HONG KONG PHARMACEUTICAL JOURNAL

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

LIPITOR®

atorvastatin calcium – crystalline form

Power to do more

More Evidence across More Patient Types

Moderate Risk

Hypertension

36% RRR

of nonfatal MI + fatal CHD in patients with hypertension ($p=0.0005$)[1]

Diabetes

37% RRR

time to first occurrence of major CV events in patients with diabetes ($p=0.0005$)[2]

High Risk

CHD

59% RRR

of nonfatal MI in patients with CHD ($p=0.0001$)[3]

CHD

22% additional RRR

of major CV events in patients with CHD ($p<0.001$)[4]

Highest Risk

ACS

16% RRR

of major CV events in patients with ACS ($p=0.005$)[5]

References: 1. Sever PS, Dahlöf B, Poulter nR, et al; for the ASCOT investigators. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial-lipid lowering Arm (ASCOT-lA): a multicentre randomised controlled trial. Lancet. 2003;361(9364):1149-1158. **2.** Colhoun hm, Betteridge DJ, Durrington Pn, et al; on behalf of the CARDS investigators. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. Lancet. 2004;364(9435):685-696. **3.** Athyros VG, Papageorgiou AA, mercouris BR, et al. Treatment with atorvastatin to the national Cholesterol education Program goal versus 'usual' care in secondary coronary heart disease prevention: the GReek Atorvastatin and Coronary-heart-disease evaluation (GREACe) study. Curr Med Res Opin. 2002;18(4):220-228. **4.** laRosa JC, Grundy Sm, waters DD, et al; for the Treating to new Targets (TnT) investigators intensive lipid lowering with atorvastatin in patients with stable coronary disease. N Engl J Med. 2005;352(14):1425-1435. **5.** Cannon CP, Braunwald e, mcCabe Ch, et al; for the Pravastatin or Atorvastatin evaluation and infection Therapy-Thrombolysis in myocardial infarction 22 investigators intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med. 2004;350(15):1495-1504. **Detailed information is available upon request.**

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INSTRUCTIONS FOR AUTHORS

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

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

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

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

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

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

Editorial

News & Short Communications

Pharmacy Education & Practice

Drugs & Therapeutics

Over-the-Counter & Health

Herbal Medicines & Nutraceuticals

Society Activities

New Products

The advancement and new breakthroughs could only be made if we think hard, plan carefully, work together and dare to try.

On 1 July 2012, Mr. Leung Chun-Ying become the new Chief Executive of Hong Kong and Dr. Ko Wing Man become the new Secretary for Food and Health. On 4 July 2012, when asked by the reporter on the priorities of his work in this term of government, Dr. Ko Wing-man said that there are many priorities in the areas of food and health. A more important issue will be to ensure the **long-term sustainable development of the dual-tracked healthcare services of Hong Kong, which is the private/public healthcare system.** More urgent matters are the long waiting time for patient consultation and manpower pressure in public hospitals.

We know that with the low fees charged by the public hospitals, it would be very difficult to divert patients of low and middle class income to the private sectors unless there is a major policy change. With the long waiting time in the public hospital, it is necessary for the Hospital Authority to think of some innovative measures to divert patients from public services to private sectors. A group of patients that come to my mind is the Elderly residing in Residential Care Homes for the Elderly (RCHEs). These patients are usually on multiple drugs and may require consultation by several specialists. Instead of sending these elderly patients to public hospitals and clinics, can private organizations be engaged to provide the medical and drug dispensing/ pre-packing services? It is worthwhile to start a pilot scheme to find out the best measures to transfer public health service to private sectors. It was also announced recently that the elders with moderate impairment will each have a single value voucher worth $5,000 per month, with the Government contributing $2,500 to $4,500. More complex features may be introduced in the second phase. The Government hopes that with this increase amount of the voucher, the elderly can actually build up a continuous relationship with the service provider in the community of their own choice. In doing so, it was hope that the use of private health care services can alleviate partially the pressure on the public health care system. In order to relieve the pressure in public hospitals, automation in dispensing of drugs could be the solution. I have recently attended the Forbidden City Forum in Beijing and learnt that a few leading hospitals in China have purchased the automatic dispensing machines to relieve the high workload of dispensing services in the Pharmacy. I can envisage the benefit of automation in our public hospitals. **The advancement and new breakthroughs could only be made if we think hard, plan carefully, work together and dare to try.**

Coming back to the Hong Kong Pharmaceutical Journal, I welcome Dr. Esther Chan and Ms. Phoebe Chan to join in as section editors, and Dr. Alan Worsley to join as advisor of the Editorial Board. They are currently the teaching staff at HKU and their presence will definitely bring new stamina to the Editorial Committee. Chong & Hui wrote about coaching for pharmacists. Coaching is one way to develop new skills and competencies and is becoming more popular due to the benefits it brings to personal and organizational development. Several health fields have reported the application of coaching in developing healthcare professionals. The article will highlight some of the effective coaching techniques. (**Page 56**).

Other than coaching, participation in international conferences and forums is another way for pharmacists to broaden their view. Representatives from the Pharmaceutical Society of Hong Kong attended the Forbidden City Forum in Beijing in May 2012 to exchange knowledge and experience with China. Anabelle Wong, a CUHK student wrote about her rewarding experience during the Forum in Beijing (**Page 85**).

The Food and Drug Administration approved lorcaserin (Belviq, Arena Pharmaceuticals, San Diego, CA) for the treatment of obesity. The approval follows an overwhelming vote by the Endocrinologic and Metabolic Drugs Advisory Committee in favor of lorcaserin as an adjunct to diet and exercise in patients with a body-mass index (BMI) >30. For patients with weight-related comorbidities, the drug is indicated for individuals with a BMI >27 (**Page 54**). Baibado et al. gave an overall view on over-the-counter medicines or food supplement for weight control (**Page 69**). There are increasing numbers of non-prescribed products claiming to offer some effects on body weight. Slimming dietary supplements, in particular, have become very popular. Some herbal substances, which have been known worldwide to induce slimming and lose weight for long time, are also easily available in the market. They are the basic ingredients included in many over-the-counter (OTC) medicines or food supplements available in pharmacies and health food stores. Though common folks claimed on the anti-obesity property of these herbs, there are very few clinical studies to support the claims and to ensure their efficacy and safety. The presence of adulterants in many OTC slimming food supplements should caution everyone on this emerging public health threat. Proper diet and strict exercise regimen are still the best way to lose weight.

In Hong Kong, traditional Chinese medicine is commonly used as both food and drug. Yang et al. gave a comprehensive report on the biochemical- and biological-based studies of Abri Herba (雞骨草). Abri Herba is the main constituent of a popular herbal tea in southern China, which contains alkaloid, hydroxylanthraquinone, sapogenol, saponins and other bioactive compounds. Biologically, the herb is hepatoprotective, and acts as an anti-cancer, anti-oxidative, anti-mutagenic, anti-inflammatory, anti-diabetic, anti-hyperlipidemia, anti-bacterial agent and has immuno-protective effects. Among the compounds that are isolated and identified from this herb are saponin compounds such as soyasaponin I and kaikasaponin III that are regarded as the main constituents responsible for the biological effects listed above. The toxic protein abrin, which has potent antitumor affects, is mainly concentrated in the seeds and can be easily removed during processing of the herbal material (**Page 73**).

Now and then, we read in the news that treatment of Invasive pneumococcal disease is becoming more difficult because of the rising antibiotic resistance of the Streptococcus pneumoniae. Prevention using pneumococcal vaccine has become an effective way to avoid the increasing difficulty in treatment. The two vaccines available (pneumococcal polysaccharide vaccine and pneumococcal conjugated vaccine) are indicated for different groups of people. Yeung & Chan's article on "Invasive Pneumoncoccal Disease in Adults" aims to discuss the properties of vaccines and the trend for development of new vaccine (**Page 62**).

Last but not the least, we have received an enquiry from a reader regarding "A consolidated List of Poisons, Antibiotics and Dangerous Drugs" which was published in Vol. 18 No 4(Supplement 1). The enquiry is on some forensic classification of various poisons and dangerous drugs. The enquiry and reply are published under News & Communication in **Page 55**. The Hong Kong Pharmaceutical Journal is the only pharmaceutical journal published in Hong Kong and we look forward to submission of articles and active communication with pharmacists and scientists in Hong Kong and all over the world.

Cheng Mary Catherine
Managing Editor
23 July 2012

Millions of Capsules made of toxic gelatin seized

Date: April 23, 2012

The China Ministry of Public Security said yesterday that it has confiscated 77 million drug capsules made from industrial gelatin containing toxic chromium. The ministry said it had arrested nine suspects, detained 54 and sealed 80 industrial gelatin and gel capsule production lines. The ministry deployed local branches in Hebei (河北), Zhejiang (浙江省) and Jiangxi (江西省) provinces to investigate the case after the scandal was exposed last week, it said. Meanwhile, an employee of the Hebei Xueyang Glair gelatin factory was detained after allegedly setting fire to the plant on the instructions of his bosses in an attempt to destroy evidence.

Source: South China Morning Post

Anti-Depressants Likely Do More Harm Than Good

Date: April 24, 2012

Commonly prescribed anti-depressants appear to be doing patients more harm than good, say researchers who have published a paper examining the impact of the medications on the entire body. "We need to be much more cautious about the widespread use of these drugs," says Paul Andrews, an evolutionary biologist at McMaster University and lead author of the article, published recently in the online journal Frontiers in Psychology.

Andrews and his colleagues examined previous patient studies into the effects of anti-depressants and determined that the benefits of most anti-depressants, even taken at their best, compare poorly to the risks, which include premature death in elderly patients.

Anti-depressants are designed to relieve the symptoms of depression by increasing the levels of serotonin in the brain, where it regulates mood. The vast majority of serotonin that the body produces, though, is used for other purposes, including digestion, forming blood clots at wound sites, reproduction and development.

