ (adopted from HKCMMS, Vol.4)⁽⁶⁾

Besides, the xylem is a vessel standing singly or in group pattern but it also has xylem fibers inside.⁽¹⁾ It is large in portion inside the xylem but the alternate arrangement with vessels can be observed.

Chemical Identifications

Modern instrumental equipment such as gas chromatographic or high pressure chromatographic techniques are the most commonly used methodologies for the identification and assay of the bioactive compounds in *Atractylodes Rhizoma*. According to a method described in the HKCMMS, a typical HPLC of the methanol extract of these two herbs should give a fingerprint similar to **Figure 3** albeit some differences of peak ratio between these two species.

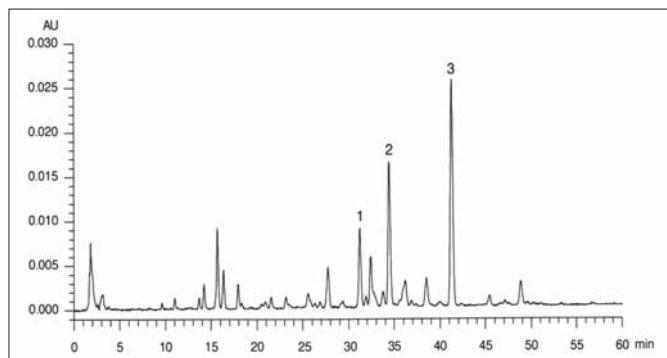


Figure 3. A reference fingerprint HPLC chromatogram of dried rhizome of *Atractylodes lancea* (Thunb.) DC. extract. Peak 3 is atractylodin, which is the referenced marker in this authentication and assay.⁽⁶⁾

BIOACTIVE COMPOUNDS

Essential oil is the major component in the Rhizoma *Atractylodes* but the chemical components between *Atractylodes lancea* and *Atractylodes chinensis* are greatly different.^(6,7) They are used in different situation. The Major component in *Atractylodes lancea* is atractylodin, hinesol, eudesmol, elemol and atractylone.⁽⁷⁻¹¹⁾

The plant nature of *Atractylodes chinensis* is similar to *Atractylodes lancea*, distributed mainly in the north of the China such as Hebei, Gansu and Qinghai. The appearance is similar to *Atractylodes lancea* but Flowering of the plant is different because it normally takes place during July to August and the fruiting period is between August and October.⁽³⁾ The leaf of the plant is oval in shape with the needle edge which is 3-5.5 cm in length and the width is about 1-1.5cm. Their leaves have shiny surfaces which are deep green on the top and pale green at the bottom of the leaf. The smell is quite good but it is not long-lasting and the taste is bitter.⁽¹⁾

Ingredient

Atractylodes rhizoma is frequently used as a traditional Chinese medicine (TCM) for strengthening digestive system, dispelling "wind" and eliminating the pain of eyes due to swelling. Its bioactive components have effects to repel convulsion, anti-inflammation, ease pain, sedation, anti-virus and anti-anoxic.⁽¹²⁾ Although some other species may have similar chemical components, they have different pharmacological properties.

Two species of *Atractylodes*, namely *Atractylodes lancea* (南蒼朮) and *Atractylodes chinensis* (北蒼朮) have been included and listed under the same monograph, different cluster of the main components in these two species were found to be slightly different.⁽⁶⁾ Based on the differences, they should be used with cautious as they have different biological activities.

For *Atractylodes lancea*, it contains volatile oil which is about 5-9% in mass.⁽⁴⁾ The major components in the volatile oil are atractylodin, hinesol, β -eudesmol, elemol, atractylol, β -selinene, 3- β -hydroxyatractylon, atractylodinol and 3- β -hydroxyatractylol.^(5,13) It also contains 9 types of atractyloside which are atractyloside A-I. Besides, *Atractylodes lancea* also contains some heavy metals such as iron, copper, manganese, chromium, molybdenum, barium, cobalt and other heavy metal.⁽⁶⁾