The researchers found that anti-depressants have negative health effects on all processes normally regulated by serotonin. The findings include these elevated risks: developmental problems in infants, problems with sexual stimulation and function and sperm development in adults, digestive problems such as diarrhea, constipation, indigestion and bloating, abnormal bleeding and stroke in the elderly.

The authors reviewed three recent studies showing that elderly anti-depressant users are more likely to die than non-users, even after taking other important variables into account. The higher death rates indicate that the overall effect of these drugs on the body is more harmful than beneficial. "Serotonin is an ancient chemical. It's intimately regulating many different processes, and when you interfere with these things you can expect, from an evolutionary perspective, that it's going to cause some harm," Andrews says.

Millions of people are prescribed anti-depressants every year, and while the conclusions may seem surprising, Andrews says much of the evidence has long been apparent and available. What is missing is an overall assessment of all these negative effects relative to their potential beneficial effects. In previous research, Andrews and his colleagues had questioned the effectiveness of anti-depressants even for their prescribed function, finding that patients were more likely to suffer relapse after going off their medications as their brains worked to re-establish equilibrium. With even the intended function of anti-depressants in question, Andrews says it is important to look critically at their continuing use.

Source: Science Daily

HKU BPharm Programme Obtained Full Accreditation

Date: April 30, 2012

HKU announced that the Bachelor of Pharmacy Programme has obtained full accreditation. HKU started the BPharmacy programme in 2009, and attracted many high calibre students to the programme. Prof. Ian Wong stated that the average A Level marks of students at entrance are 2A1B, and some students with 6A in O Level. The first batch of 25 pharmacy students will graduate in July 2012 to start the one year internship. HKU collaborates with Queen Mary Hospital to provide hospital and clinical pharmacy training for the students. The course also provides training in research, hospital pharmacy, manufacturing and community pharmacy.

Source: Apple Daily News

The truth is out: sugar really does rot your brain

Date: May 17, 2012

Researchers at the University of Los Angeles fed 2 groups of rats a solution containing high fructose corn syrup – a common ingredient in processes food - as drinking water for six weeks. One group of the rats was supplemented with brain boosting omega-3 fatty acids in the form of flaxseed oil and docosahexaenoic acid while the other group was not. Before the sugar drinks began, the rats were enrolled in a five-day training session in a complicated maze. After six weeks on the sweet solution, the rats were then placed back in the maze to see how they fared. The DHA-deprived animals were slower, and their brain showed a decline in synaptic activity. Their brain cells had trouble signaling each other, disrupting the rats' ability to think clearly and recall the route that they had learned six weeks earlier. A closer look at the rat brains revealed that those who were not fed DHA supplements had also developed signs of resistance to insulin, a hormone that controls blood sugar and regulates brain function. Because insulin can penetrate the blood brain barrier, the hormone may signal neurons to trigger reactions that disrupt learning and cause memory loss. In other words, eating too much fructose may interfere with insulin's ability to regulate how cells use and store sugar, which is necessary for processing thoughts and emotions. Insulin is important in the body for controlling blood sugar, but it may play a different role in the brain, where insulin appears to disturb memory and learning. The findings illustrate that what you eats affect how you think. Eating a high fructose diet over the long term alters your brain's ability to learn and remember information. But adding omega-3 fatty acids to your meals can help minimize the damage

Source: South China Morning Post

FDA Approves Lorcaserin for Treatment of Obesity

Date: June 27, 2012

The Food and Drug Administration approved lorcaserin (Belviq, Arena Pharmaceuticals, San Diego, CA) for the treatment of obesity [1].

The approval follows an overwhelming vote by the Endocrinologic and Metabolic Drugs Advisory Committee in favor of lorcaserin as an adjunct to diet and exercise in patients with a body-mass index (BMI) >30. For patients with weight-related comorbidities, the drug is indicated for individuals with a BMI >27.

In October 2010, the FDA rejected lorcaserin because of concerns about a cancer signal detected in preclinical animal studies and asked for more data, including results from the BLOOM-DM trial, a study testing the weight-loss drug in overweight and obese subjects with diabetes. In addition, the 2010 advisory panel considered the weight loss in nondiabetic overweight and obese subjects "marginal." In the phase 3 clinical trials, known as BLOOM and BLOSSOM, the average weight loss in the lorcaserin-treated patients was 5 to 6 kg.

In May, the FDA advisory committee was presented with the new data, and the panel appeared satisfied that there was no increased risk of cancer with lorcaserin. The FDA, in its own review, also agreed that the risk of tumors in treated patients was "negligible." That said, it still expressed some concern about a possible increased risk of valvulopathy and adverse cardiovascular events associated with lorcaserin.

Dr Robert Eckel (University of Colorado School of Medicine, Denver) said there is a need for pharmacotherapy for the treatment of obesity and that the decision by the FDA opens the door to other pharmacological agents that also reduce body weight in overweight and obese patients. He noted that lorcaserin has a moderate effect on weight loss, with a reduction of 3% to 4% of the individual's body weight.

"The question then comes up, 'Does weight loss per se reduce cardiovascular disease events or related mortality?' " Eckel told heartwire. "We just don't know the answer to that yet. I think the bariatric-surgery data put forward by the Swedish group indicates that it does, but in terms of medical management of obesity with drug therapy or with lifestyle, we don't have any data that substantiate the hypothesis that weight loss is effective in reducing cardiovascular disease events or mortality."

Regarding the issues of cardiac valvulopathy, Eckel said he is comfortable with the data at this stage where clinicians can safely and confidently prescribe lorcaserin to patients. He cautioned, however, as with any drug, adverse events undetected in clinical trials can arise. In contrast to Eckel's confidence, Public Citizen, a nonprofit consumer-advocacy group, urged the FDA not to approve lorcaserin on the basis of the heart-valve concerns. The combination of fenfluramine/phentermine, popularly known as fen-phen, was pulled from the market in the late 1990s, given the risks of heart-valve damage. The risks from the drug were attributed to fenfluramine.

In February, as reported by heartwire, the FDA advisory committee also voted in favor of approving the obesity drug Qnexa (Vivus, Mountain View, CA), a combination of phentermine and controlled-release topiramate, but the FDA has still not approved the drug. A decision on Qnexa is expected in July, after the FDA requested additional time in April to review material from the company.

References

(1) Food and Drug Administration. FDA approves Belviq to treat some overweight or obese adults [press release]. June 27, 2012.

Source: www.medscape.com

Letter to Editor:

On 25 Jun, 2012, at 2:35 PM, "Verna.Wan@health.vic.gov.au" <Verna.Wan@health.vic.gov.au> wrote:

Dear Editor,

As an overseas-trained pharmacist practising in Australia, I commend the efforts of your editorial team at the Hong Kong Pharmaceutical Journal for publishing a very useful text- "A Consolidated List of Poisons, Antibiotics and Dangerous Drugs".

I wish however to clarify on some points of the text which are unclear:

1. In the Preface (on page 1) it states that- "Articles listed in the Second Schedule are exempted from the provisions of the ordinance & the regulations." Does this mean that such drugs/poisons are considered as "Non Poisons"? That is, it may be sold by retail without limitations? Examples are oral contraceptives, ipecacuanha tinctures, clioquniol preparations intended for external application only, etc?

2. I find it difficult to understand the exceptions in the three columns for Part I Poison- for example in the case for codeine, could you please confirm whether my interpretation of the text is correct:
   - at up to and including 0.1% of codeine, it is classified as a Part I poison;
   - at greater than 0.1% but less than 0.2% codeine, it is classified Part I First Schedule;
   - at greater than and equal to 0.2% codeine but less than 0.5% it is classified Part I First Schedule and Third Schedule;
   - and then at greater than or equal to 0.5%, codeine is classified as a Drug of Dependence? Or is codeine a drug of dependence REGARDLESS of its concentration?

3. Similarly for morphine, is it a Part I poison at less than 0.2%, but greater than or equal to 0.2% it is PIS1. When is it a drug of dependence?

4. The exception note for loratadine under "antihistamine" class states that it is exempted where- "...contained in pharmaceutical products labelled for the relief of the symptoms of allergic rhinitis only." Does this mean that loratadine where labelled for the symptomatic relief of allergic rhinitis is classified as a "non poison"

Many thanks in your assistance clarifying my understanding of the classification system of drugs and poisons in Hong Kong.

Kind regards,
Ms Verna Wan

Reply to Ms. Wan by the Editorial Committee

Dear Ms. Wan,

1. Yes, articles listed in the Second Schedule are considered as "Non-Poisons", it has to fulfil the criteria as listed in the second column. For example, an oral contraceptives containing not more than 0.15 mg of Desogestrel per dose are non poisons; like-wise Ipecacuanha tinctures containing less than 0.05% of emetine and clioquniol preparations intended for external application only are also listed as non poisons;

   [The exemption of articles specified in the Second Schedule is provided under Regulation 8 of the Pharmacy and Poisons Regulations. Please refer to the regulation for further detail.]

2. I find it difficult to understand the exceptions in the three columns for Part I Poison- for example in the case for codeine, could you please confirm whether my interpretation of the text is correct:
   - at up to and including 0.1% of codeine, it is classified as a Part I poison;
   - at greater than 0.1% but less than 0.2% codeine, it is classified Part I First Schedule;
   - at greater than and equal to 0.2% codeine but less than 0.5% it is classified Part I First Schedule and Third Schedule;
   - and then at greater than or equal to 0.5%, codeine is classified as a Drug of Dependence? Or is codeine a drug of dependence REGARDLESS of its concentration?
     Answer: A product containing less than and equal to 0.1% of codeine, it is classified as a Part I poison;
   - At concentration greater than 0.1% but less than 0.2% codeine, it is classified as Part I First Schedule poisons;
   - At concentration greater than or equal to 0.2% codeine but less than or equal to 0.5%, it is classified Part I First Schedule and Third Schedule poisons and Part II dangerous drug;
   - At concentration greater than 0.5%, codeine is classified as a Dangerous Drugs [and Part I First Schedule and Third Schedule poisons]. Dangerous Drugs means any of the drugs or substances specified in Part 1 of the First Schedule of the Dangerous Drugs Ordinance;

     [Regarding the part II Dangerous Drug, the preparation, apart from a concentration not more than 0.5%, should also has no risk of abuse and the substance cannot be readily recoverable. Please see paragraph 13 of Schedule 1 to the Dangerous Drugs Ordinance for further detail.]

3. Similarly for morphine, is it a Part I poison at less than 0.2%, but greater than or equal to 0.2% it is PIS1. When is it a drug of dependence?

   Morphine is a Part I poison at less than 0.2%, but greater than or equal to 0.2% it is a "PIS1"; it is a Dangerous drug when containing greater than 0.2% morphine.

4. The exception note for loratadine under "antihistamine" class states that it is exempted where- "...contained in pharmaceutical products labelled for the relief of the symptoms of allergic rhinitis only. "Does this mean that loratadine where labelled for the symptomatic relief of allergic rhinitis is classified as a "non poison"

   No, they are Part II poisons. Please refer to Part II of Schedule 1 to the Poisons List Regulations.

We hope you find this information useful. Once again thank you for your enquiry which is important to our continued effort on making the HKPJ better. We take this opportunity to thank for your continued support to the Hong Kong Pharmaceutical Journal.

Kind regards,
HK Pharm J Editorial Committee

Coaching for Pharmacists (3) – Technical Coaching

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ABSTRACT

In a world of constant changes, healthcare professionals are no longer secure in our once familiar environments. Instead we face constant uncertainties every day. We therefore need to develop new skills and competencies to cope in this new world. Coaching is one way to achieve these goals. Coaching is becoming more popular due to the benefits it brings to personal and organizational development. Several health fields have reported the application of coaching in developing healthcare professionals. This article will highlight some of the effective coaching techniques. After a brief introduction of different types of coaching models, various skills and tools used in coaching will be discussed.

Keywords: *coaching; pharmacists; coaching models; coaching skills, coaching tools.*

INTRODUCTION

Healthcare professionals are living in a world of constant changes. Pharmacists are of no exception. The healthcare environment is becoming more and more complex. We are being challenged all the time to stay up-to-date and to develop new skills and competences. Many young practitioners would like to have some form of support to help accomplish their career goals through professional and leadership development. Coaching is one way to accomplish this in any individual or organization.

As discussed in the previous article Coaching for Pharmacists (2) – An Irresistible trend, coaching culture is beneficial for the sustainable development of both the people and the organization. Coaching techniques have been used in organizations to enhance performance among teams. Coaching has also been a tool for professional development. Several health fields have reported the application of coaching in developing nurse leaders, nursing staff, medical residents, dentists, physicians, pharmacists and pharmacy leaders. This article will highlight some of the coaching techniques. After a brief introduction of different types of coaching models, various skills and tools used in coaching will be discussed.[1,2]

COACHING MODELS

Basically all the coaching models arise from two main ones. The traditional view of coaching called directive coaching involves instructing the coachee in a specific skill set and giving specific guidance and instruction to the coachee. This model is similar to tuition. The contemporary non-directive model of coaching is widely advocated in business and personal and life coaching stem from this model. Instead of giving specific instruction, the coach initiates the process of inquiry that leads to the coachee creating his/her own solutions.[3,4]

Different types of non-directive coaching models include:

1. Management coaching
2. Performance-centered coaching
3. Co-active coaching model
4. Group coaching
5. Peer coaching

MANAGEMENT COACHING

Management coaching is probably where coaching is first exposed to the corporate world from the sports field. Managers started to see benefits from coaching their staff instead of dictating them or simply giving instructions. Inspirational, transformational, motivational and organizational psychology have contributed to the increasing popularity of management coaching. Management coaching creates a spirit of collaboration, allows for open communication, and builds trust and respect in the relationship.[3,5]

PERFORMANCE-CENTERED COACHING

In many contexts, coaching is directly related to performance. Performance coaching is a vital initiative for any organization that wishes to improve customer experience or drive sales transformation. Coaching frontline staff is an impactful activity in driving performance improvement in people-intensive organizations. The business impact of coaching is prominent in departments related to sales and services, where employee skill, knowledge and motivation are experienced first-hand by customers. Since pharmacists may also work in the frontline as salespeople in pharmaceutical companies and interact with customers directly, performance-centered coaching is also applicable to pharmacists.[3,6]

CO-ACTIVE COACHING

Laura Whitworth, Karen Kimsey-House, and Henry Kimsey-House are internationally recognized pioneers in the coaching field and also cofounders of The Coaches Training Institute (CTI). Together with Phillip Sandahl, cofounder of Team Coaching International, they created the Co-Active Coaching model to help people achieve their goals in work and life. This coaching model can be applied to any aspect of young practitioner's life, career, or business.

The term co-active coaching refers to the co-creative and partnership nature of the coaching relationship. Effective non-directive coaching is co-active in that both the coach and coachee are active participants in the co-creation of results and solutions for the coachee.

Co-active coaching requires the coach to use a broad range of communication skills, including active listening, asking insightful questions, and giving encouragement and sincere praise.

Visually, the coaching model can be symbolized as a five-pointed star as illustrated in **Figure 1**. Each point of star is a context that the coach brings to the coaching and each represents a point of contact with the client. The coach consistently draws from these contexts in the practice of coaching. At the foundation of all coaching is an agenda that shows the client's desire for fulfillment, balance, and process – called the three core principles. The coachee and his/her agenda are in the center of the co-active coaching model. This protective circle is named the designed alliance. In co-active coaching, power is granted to the coaching relationship instead of the coach. Coachee and coach work together to design an agreement that meets the coachee's needs because coachees play an important role in deciding how they want to be coached. They help create a powerful relationship that fits their working and learning styles. The relationship is adapted to the communication approach that works best for them. Designing the alliance is a mutual responsibility of the coach and coachee. Coachees need to know that they are in control of the relationship and, eventually, of the changes they make in their lives or careers.[2,4,7]

GROUP COACHING

One of the most influential uses of coaching is within a group dynamic. No matter we are part of a team within a clinical setting or part of a team that meets regularly to work on a particular task, coaching can drastically improve the performance of the group as a whole.

Coaching with a group is not significantly different from one-to-one coaching, although different skills may be involved. The focus in group coaching is on discovering the most appropriate way to support each individual coachee, because people are unique individuals and what motivates one person may actually demotivate another.

When working as a coaching group, participants can rapidly share their individual/team best practices, for mutual benefit. As a result, great ideas are quickly integrated and distributed. Through the transfer of knowledge, each participant and their company reach their goals faster. Furthermore, people inspire each other and come up with great solutions together.[3,8]

PEER COACHING

Peer coaching is a more unique form of coaching. A peer coach is typically a colleague, co-worker, or friend who participates in what might be called reciprocal coaching: you take some time to coach me; then I will spend some time to coach you. Unlike executive coaching or other forms of professional coaching, peer coaching takes place between people who expect to coach each other. Peer coaches, therefore, normally share similar professional or job responsibilities.

The intention in peer coaching is to assist your colleagues in developing their own solutions, responsibility, accountability and proactivity. Peer coaching builds on prior knowledge and skills. It involves establishing rapport; forming a trusting relationship; sharing a mutual desire to learn and incorporate newly learned knowledge and skills into practice; and setting goals for performance, observation, reflection and feedback.[3,9]

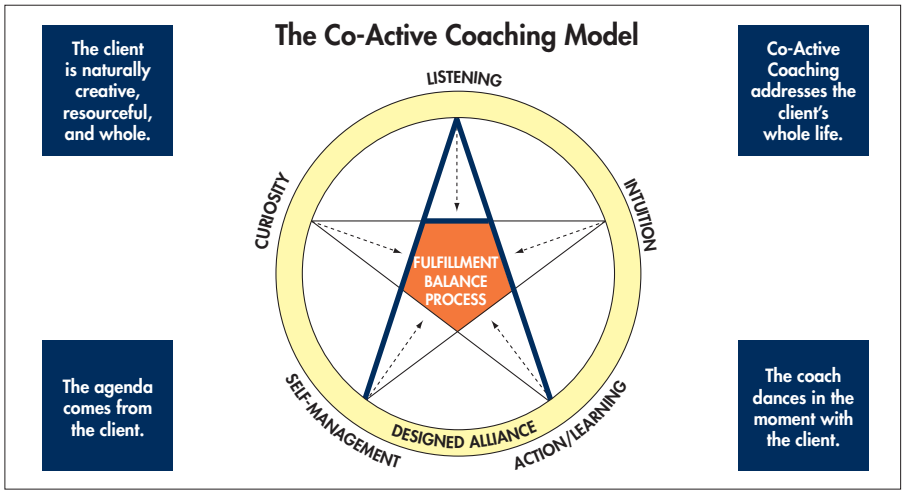

Figure 1. *The Co-Active Coaching Model*

COACHING SKILLS AND TOOLS

Coaching is diverse and draws upon many techniques to fulfill its aim of facilitating personal and organizational growth. This section outlines some skills and tools used in coaching. There are a lot more and coaches are free to create new tools, metaphors and techniques as he/she interacts with each coachee.

NLP

Neuro Linguistic Programming (NLP) was developed by two pioneers of excellence in the 1970s. It started off in the field of mental health therapy and was rapidly spread into business contexts to improve individual and team performance with immense effect. NLP is famous for its ability to transform communication and team work, as well as working with people to release personal blocks, which hinder achievements. The two elements, coaching and NLP, are not considered two separated entities, but they supplement each other to create a synergistic effect.