Atractylodes chinensis is another species of *Atractylodes* Rhizoma which contains slightly different component when compared with *Atractylodes lancea*. It contains 3-5% of volatile oil in mass such as atractylodin, hinesol, β -eudesmol, elemol, atractylol.^(1,9,13) Besides, it also contains α - bisabolol and other essential compounds. Besides, it has a small portion of arabinose, glucose, galactose and sucrose.⁽⁴⁾

PHARMACOLOGICAL EFFECTS

Atractylodes Rhizoma has been proved in use for sterilization, stomach and intestinal protection, to prevent damage of the stomach. Nowadays, some research also proved that it has several pharmacological effects such as effect on digestion system, nervous system and anti-oxidant, decrease blood sugar, liver protection and Anti-tumor effect.

Anti-inflammatory

The leaves of the *Atractylodes* Rhizoma can make some drugs which can damage some bacteria such as Group B *Streptococcus*, staphylococcosis, *Streptococcus pneumoniae* or other bacteria. It can inhibit the movement of the bacteria and simply denature them.^(12,14)

Stomach and intestines improvement

When using acetone to extract the *Atractylodes* Rhizoma, some portions of eudesmol and hinesol were obtained stimulating actions of stomach and intestines and alleviates failure in excretion.^(8,11,15,16) However, the alcohol and water extractable components can also inhibit the damage of Duodenum and comfort the stomach. Besides, some researchers found that 60 mg/kg of atractylone can improve the peristaltic motion of intestines.

In fact, *Atractylodes* Rhizoma can have pharmacological effects on ulcers. Some people do researches on pharmacological effects of different sources of *Atractylodes* Rhizoma to deal with ulcer problems by using rats as samples, the result showed that the herbal can increase the rat's weight and inhibit peristaltic motion of intestines. It can also increase the zinc content and decrease the copper content in blood. As a result, it helps the rat to resist the ulcer. Besides, the herbal can also activate the enzymes in stomach. It improves the functions of digestive system.

Decrease blood sugar level

The major function of the *Atractylodes* Rhizoma is the gastrointestinal protection; it decreases the blood sugar level which is the major problem for us. The water extractable components of *Atractylodes* Rhizoma can affect the Zanosar to decrease the blood sugar level in mouse by increasing the Insulin concentration.^(8,17)

Liver improvement

Some of the researches show that *Atractylodes* rhizome can protect the liver. Some evidence showed that when 50 mg/kg of hinesol was injected into the mouse body, the mouse has a special effect which can protect the liver and provides a function of decreasing the enzyme.^(8,11,15,16,18,19) If using the ethyl acetate to extract the *Atractylodes* Rhizoma, it can greatly increase the amount of the gall juice produced.

Anti-tumor effect

Anti-tumor treatment activeness test indicated the volatile oil in *Atractylodis rhizome* can inhibit about 109 kinds of the mouth cancer cells. Some researchers showed that the *Atractylodis Chinensis Rhizoma* contains approximately 100 µg/ml of volatile oil while the *Atractylodis lanceae Rhizoma* contains approximately 100 µg/ml of volatile oil, 100 µg/ml eudesmol and 500 µg/ml of atractylodin. These essential components can contact with the mouth cancer cells for about 24-48 hours when someone intakes *Atractylodis Rhizoma*. This action can produce some special effects on the body such as inhibition of the migration of the cancer cell, cell collapse, decrease in the size of nuclei and ribosome of the cell. As a result, the cell will be damaged.^(11,15,16,18,19)

Anti-anoxic effect

Atractylodis Rhizoma has a portion of β-eudesmol which has anti-anoxic effect. Some of the researches shown that β-eudesmol can increase the life-span of rat when the rat intake the potassium cyanide. Due to decreasing the dead rate, hence, it is believed that β-eudesmol has a strong anti-anoxic effect.^(8,10,20)

Effect on nervous system

β-eudesmol not only have an anti-hypoxia effect, but also have an effect on the nervous system. It is found that β-eudesmol is able to reduce the repetitive stimulation of acetylcholine. β-eudesmol can also enhance the succinylcholine induced to block the muscle nervous system.⁽⁸⁾

Resist the heart rate disorder

In fact, some components of the *Rhizoma Atractylodis* can resist the heart rate disorder. Some researchers showed that the rat injected butanol has adjustment on heart rate.^(8,10)

MEDICINAL APPLICATIONS

Atractylodes is a dampness-dispelling medicinal. It is used for indigestion, stomachache, bloating, fluid retention, diarrhea, loss of appetite, weight loss due to cancer, allergies to dust mites, and joint pain (rheumatism).