NLP presupposes that everyone has the resources they need or can acquire them. Coaches should therefore always treat their coachees as resourceful. We do not have the answer, but our coachees do. We shall make the coaches become aware of their own strengths and weaknesses and we work with them on their goals and values. On some occasions, we need to point out where the coachees can make their own choices and fight habits that are hindering them from excellence in practice. We also need to support them in the changes they make.

Another concept in NLP is the "representational systems". There are basically four systems, namely the auditory, olfactory, kinaesthetic, and the usual systems. Each person has his/her preferred "representational system" which is linked to a "preferred acute sense". For example, if one pays a lot of attention to what he/she sees, then he/she is likely to use the usual representational system in thinking. Therefore, when coaching, coaches should listen as much to the kind of words the coachee uses. This is not as easy as it sounds. There is more to it than meets the eye and the concept can be a slippery one, because we are used to making sense of what others say instead of how they say it. Following on from this, we think with our whole body, not just with our brains. We "tune" our body into postures, gestures and breathing patterns to help us think in

certain ways. Coaches should also reply in the same representational system, making the coachees unconsciously receive that the coaches understand them at a deep level.

NLP is a powerful tool to add onto coaching. If well mastered and used, NLP allows us to do better coaching. A coach with knowledge in NLP can understand the reality of how a coachee thinks and can use language more precisely to help the coachees achieve their goals.[1,10]

EQ

Emotional quotient (EQ) is increasingly regarded as an indispensable competency for personal success, organizational effectiveness and professional recognition in healthcare professionals. It is clear that healthcare leaders must exhibit certain core competencies and display a fairly high degree of emotional intelligence to accomplish change goals. EQ coaching specifically focuses on the development of emotional skill and competency in the workplace. The result is increased personal effectiveness that brings balance and success at work and in life. As with all coaching, EQ coaching involves a process of creating discovery that supports the coachee's awareness and understanding of their own emotions and the emotions of others.

The outcomes of EQ coaching include better management of change and uncertainty in the workplace, viewing situations from the perspective of others, increased ability to handle adversity and setbacks in work and life, and learning to deal with difficult people more effectively.[11,12]

GOAL SETTING

Even though goal setting is fundamental, its significance and value should not be underestimated. Goal setting gives coachees a precise direction and an action plan for making something real. Helping clients with the basics of goal setting can make a big difference in their success. Splitting the goal into smaller manageable ones is the first step for some coachees. Goals can be immediate, short-term, medium-term or long-term. They can be linked directly to our vision and strategy or may be smaller goals to achieve a specific result. Goals, however large or small, should be SMART: specific, measurable, achievable, relevant and time-oriented. Coaches need to have a clear understanding with clients about how they will handle goal setting and look for ways that work best for each client.[13,14]

QUESTIONING

Questioning is considered an indispensable tool in coaching. It is also referred to as effective questioning, artful questioning or powerful questioning. A well-placed question might result in a huge shift in perspective on the part of the coachee and give them new insights.

It is difficult to have a profound effect on somebody simply by trying to. Experienced coaches raise questions naturally, out of curiosity and genuine desire to facilitate the development of coachees. However, coachees may feel they are being interrogated if the coaches try too hard and this will lead to ineffective coaching.

To some coaches the "great coaching question" becomes the key of effective coaching. They believe that when that one profound question is found, all the coachee's problems would fade away as the solutions would neatly fall into place.[3]

CONCLUSION

The dynamic environment of the pharmacy profession requires pharmacists to be equipped with essential skills and competencies to cope with all the challenges and uncertainties. Coaching assists in taking a pharmacist's personal and professional development further and faster. Apart from personal and organizational benefits, it also leads to better healthcare for patients in the community.

There are different kinds of coaching models that can be adopted but the two main ones are directive coaching and non-directive coaching. Directive coaching involves giving specific guidance and instruction to the coachee and is similar to tuition. Non-directive model of coaching is gaining popularity and it involves the coach initiating the process of inquiry and helping the coachee create his/her own solutions. Different types of non-directive coaching models include management coaching, performance-centered coaching, co-active coaching, group coaching and peer coaching.

To coach effectively, various techniques could be used. Some of the examples include Neuro Linguistic Programming (NLP), Emotional Quotient (EQ), goal setting and questioning. These skills and tools allow coaches to understand how cochees think, increase the ability of coachees in handling difficult situations, give them new insights and help them achieve their goals.

Coaching is a way to lead pharmacists to an advanced level. When coaching techniques are applied appropriately and effectively, pharmacists can utilize their potential to deal with challenges and achieve their goals.

Author's background

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Implementation of Medication Therapy Management Clinic (MTMC) in Ambulatory Care

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ABSTRACT

In the ambulatory care setting, opportunities thrive for pharmacists to actively participate in direct patient care for the improvement of chronic diseases management. Medication Therapy Management (MTM) is a pharmacy practice model first introduced in January 2006 by the Medicare Part D prescription drug benefit of the United States. The MTM services are patient-centered services designed to improve collaboration among pharmacists, physicians, and other healthcare professionals with an aim to optimize medication use for improved patient outcomes. MTM services in the form of a pharmacist consultative clinic known as Medication Therapy Management Clinic (MTMC) has been implemented in the Renal Day Centre of Alice Ho Miu Ling Nethersole Hospital since January 2010. The goals of implementing MTMC in ambulatory end-stage renal disease (ESRD) patients are to improve the health of ESRD patients with better management of coexisting diseases, delay the progression of chronic kidney disease (CKD)-related complications, increase patient survival rate, optimize patient education and empowerment, and reduce health care costs. Future direction of MTMC may target its impact on the management of other common chronic diseases such as diabetes mellitus, hypertension, hyperlipidemia, chronic obstructive pulmonary disease (COPD) in their early stages before the onset of any clinical complications.

Keywords: *medication therapy management clinic, MTM, MTMC, ambulatory care, end-stage renal disease, ESRD*

INTRODUCTION

In the United States, the provision of pharmacist-provided Medication Therapy Management (MTM) has been a long standing goal of the American Society of Health-System Pharmacists (ASHP) to improve patient's access to care, provide disease management, and focus on quality-related outcomes which contribute to containment of drug costs at outpatient level.[1]

In Hong Kong, problems pertaining to the healthcare system such as low prices for healthcare services, long waiting times for specialist services, and shortage of doctors all increase the population's dependency on the public healthcare services. All of the above threaten the quality of service for Hong Kong health services. In addition, the aging population of Hong Kong has shifted the health problems towards chronic disease management which causes extra costs and demands on the healthcare system.

The intent of targeting patients who have multiple chronic diseases and are taking on multiple medications is to ensure appropriate use of prescribed drugs in conjunction with MTM services, thereby optimizing therapeutic outcomes, reducing the risks of drug-related problems (DRPs) such as adverse drug reactions, drug-to-drug interactions, etc.[2]

DEFINITION OF MTM SERVICES

MTM services are patient-focused pharmacy services which are distinct from medication dispensing that enable a pharmacist to provide patient care through face-to-face assessment and intervention in a specialized area of care. MTM services take the approach of:

- pharmacist-physician collaborative practice and direct patient care practice to improve collaboration among pharmacists, physicians, and other healthcare professionals;
- enhanced communication between patients and their healthcare team;
- optimized medication use for improved patient outcomes.

MTM services also empower patients to take an active role in managing their medications and healthcare through enhanced patient's understanding of appropriate drug use, increased medication compliance, and improved identification of adverse drug events.

MEDICATION THERAPY MANAGEMENT CLINIC (MTMC) MODEL IN AMBULATORY CARE

In ambulatory care setting, MTM services can be offered in the form of a pharmacist consultative clinic namely as Medication Therapy Management Clinic (MTMC) by either an appointment or a walk-in basis in either a hospital institution or a community pharmacy. In delivering MTM services in a private or semi-private area such as a pharmacist consultation area, a pharmacist can devote the time for patient care activities during this service.

OBJECTIVES OF MTMC IN AMBULATORY CARE

The objectives in the provision of MTMC in ambulatory care are summarized as below:

- To provide multidisciplinary care on medication therapy management
- To minimize drug-related problems

- To promote patient's self-care and disease prevention
- To achieve cost containment on drug therapy
- To establish the roles of clinical pharmacist in specialty of care

IMPLEMENTATION OF MTMC IN ALICE HO MIU LING NETHERSOLE HOSPITAL

In January 2010, MTMC was formally implemented in delivering patient-centered care to end-stage renal disease (ESRD) patients in the renal day centre of Alice Ho Miu Ling Nethersole Hospital (AHNH).

The pharmacist-managed MTMC is conducted in the form of pharmacist consultation that is held within the renal day centre of AHNH (Fig. 1) The target population is mainly ESRD patients who are on peritoneal dialysis in the form of continuous ambulatory peritoneal dialysis (CAPD) and regularly attend the CAPD outpatient clinic for follow-up at AHNH.

All patients either referred or recruited for MTM services attend the pharmacist-managed MTMC immediately prior to their regular physician follow-up at the CAPD clinic (Fig. 2). The priority of MTMC visit over the physician appointment at the CAPD clinic is to facilitate prescription recommendations to be initiated by clinical pharmacist in the form of pharmaceutical care plan. The MTMC is operated within the renal day centre in close proximity to the renal outpatient clinics.

Figure 1: *ESRD patient is attending a pharmacist consultation during MTMC*

Figure 2: *ESRD patient is attending a routine physician follow-up at CAPD clinic*

In order to enhance the feasibility of MTM services in Hong Kong, the MTMC model is modified from the US model[1] to include the following four core elements (Fig. 3):

i. Medication therapy review,
ii. Medication reconciliation and record update,
iii. Intervention and/or referral,
iv. Documentation and follow-up.

INTEGRATION OF MTMC IN RENAL OUTPATIENT CLINICS

The structural model demonstrates the role of clinical pharmacist in-charging the MTMC at ambulatory level in AHNH who acts as a member of the multidisciplinary care team in the provision of specialized pharmacy services (Fig. 4). The provision of MTM services is an important process to collaborate patient care with other members of the multidisciplinary care team in the management of chronic kidney disease (CKD)-related medical conditions (Table 1)[3] in terms of treatment adequacy and goal achievement. Generally, MTM services include assessment of drug choices based on medical indications, review of specific drug dosages, monitoring for efficacy and toxicity, identification and resolution of any DRPs. If necessary, the MTMC pharmacist may arrange appropriate laboratory investigations for monitoring of therapeutic parameters, and arrange for further follow up via the MTMC until the therapeutic goals have been achieved.

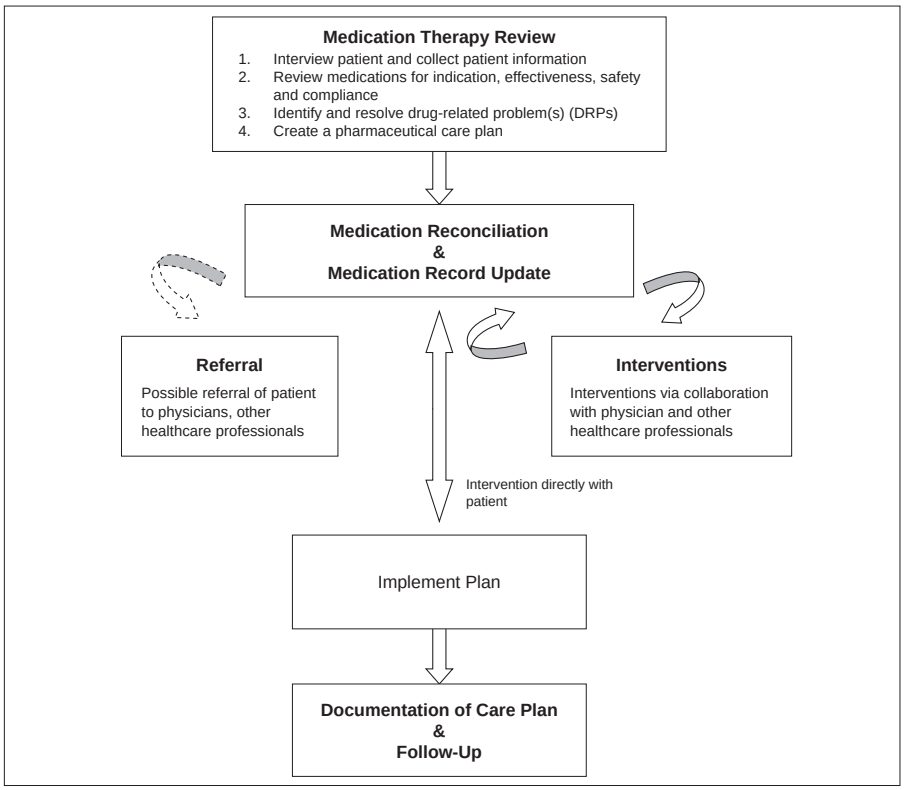

Figure 3: *Flow Chart of Four Core Elements in a MTMC Model*

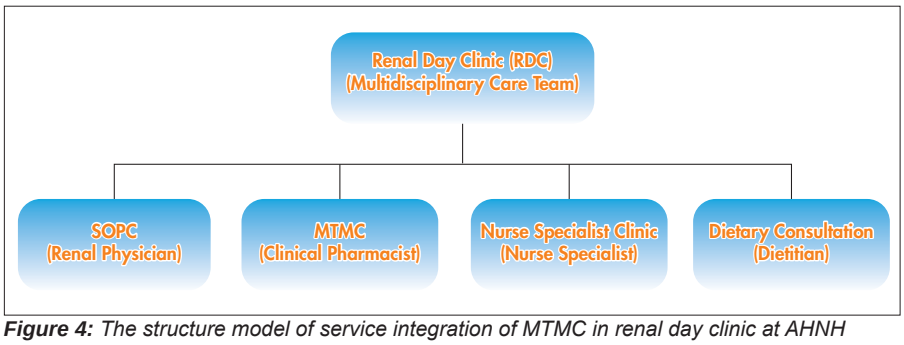

Figure 4: *The structure model of service integration of MTMC in renal day clinic at AHNH*

THE EFFECTS OF MTMC IN AMBULATORY CARE

Medication therapy management (MTM) was officially recognized by the US federal government in 2003, in which the pharmacist profession has been moving from a product-focused to a patient-focused practice.[1,2] Several studies have demonstrated the effectiveness of MTM services in improving the control of chronic disease states such as hypertension, diabetic mellitus, CKD.[3] Overall, the conclusion that can be drawn from these studies is that the implementation of a MTM program is associated with improved clinical outcomes, cost savings, and high patient satisfaction.[4]

FUTURE IMPLICATIONS FOR MTM PRACTICE OR RESEARCH

In Hong Kong, the practice model of MTMC in the management of chronic diseases holds great potential. The chronic shortage of health care professionals including doctors, nurses, and allied health professions result in extremely long waiting times of follow-up or consultation at the specialist outpatient clinic. As such, patients suffering from chronic illnesses like CKD often deteriorate in health with the onset of multiple complications leading to unplanned hospital readmission, increased morbidity and mortality. Future research should target the impact of pharmacist-managed MTMC for the management of other common chronic conditions such as diabetes mellitus, hypertension, hyperlipidemia, chronic obstructive pulmonary disease (COPD) in their early stages before the onset of any clinical complications. However, the standardized framework for MTM service delivery that is most suitable and feasible in the ambulatory care setting of Hong Kong is yet to be defined by future research.

Table 1. Collaborative management of chronic kidney disease-related medical conditions

Conditions	Outcomes
Hypertension	Appropriate therapy adjustments Lower systolic and diastolic blood pressure (SBP & DBP) Improved quality of life High patient satisfaction level Improved medication adherence Reduce hospitalizations
Diabetic mellitus	Reduced haemoglobin A_{1c} level Reduced inpatient visits for complications Reduced physician time for long-term management Improved patient self-management Improved microalbuminuria screening
Hyperlipidemia	Reduced low-density lipoprotein (LDL) cholesterol level Improved patient satisfaction Improved quality of life Improved achievement of adenosine triphosphate goals
Anemia	Improved K/DOQI haemoglobin (Hb) goals Improved K/DOQI iron goals Reduce erythropoietin (EPO) doses Economic benefits
Secondary hyperparathyrodism	Reduced elevation of parathyroid hormone (PTH) level Reduce calcium-phosphorus (Ca x P) product

Note. From [3] "Clinical pharmacists as multidisciplinary health care providers in the management of CKD: a joint opinion by the nephrology and ambulatory care practice and research networks of the American College of Clinical Pharmacy." by Joy et al., 2005, *Am J Kidney Dis*, 45, 6, p. 1110.

Abbreviations

AHNH	Alice Ho Miu Ling Nethersole Hospital	ESRD	End-stage renal disease
ASHP	American Society of Health-System Pharmacists	Hb	Hemoglobin
Ca	Calcium	K/DOQI	Kidney Disease Outcomes Quality Initiative
Ca x P	Calcium-phosphorus product	LDL	Low-density lipoprotein
CAPD	Continuous ambulatory peritoneal dialysis	MTM	Medication Therapy Management
CKD	Continuous ambulatory peritoneal dialysis	MTMC	Medication Therapy Management Clinic
COPD	Chronic obstructive pulmonary disease	P	Phosphorus
DBP	Diastolic blood pressure	PTH	Parathyroid hormone
DRPs	Drug-related problem(s)	SBP	Systolic blood pressure
EPO	Erythropoietin	US	United States

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- Ms Flora Wong, Ward Manager, Renal Unit, AHNH
- Ms Chow, Ngar Yee, Advanced Practice Nurse(Medicine), Renal Day Centre, AHNH
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Invasive Pneumococcal Disease in Adults

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ABSTRACT

Currently, invasive pneumococcal disease can be treated by antibiotics such as Ceftriazone, penicillin G depending on the site of infection and level of antibiotic resistance. However, treatment of Invasive pneumococcal disease is becoming more difficult because of the rising antibiotic resistance of the *Streptococcus pneumoniae*. Prevention using pneumococcal vaccine has become an effective way to avoid the increasing difficulty in treatment. The two vaccines available (pneumococcal polysaccharide vaccine and pneumococcal conjugated vaccine) are indicated for different groups of people. This article aims to discuss the properties of pneumococcal vaccines and the trend for development of new vaccine.

Keywords: *pneumococcal disease, vaccine, adults, polysaccharide vaccine, conjugate vaccine*

INTRODUCTION

Pneumococcal infections represent various kinds of diseases caused by *Streptococcus pneumoniae* (pneumococcus). Pneumococci are divided into >90 serotypes based on capsular polysaccharide structure. Less than 30 serotypes contribute to 90% of isolates that cause invasive pneumococcal disease. [1]

Illness caused by the infection can be mild, such as sinusitis or it can be severe and life threatening such as pneumonia and meningitis. Invasive pneumococcal disease (IPD) differs from the non-invasive pneumococcal disease by the infection of a normally sterile site such as blood, cerebrospinal fluid and other body fluids like joint or pericardial fluid.[2] Vaccination is the only available strategy to prevent this potentially fatal disease.[3]

Two types of vaccines are available: 23-valent pneumococcal polysaccharide vaccines (PPV23) and pneumococcal-conjugated vaccines (PCV). PPV23 includes 23 most common pneumococcal serotypes associated with pneumococcal disease and these 23 serotypes are responsible for up to 95% of IPD in children and adult worldwide.[4] Only the PPV23 is indicated for use in adult and children age ≥ 2 years whilst the use of conjugated vaccines in adults is still under evaluation by different health authorities.