When combine with other herbs in Traditional Chinese Medicine (TCM), it is used for treating lung cancer (ninjin-yoei-to) and complications of dialysis, a mechanical method for "cleaning the blood" when the kidneys have failed (shenling baizhu san).

DOSAGE

3~9 gm daily⁽²⁾

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Author's background

Mr. TO Ka-Wing, hold a BSc degree in Chemistry from City University of Hong Kong. This report is based on his final year project under Dr. HY Cheung's supervision as partial fulfillment for graduation from the University. He is now working as an analytical chemistry in industry. **Dr. LAU, Terrence CK** is an associate of City-U. He is now working as an analytical chemistry. **Dr. CHEUNG Hon-Yeung**, who has retired recently was an Associate Professor of Pharmaceutical Microbiology & Biotechnology at the City University of Hong Kong, is a Manufacturing Pharmacist and Biotechnologist. He has more than 400 publications and received many awards for both of his research and academic works.

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SHPHK - Review of the Year 2017

Reported by **Vienna Leung**

Pharmacist of the Society of Hospital Pharmacists of Hong Kong

SHPHK 30th Anniversary Gala Dinner

The 30th Anniversary Gala Dinner of the Society of Hospital Pharmacists of Hong Kong (SHPHK) was successfully held on 18th November 2017 at the Hong Kong Jockey Club, Racecourse.

More than 150 guests and members including our Guest of Honour, Dr. Chui Tak-yi, Under Secretary for Food and Health, and the former and present Presidents of SHPHK joined us in our anniversary celebration!



From left: Dr. Chui Tak-yi, Under Secretary for Food and Health, and Mr. Chui Chun-ming, President of SHPHK.

All the guests were given a SHPHK Memoir as a special anniversary gift. The memoir collects a series of articles written by Mr. Ng Kim-wah and other reputed pharmacists in Hong Kong. It is a must-read for pharmacists who wish to know more about the history of the Hong Kong pharmacy profession.

The 'Opening of Time Capsules' ceremony was definitely one of the highlights of the evening. Wishes made by a group of pharmacists a decade ago were unveiled. The 30th anniversary time capsules full of hopes and wishes from guests were also collected and sealed. These time capsules will be re-opened again at the SHPHK 35th Anniversary Gala Dinner!



Group photo of the former and present Presidents of SHPHK. From left: Mr. Chui Chun-ming, Mr. Ho Kai-wai, Mr. Ling Ho-ming, Mr. Ng Kim-wah and Mr. Lee Shing-cheung.

During the dinner, the winners of the 30th anniversary activities, namely 'Treasure Hunt', 'Photo Competition' and 'Our Future Pharmacists Pearl Election', were presented with their awards. Congratulations to all the awardees!

The Society would like to extend its gratitude and thankfulness to all the SHPHK 30th Anniversary Organising Committee Members for their help in making this event a success!