BURDEN OF PNEUMOCOCCAL DISEASE

A total of 93 pneumococcal serotypes have been identified. Among these 93 serotypes, 30-40 serotypes are known to cause human infection and of which 15 serotypes cause 80% of pneumococcal infection in the world.[5,6] However, new serotypes continue to be identified, such as serotypes 6C and 6D which are recently characterized.[7] The emergence of new serotypes is partly due to the widespread use of pneumococcal vaccination, resulting in selective pressure which favors the growth of replacement serotypes. Approximately 1.6 million people die from pneumococcal disease in the world.[8] According to the IPD laboratory surveillance system maintained by the Public Health Laboratory Services Branch (PHLSB) of the Centre for Health Protection (CHP), the number of isolates analyzed in January to September in 2011 was 118 for persons of all ages.[9]

TREATMENT OF IPD

Streptococcal infection involving the central nervous system (CNS) is empirically treated with ceftriaxone plus metronidazole or ceftriaxone alone, depending on the site of infection (Table 1).[10] For treatment of infection involving sites outside CNS, IV penicillin G or IV ceftriazone can be used depending on the penicillin susceptibility (Table 2).

ANTIBIOTIC RESISTANT PNEUMOCOCCUS SEROTYPES

Strains of Drug-resistant *S. pneumoniae*

Table 1. Recommendation for empirical therapy of CNS infections (Adapted from IMPACT) [10]

CNS infections	Usual organisms	Preferred regimens	Alternatives
Brain Abscess	Usually polymicrobial with aerobes and anaerobes	Ceftriazone + metronidazole	Cefotaxime + metronidazole
Meningitis	*S. suls*, ***S. pneumoniae***, *N. meningitides*, group B *Streptococcus*	Ceftriaxone or cefotaxime	Meropenem

Table 2: Guidelines for known pathogen (*S. pneumoniae*) therapy (Adapted from Inter-hospital Multi-disciplinary Programme on Antimicrobial ChemoTherapy- IMPACT)[10]

S. *pneumoniae*[a] infection outside the CNS	Drug of choice	Alternatives	Remarks
Penicillin-sensitive	IV penicillin G (4 to 8 MU/day, q6h)	- Beta-lactam/ beta-lactamase inhibitor combination with the exception of cefoperazone-sulbactam (for mixed infections). - Erythromycin or clindamycin (if allergic to penicillin).	- For pure pneumococcal infection, penicillin G instead of amoxicillin-clavulanate is preferred, switch therefore recommended. - >70% resistant to erythromycin. Cross-resistance to clindamycin very common - Resistance to erythromycin = resistance to other newer macrolides (clarithromycin, azithromycin, roxithromyxin).
Penicillin-intermediate	IV penicillin G (high dose, 12 to 18 MU/d; q4h)		
Penicillin-resistant	IV cefotaxime or ceftriaxone		

[a] CLSI (NCCLS) MIC (mcg/mL) breakpoints for penicillin G: sensitive, ≤0.06; intermediate 0.12-1; resistant ≥2.

(DRSP) have become more common in the U.S. and other parts of the world. In Hong Kong, the penicillin resistance rates remains low (1%) in non-meningitis case but the penicillin resistance rate increases to around 20% in meningitis case.[11] Many penicillin-resistant pneumococci are also resistant to other antimicrobial drugs such as erythromycin, trimethoprim-sulfamethoxazole. According to surveillance studies conducted between 1998 and 2001, the erythromycin resistance rate in Hong Kong has increased to above 70%.[12,13] In 2007, levofloxacin resistance rate remains about 5.1%.[14] Management of pneumococcal infection and choosing empiric antimicrobial therapy for suspected case of meningitis and pneumonia becomes more difficult because of penicillin resistance and multidrug resistance. More expensive alternative antimicrobial agents may be required for the treatment and prolong hospitalization which results in increased medical cost. Although the impact of antimicrobial resistance on mortality is not clearly defined, it is suggested that people who are at risk should be vaccinated to prevent pneumococcal infections.

PNEUMOCOCCAL POLYSACCHARIDE VACCINE (PPV23)

Pneumococcal polysaccharide vaccine is the only type of pneumococcal vaccine that is currently indicated for adults in Hong Kong. PPV are manufactured using polysaccharide capsule of pneumococcus which is an immunogen that induces antibodies that can activate complement and bacterial opsonization (It refers to the binding of complement protein which circulate in the blood and tissue fluid to bacteria. The complement protein bound bacteria would be more easily caught by phagocytes and enhances phagocytosis.). The polysaccharide antigens from the capsule of pneumococcus are extracted, purified and incorporated into the vaccine that is able to induce a T-independent B-cell response. The antibodies generated from the response promote bacterial phagocytosis and clearance from macrophages and neutrophils.[15] Twenty-three most common *S. pneumoniae* serotypes associated with pneumococcal disease are covered by PPV 23 (serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, 33F). These serotypes are responsible for up to 95% of invasive pneumococcal disease worldwide.[4]

Mechanism of action

The polysaccharide antigens included in PPV23, which is a T-independent antigen would only elicit a primary immune response and produce IgM as the predominant immunoglobulin isotype.[4] The IgM secreted by B-cells helps B-cells to capture and internalize soluble antigen by immunoglobulin receptors, which then increases their capacity to mount increased IgM responses (Fig.1).[16] This type of antigen would not generate a robust immune response even after reexposure to the same antigen and immunologic memory will not be produced because of the lack of secondary immune response induced. Also, because of the immature immune system of children <2 years of age, they are not able to mount an immune response to this type of vaccine. Therefore, PPV is not recommended for use in children <2 years of age.[16]

Clinical efficacy of pneumococcal polysaccharide vaccines

An effectiveness ranging from 50% to 80% for prevention of IPD among immunocompetent older adults and adults with various underlying illnesses was suggested in observational studies.[17-20] According to meta-analyses assessing PPV23 efficacy and effectiveness, protective effect against IPD among generally healthy young adults is consistent, however, efficacy against IPD in population at higher risk such as immunosuppressed individuals of any age has not been demonstrated.[21,22] The meta-analysis consists of 15 randomized controlled trials (RCTs) and seven nonrandomized observational studies of PPV23 efficacy and effectiveness was conducted. Based on pooled results of 10 of the RCTs, PPV23 showed an overall efficacy of 74% against IPD (CI= 56%-85%).[21]

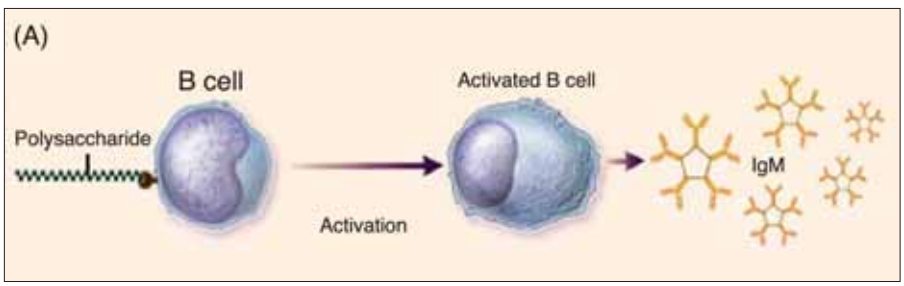

Figure 1: *T-independent B-cell response elicited by PPV (Adapted from M.W. Pletz et al.)[16]*

Results of the seven observational studies showed a pooled vaccine effectiveness of about 52% (CI= 39% -63%). On the other hand, another meta-analysis consisting of six RCTs estimated that the combined PPV23 efficacy against pneumococcal bacteremia at only 10%, with a wide CI (CI = -77% - 54%).[22] The large difference between these studies may be due to the inclusion of different trials.

Safety

PPV23 is considered safe in terms of severe immediate reactions and potential long-term adverse consequences. Possible side effect includes minor local adverse reactions, such as transient redness and pain at the site of injection, occurring in 30-50% of people who have been vaccinated.[22] These minor reactions occur more frequently in subcutaneous injection than intramuscular injection. Local reactions are more commonly seen in patients receiving second dose of injection which was found recently in Australia.[23]

In March 2011, a batch recall of Pneumovax 23 (PPV23) was ordered by Therapeutic Goods Administration (TGA) in Australia because a cluster of severe local injection site reactions was reported after Pneumovax 23 injection. In April 2011, health professionals were advised not to administer a second dose of Pneumovax 23 following a continued increase in severe injection site reaction reported. After analysis, TGA determined that the increased number of adverse events were due to higher rates of local reactions following a repeat dose of Pneumovax 23 and increased number of people having a repeat dose following the inclusion of Pneumovax 23 vaccine in the National Immunisation Program with revaccination after five years.[23] Therefore, routine revaccination is not recommended to immunocompetent individuals.

Unmet medical needs

Since immune response to PPV23 is T-cell independent, the immunity resulted would not be long lasting and the efficacy is limited to 3 to 5 years after a single dose.[24] Besides, failure of polysaccharides antigen to establish a B-cell memory would decrease the people's response to a second dose, limiting the ability to respond to multiple immunizations.[25] Therefore, a vaccine that can induce robust durable antibody response and permit revaccination to reduce the adult pneumococcal disease burden is desired.

PNEUMOCOCCAL CONJUGATED VACCINE (PCV)

PCV is composed of bacterial polysaccharides that have been chemically conjugated to highly immunogenic cross-reactive material 197 (CRM_{197}) for PCV13, a non-toxic diphtheria toxoid protein (Bacterial polysaccharides are conjugated to non-typable H. influenza (NTHi) protein D for PCV 10). Antigen presenting cells present the processed CRM_{197} protein along with MHC II to effector T-cells. The CRM_{197}-specific type 2 helper T (Th2) cells subsequently interact with B-cells that have bound and internalized the polysaccharide-CRM_{197} complex via polysaccharide specific IgM. The result of the interaction would be the generation of memory B-cell and switching of antibody isotype from IgM to IgG (Fig. 2).[9] The antibody response induced is longer lasting and the responses can be maintained through revaccination in children and adults.[26]

There are three types of PCV developed, namely 7-valent pneumococcal conjugated vaccine (PCV7), 10-valent pneumococcal conjugated vaccine (PCV10) and 13-valent pneumococcal conjugated vaccine (PCV13). In Hong Kong, PCV7 was the first PCV incorporated into the Childhood Immunisation Programme in September 2009. Since October 2010, PCV7 was replaced by PCV10 which has an additional serotype 1, 5, 7F coverage. After the registration of PCV 13 which included three more serotypes (3, 6A, 19A), the Scientific Committee on Vaccine Preventable Diseases recommended the incorporation of PCV13 into the Childhood Immunisation Programme.[27] Unlike foreign countries such as European countries where PCV is indicated for adults aged 50 years and older and children aged 5 years or younger, PCV is only indicated for children <5 years of age in Hong Kong.[28] This is because the indication for adults is still under evaluation and pending approval for registration in Hong Kong.

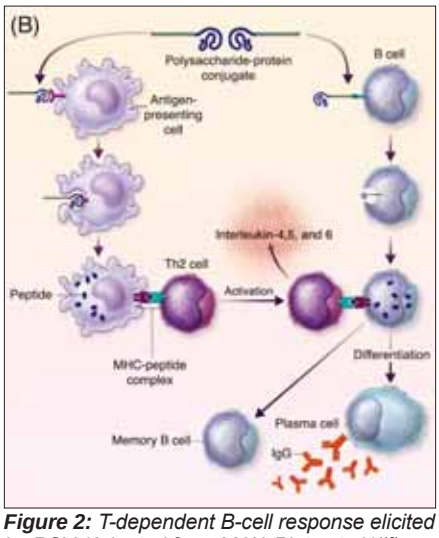

Figure 2: *T-dependent B-cell response elicited by PCV (Adapted from M.W. Pletz et al.)*[16]

Herd immunity

Although, people aged between 2 to 50 years are not indicated for PCV, people in this age group can still get protection from herd immunity. That is when a certain portion of community is immunized with vaccines against a contagious disease, members who are not immunized can still be protected from the disease because there is little opportunity for an outbreak (Fig. 3).

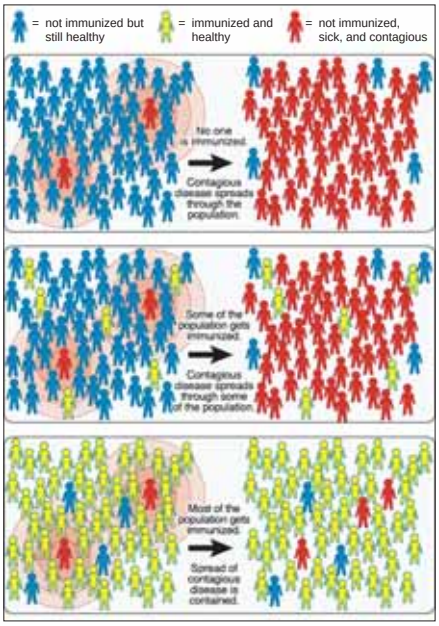

Figure 3: *How does herd immunity work? (Adapted from National institute of Allergy and Infectious Disease)*[29]

In the case of IPD, pneumococcus would colonize in the nasopharyngeal area; vaccination with PCV in children can reduce their nasopharyngeal carriage of the PCV serotypes and hence reduce the transmission of these serotypes to unvaccinated adults.[30]

For the vaccine ability to reduce the burden of IPD in adults, the US Centre for Disease Control (CDC) has assessed the IPD burden beginning in 1997 before the introduction of the heptavalent PCV (PCV7), through introduction of a PCV7 pediatric national immunization program (NIP) in 2000 that continue to present. Before the introduction of PCV7, annual IPD rates increase at 35 years of age, and increase with each subsequent decade of life and death rates in adults age ≥ 65 years were approximately 3 times that of infants age <1 years. Thus, immunization with PPV23 did not show any apparent effect on US rate of IPD, based on CDC surveillance data and population-based studies.[31,32] In contrast, after launching the PCV7 NIP, a reduction in pneumococcal disease due to vaccine serotypes over a 7-year period in older children and adults in all age groups, including adults over 65 years of age in the US can be seen and this is believed to be due to the herd immunity as described above.[33] Since the inclusion of more serotypes in PCV is continuing, the reduction in disease due to herd immunity is expected to be more apparent. However, the herd immunity is not universally observed after launching PCV7, for example, rate of adult IPD in Denmark and Germany remain relatively unchanged over past 5 years, and extent of decrease in Spain is not as apparent as that seen in the US.[34-36] This discrepancy may be due to the variations in PCV7 vaccination programs in different countries, such as difference in primary and booster dose uptake, and application of 'catch-up' immunization campaigns. Therefore, caution should be made when extrapolating the PCV7 herd immunity effect to PCV13 effect in other countries setting.

Serotype replacement

Serotype replacement is a phenomenon describing a rise in IPD caused by non-PCV7 serotypes following the reduction of rate of IPD by PCV7. This can be explained by the elimination of PCV7 serotypes which unmask the non-PCV7 serotypes which were previously minority strains. The lack of immunity against the non-PCV7 serotypes would cause the bacterial serotypes switching and resulting in serotype replacement.[37] The most common replacement serotypes in Hong Kong is 19A that is now becoming an important cause of IPD and multiple antibiotics resistant strain.[11] Other replacement serotypes that are not covered by PCV7 include 1, 3, 5, 6A and 7F.[38] These 5 serotypes (1, 3, 5, 6A, 7F) are covered by the PCV13 (Table 3) which has replaced PCV7 and PCV10 as part of the childhood immunization program of the Department of Health in Hong Kong for children <2 years of age.[27]

Table 3: Coverage of different pneumococcal vaccines

Vaccine	Coverage
PPV23	1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, 33F
PCV13	1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F
PCV10	1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 23F
PCV7	4, 6B, 9V, 14, 18C, 19F, 23F

DUAL PPV23 AND INFLUENZA VACCINATION DURING INFLUENZA PANDEMIC

Influenza predisposes individuals to bacterial community-acquired pneumonia and during influenza pandemic, secondary bacterial pneumonia has been an important cause of morbidity and mortality.[23] Therefore, PPV23 vaccination might reduce the risk of pneumococcal bacteraemia and related complication during influenza pandemic that may heavily affect healthy young adults.[39] The benefit of dual PPV23 and influenza vaccination was shown by the risk reduction of ICU admission and death by dual vaccination with PPV and TIV (Trivalent influenza vaccine) in elderly persons.[40]

VACCINATION PROGRAM CURRENTLY AVAILABLE FOR ADULTS IN HONG KONG

Elderly Vaccination Subsidy Scheme (EVSS) is held by the government and aims at encouraging elders aged 65 or above to receive vaccination against seasonal influenza and pneumococcal infection. The subsidy for pneumococcal polysaccharide vaccine (PPV) was effective since its launch in October 2009 while the subsidy for seasonal influenza vaccine was commenced on 26 September 2011. Elders who are aged 65 or above are entitled to a $130 Government subsidy per dose of seasonal influenza vaccination received from private doctors enrolled in the Scheme. Elders are also entitled to a $190 Government subsidy per dose of pneumococcal vaccination if they aged 65 or older and have never received pneumococcal vaccine before. Some elders aged 65 years or above may get free vaccination under Government Vaccination Programme if they meet the following criteria.[41]

- Residents of RCHEs [a] and eligible residents of RCHDs [a]
- Community living persons aged 65 years or above with chronic medical problems [b] attending public clinics
- Community living persons aged 65 years or above receiving CSSA [a]
- In-patients under HA [a] and aged 65 years or above:
  - with chronic medical problems [b], or
  - in infirmary psycho-geriatric, mentally ill and mentally handicapped units/wards

[a] Abbreviations:

RCHDs: Residential Care Homes for the persons with disabilities
RCHEs: Residential Care Homes for the Elderly
CSSA: Comprehensive Social Security Assistance
HA: Hospital Authority

[b] Chronic medical problems includes:

- Chronic cardiovascular disease (except hypertension without complications)

- Pulmonary, metabolic or renal disease
- Obesity (BMI 30 or above)
- Immunocompromised
- Children and adolescents (aged 6 months to 18 years) on long-term aspirin therapy
- Chronic neurological condition that can compromise respiratory function or the handling of respiratory secretions or increase the risk for aspiration
- Lack the ability to care for themselves for their increased risk of complications and death associated with influenza infection

VACCINATION SCHEDULE

PPV23 is recommended for elders aged 65 years or above, with or without additional risk conditions. Other people who are at high risk groups are also advised to consult family doctors on having the vaccination for personal protection.[23] The high risk groups include:

- Persons aged between 2 to 65 years with history of IPD
- Weakened immunity, such as cancer patients, HIV/ AIDS patients
- Chronic illnesses such as diabetes mellitus
- Cochlear (inner ear) implants.

According to the Scientific Committee on Vaccine Preventable Disease,[23] PPV23 is recommended for:

- Elders aged 65 or above who have never received PPV23 before
- Elders aged 65 who have received one dose before age 65 years but were more than 5 years earlier.

Elders who have received PPV23 after age 65 do not require revaccination. Routine revaccination with PPV23 was not recommended because The Scientific Committee on Vaccine Preventable Disease has concluded that there is insufficient data regarding safety of receiving three or more doses of PPV23.

PATIENTS COUNSELING POINTS (PPV23)

Patients should be informed that pneumococcal vaccine is generally safe and usually well tolerated

Side effects of pneumococcal vaccine include:

- Mild, local side effect (swelling and pain at the injection site)[42]*
- More severe systemic reactions are rare

*Local reaction may be more severe upon revaccination, but they will resolves within a few days without treatment.

The health condition of the patients should also be checked before vaccinating because there are several precautions for PPV23. These includes:[43]

- Persons with severely compromised cardiovascular or pulmonary function. Risk is significantly higher if systemic reaction occurs.
- Persons who have chronic cerebrospinal fluid leakage. Vaccine may not be effective.
- Persons who have moderate or severe acute illness. Vaccination should be deferred.