SHPHK 30th Anniversary Activities: 2017 In Review

April	Movie Night: Beauty and the Beast A micro movie of SHPHK introducing the role of hospital pharmacists was played on a cinema screen for the first time before the start of the movie
	Total Parenteral Nutrition (TPN) Seminar - Part One Local and overseas experts in TPN were invited to share their experience in providing nutrition support to their patients
May	AGM & Antiviral ABC Lecture – AIDS HIV infection specialists of Queen Elizabeth Hospital were invited to deliver a lecture on HIV treatment updates
	Hiking trip A fun day-trip to Lamma Island followed by a delicious seafood dinner in Sai Kung
June	Oncology Symposium Oncology experts of various sectors including hospital, community and industry were invited to discuss the treatment options for chronic myeloid leukaemia, breast cancer and lung cancer
	Photo Competition The photos of the finalists for the two competition categories, 'Curing with Medicine' and 'Caring with Heart' were displayed at the Gala Dinner
July	Diabetes Symposium Consultants in Endocrinology of various health professions were invited to review the clinical needs for new basal insulin analogues for diabetic patients
	Antiviral ABC Lecture – Hepatitis B A leading expert in Hepatology and an experienced pharmacist were invited to discuss the challenges of treating hepatitis B patients who have comorbidities and other advanced diseases
	Treasure Hunt Each team had to follow the instructions given by the organising committee, and complete different tasks at various checkpoints in their shortest possible time
September	Total Parenteral Nutrition Seminar - Part Two Paediatric physician, dietitian and pharmacists were invited to share their views on the standardisation of paediatric parenteral nutrition protocol
	Antiviral ABC Lecture – Hepatitis C Professor in Hepatology and pharmacist of an NGO were invited to give a lecture on the management of hepatitis C virus infection
	'Our Future Pharmacists Pearl' Election An opportunity to recognise our outstanding hospital pharmacists
November	30th Anniversary Gala Dinner The 'Pearl' of the crown event!
December	"Hospital Pharmacist as an Integrated Team Member on the Ward – What can we do?" Seminar Ward pharmacist of the National University Hospital, Singapore, and two local clinical hospital pharmacists were invited to share their experience in performing medication reconciliation for patients and prescribing discharge medicines for doctors.

Looking towards 2018

In 2018, the Society will continue to organise a wide range of seminars and activities to support its members in their professional development. In addition, a number of projects are on-going, for examples, the revamp of the SHPHK website, the development of a drug search mobile app, and the promotional campaign of the DERC website.

If you wish to enjoy the full benefits of SHPHK, now is the best time to join us as a member! Good news! Any Hong Kong registered hospital pharmacist who subscribes to the 3-year SHPHK membership package in 2018 will be offered a FREE 3-year LEXICOMP account, on a first-come-first-served basis. Do not miss this great opportunity to get your FREE LEXICOMP account!

As we come to the end of another year, the Society would like to sincerely thank the SHPHK General Committee Members for serving the Society tirelessly all year round, and our members for their continuous support to the Society!

We wish you all a fabulous holiday season and a happy, healthy and prosperous year ahead!

You are most welcome to follow the Society's Facebook page (@SHPHK) to know more about the Society's development and activities. You may also visit the Drug Education Resources (DERC) Website: www.derc.org.hk to learn more about the latest development of drugs in Hong Kong.

Public Engagement of Pharmacists and Pharmacy Students

Reported by **Livia Ngai**

Pharmacist, *The Pharmaceutical Society of Hong Kong*

Pharmacists are part of the health care team to ensure quality pharmaceutical care of patients. Our roles are not limited in medication therapy, but also in disease prevention and health promotion. To increase the awareness and understanding of pharmacists' roles by the general public and other health professionals, the Pharmaceutical Society of Hong Kong (PSHK) has been actively engaging in public educational activities:

Pharmacy Home Visit Outreach

The Young Pharmacist and Student Chapter (YP&SC) of PSHK has formed an outreach team since 2016 summer and started the first outreach in March 2017. Up to the end of 2017, we have already organised 6 outreach sessions and visited more than 150 elders in the community. The aim of our outreach is to identify the drug-related problems of elders so that any manifest or potential adverse drug events and suboptimal treatment can be solved or prevented early on.

It was identified that half of our participants had at least one drug-related problems (DRPs). Patient-related factors were the most prominent cause of the identified DRPs, including the practice of keeping old stock or expired drugs which were put together with the new drugs (**Figure 1**), and keeping different drugs in the same box (**Figure 2**). Low medication adherence was also common, due to patient's forgetfulness or intended under-administration. These factors could lead to suboptimal treatment effectiveness and adverse drug events. Therefore, our outreach pharmacists provided interventions such as counselling and adherence tools to help them solve the problems. More follow-up outreach activities will be carried out in the coming year to demonstrate the outcome of pharmacist home visit interventions.



Figure 1



Figure 2

Public talk

To raise public awareness on disease prevention and medication management, health education is also very important. From September to December, we delivered four public talks with topics on pain management, and osteoporosis and osteoarthritis. Our audience consisted of general public, teachers, elderly and also volunteer elderly caregivers, as we believe that public talk is not just about educating the ill patients, but also empowering the laymen to spread the knowledge of health promotion and create a healthy atmosphere among their community.



Public talk on low back pain in Central Library



Talk on Osteoporosis and Osteoarthritis to volunteers

Mini-pharm exhibition

Not only the laymen, we noticed that very often our roles are not well recognised by fellow health professionals. To increase the understanding of pharmacists' work in different sectors, our young pharmacists and pharmacy students organised two mini exhibitions in CUHK and HKU respectively for the future health professionals. Students from various departments, especially those from the faculty of medicine came and participated in the games and demonstrations, such as clinical case sharing and over-the-counter product counselling by community pharmacists. They surely had fun learning about pharmacists' various roles, and enjoying the pop corns and cotton candy as reward!



Exhibition in HKU Medical Campus



Exhibition in CUHK main campus

PSHK will continue our effort to engage in public educational and promotional activities. If you also wish to participate and contribute as a team, join us as our member now and like us on Facebook@pshongkong!

PSHK AGM and Annual Dinner 2017

PSHK AGM and Annual Dinner 2017 was held on 16th December 2017 at the Headquarters of the Pharmaceutical Society of Hong Kong at Room 1302, Rightful Centre, 12 Tak Hing Street, Jordan, Hong Kong at 5:00p.m.

General Council Members elected for 2018 are as follows:

President	Ms. Scarlett PONG, BBS, JP			
Vice Presidents	Mr. Philip CHIU	Mr. Dick SUNG		
Hon. Secretary	Mr. Edward YAU			
Hon. Treasurer	Mr. Paul LAM			
Council Members	Ms. Leng Leng CHEW	Mr. Chris LEE	Ms. Beverley TAM	Mr. WONG Chi Ming
	Ms. Cecilia CHOI	Mr. Peter SUEN	Ms. Sandra TSANG	
Pharmacy & Poisons Board Members	Mrs. Mary Catherine CHENG		Mr. Matthew WONG (from Aug 2018)	
	Ms. Sau Chu CHIANG (till Aug 2018)		Mr. Rico YAU	

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許冠文



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- 🏆 有效延遲傳統針劑治療^{3b}
- 🏆 有助控制指標^{4a}



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達5.7年(中位數達3年)，研究顯示不會增加心血管疾病風險(HR=0.98, p<0.001)，並較少需要開始某種傳統針劑的長期治療(HR=0.70, p<0.001)

*與同類型口服產品比較^{1,2}

重要信息: JANUVIA 健諾胰^a不適用於對其成份過敏及某些人士(詳情請向醫生查詢)。服用後有機會引起過敏反應(可能很嚴重)。假如出現過敏反應如呼吸或吞嚥困難，應立即停止服用並盡快與醫生聯絡。醫生處方時可能會跟其他藥物一起處方，如有腎臟問題，可能會減少處方劑量。使用後(單獨及/或與其他同類藥物一起使用)後曾經發現的副作用包括過敏反應、胰臟發炎、腎臟問題(或需洗腎)、上呼吸道感染、鼻塞、流鼻涕和喉嚨痛、便秘、嘔吐、頭痛、關節痛、肌肉痛、四肢痛、背痛、痕癢。JANUVIA 健諾胰^a、JANUMET 康諾胰^a及 JANUMET XR 康諾胰XR^a為醫生處方藥物，使用前須遵從醫生之專業意見，並需配合適當的飲食和運動，詳細請閱讀盒內說明。

資料來源: 1. Global IMS data of DPP-IV Inhibitor (MAT Dec 2007- MAT Mar 2017). 2. Hong Kong IMS data of DPP-IV Inhibitor (MAT 2006 - MAT 2017).

3. Green JB, Bethel MA, Armstrong PW, et al. N Engl J Med. 2015;373(3):232-242. 4. Hong Kong Product Circular (Januvia, MSD).

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