For smokers aged between 19 to 64 years, they are recommended to quit smoking in addition to PPV23 vaccination to reduce the risk of pneumococcal disease.[44] This is because:

- The risk for IPD decreases by about 14% each year after quitting smoking.
- In about 13 years after quitting smoking, the risk would return to a level similar to a person who have never smoked.

TREND FOR PNEUMOCOCCAL VACCINE DEVELOPMENT

Before recommending the type of pneumococcal vaccine for elderly adults, comparative evaluations of PPV23 and PCV13 with regard to the long-term immunogenicity and effectiveness have to be done. If PCV can successfully replace PPV23 in protecting adults, the next challenge would be to introduce a large number of serotypes using conjugation methods because the number of serotypes included in PCV 13 is fewer than the serotypes contained in PPV23.

Although PCV13 currently covers 80% of serotypes causing IPD in Hong Kong in 2011 including serotypes 3 (24%), 14 (14%) AND 19a (14%),[9] the formulation of PCV may need to change soon because of serotype replacement. However, introducing a large number of serotypes is technically difficult and larger number of carrier protein molecules can reduce the antibody response to polysaccharide antigen.[46] Currently, there is a 15-valent PCV (PCV15) under investigation which includes more serotypes.[47]

CONCLUSION

Studies have shown that vaccination with PPV23 in elderly is cost-effective in preventing IPD.[8] Therefore, recommendation for PPV23 vaccination in elders aged ≥65 years was issued worldwide. Despite these recommendations, there are several limitations for using PPV23, such as the poor vaccine uptake in adults resulting in variation in effectiveness for different individuals,[45] the short duration of efficacy which can only last for 3 to 5 years and the incapability to establish a B-cell memory which limits the ability for an individual to receive multiple vaccinations. The value of PPV23 has also been challenged by the introduction of PCV due to the impact of herd immunity. Lastly, investigation on the use of PCV13 on adults is ongoing. It is hoped that indication for adults will be approved in Hong Kong soon so that adults will be benefited by having longer period of protection.

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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.)

2 CE Units

Invasive Pneumococcal Disease in Adults

1. ***Pneumococcal disease is caused by:***

   A) Influenza A
   B) Staphylococcus aureus
   C) Streptococcus pneumoniae
   D) Group B Streptococcus

2. ***Types of Pneumococcal Disease can include:***

   A) Invasive pneumococcal disease only
   B) Otitis media in children
   C) Non-invasive pneumococcal disease only
   D) Invasive pneumococcal disease, sinusitis, pneumonia, meningitis and otitis media, etc.

3. ***Which one of the followings is a false statement regarding pneumococcal polysaccharide vaccine (PPV23)?***

   A) The pneumococcal polysaccharide vaccine contains 23 pneumococcal serotypes associated with pneumococcal disease
   B) The pneumococcal polysaccharide vaccine is a type of conjugate vaccine
   C) PPV23 is recommended for elders aged 65 years or above, with or without additional risk conditions.
   D) PPV23 is not recommended for use in children less than 2 years of age

4. ***Which body in Hong Kong conducts pneumococcal serotype surveillance?***

   A) The Agriculture, Fisheries and Conservation Department
   B) Food and Environmental Hygiene Department
   C) Each private GP clinic
   D) Public Health Laboratory Services Branch (PHLSB) of the Centre of Health Protection

5. ***The problems with treating pneumococcal disease include:***

   A) Antibiotics such as erythromycin is becoming increasingly resistant with rates in HK increasing to above 70%
   B) More expensive alternative antimicrobial agents may be required which may prolong hospitalization and increase medical costs
   C) Antibiotic resistance is a worldwide problem. Not just in Hong Kong.
   D) A & B
   E) A, B & C

6. ***Which of the followings is/are correct regarding the mechanism of pneumococcal polysaccharide vaccines in the body:***

   A) Pneumococcal polysaccharide vaccines produce a T-cell independent response in the recipients' body
   B) T dependent antigens will only elicit a secondary response and only produce IgM antibodies.
   C) IgM antibodies do not produce an adequate immunologic memory response even after re-exposure to the same antigen
   D) A & B
   E) A & C

7. ***Cross-reactive material 197 (CRM197) is a type of:***

   A) Antigen
   B) Antibody
   C) Protein for conjugation
   D) T cell

8. ***Pneumococcal Vaccines available for use now in elderly patients include:***

   A) PCV7, PCV10, PCV13
   B) PCV13
   C) PPV23
   D) PCV13 & PPV23

9. ***"Herd immunity" is a phenomenon for when no one is immunized and the contagious disease spreads throughout the population***

   A) True
   B) False

10. ***The Elderly Vaccination Subsidy Scheme (EVSS):***

    A) is provided by the HK Government and targets adults aged 65 years and older.
    B) It encourages the population to receive pneumococcal and influenza vaccination.
    C) Elders are entitled to $190 Government subsidy per dose of pneumococcal vaccination
    D) Was launched in 2009
    E) All of the above

Answers will be released in the next issue of HKPJ.

Over-the-Counter Medicines or Food Supplements for Weight Control

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ABSTRACT

Obesity is regarded as a health risk to a person and also a social burden as it may increase the risk of many diseases and lead to economical lost. Therefore, there is a need for everyone to maintain a healthy body weight. There are increasing numbers of non-prescribed products claiming to offer some effects on body weight. Slimming dietary supplements, in particular, have become very popular. Some herbal substances, which have been known worldwide to induce slimming and lose weight for long time, are also easily available in the market. They are the basic ingredients included in many over-the-counter (OTC) medicines or food supplements available in pharmacies and health food stores. Though common folks claimed on the anti-obesity property of these herbs, most popular products are having minimal clinical studies to support the said claims and to ensure their efficacy and safety. The presence of adulterants in many OTC slimming food supplements is imperceptible that everybody should be very cautious on this emerging public health threat. Proper diet and strict exercise regimen are still the best way to lose weight.

Keywords: *obesity, weight control, OTC products, slimming dietary foods, adulterants, sport exercise*

INTRODUCTION

Obesity is a physical state in which excessive fat is stored at various sites of the body. Ordinary obesity is quite common, especially in adults at middle age. Extreme obesity or localized accumulation of body fat is less common and suggests unusual etiologic factors. Although heredity may play a contributory role, there is only one prim cause of obesity; i.e. caloric intake persistently exceeding caloric output. Since the capacity of the body to store protein and carbohydrate is strictly limited, excess food in any form is converted into, and stored as, fat.

There are various reasons why many people want to get rid of their excess fats. The most trending reason is to improve body image or to enhance energy. Setting a reasonable goal is important to succeed in weight loss efforts. A steady regimen for weight loss is needed for a safe and healthy weight loss. Recently, people with serious health problems related to body weight may have a good reason to lose weight. Accumulation of excess body fats resulting to unhealthy state is the condition commonly known as obesity.[1-2] This is determined based on the measurement of an individual's body mass index (BMI), waist-hip-ratio, and abdominal circumference.[3] Obesity is considered as one of the leading public health problems nowadays.[4-5]

Table 1. Over-the-counter products or food supplements originated from plants that possess slimming effects[7-12]

Trade or Brand Name	Form	Source	Common Names	Chemical Components	Dosages
Atlantic Kelps, Kelp Norwegian, Kelp	Capsules	*Laminaria japonica, L. saccharina, L. digitata, Macrocystis pyrifera*	Brown Algae, horsetail, *Laminaria*, Sea girdles, Sea weed, sugar wrack, tangle weed	Fucoidans, 1-3β glucans, laminarin, laminine, histamine	1 tablet or capsule P.O. in 1 day
Bladderwrack, Kelp/ Lecithin/B6,Pacific Kelp, Kelp Combination tabs	Dried plants, liquid extract, soft gel, tablets	*Fucus vesiculosus*	Black tang, Sea oak, Bladder focus, Sea wrack	iodine, bromine, mannite, fucoidan	4-8 ml P.O. before meals, 3 tablets daily,16 g plant 1 pt of water and then administer 2Fl oz P.O. t.i.d
Khat	Raw leaves	*Catha edulis*	Cat, Chat, Gad, Miraa	Cathinone, cathine	100-200 g leaves chewed at a time
Ananase	Candy, extracts, juices, syrups, whole fruit	*Ananas comosus*	Golden rocket, Pineapple, Ananas	Citric acid, malic acid, Vitamin A, bromelain	No consensus exists
Ephedra*	powder	*Ephedra sinica*	Ma Huang	Ephedrine	Combined with caffeine
Guarana	fruit	*Guarana antarctica*	guarana	Guaranine	Combined with caffeine
Gymnema	leaves	*Gymnema sylvestris*	Gurmar, Gymnema, miracle fruit, cowplant	flavonol glycosides, saponins, gymnemic acid	Used as tea
Apple Cider Vinegar	essence of apple cider	Compounded product	Apple	vinegar	500 mg
Green Tea Phytosome Complex	Extract of green tea	*Camelia sinensis*	Compounded product of green tea	Catechol, EGCG, Soya lecithin	140 mg
Herbalife	Tablet, powder	Formulated product	Extract of various plants	Cellulose, minerals, vitamins etc	Not specified

*known to have toxicity and it has been banned.

ANTI-OBESITY HERBS

There are many plants that are known to have anti-obesity effects. Although the effects may be slower compared to anti-obesity drugs, it gains worldwide acceptance because these herbal plants are naturally occurring, safer, and are usually part of our daily diet. These herbs include garlic, tamarind, guggul, nutmeg, pride of India, and black pepper which are responsible for their ability to decrease cholesterogenesis.[6] Tartaric acid is present in cabbage which is responsible for inhibiting conversion of carbohydrates to lipids in the body.[6] Black pepper contains piperine responsible for reducing the levels of very low-density lipoprotein (VLDL), low density lipoprotein (LDL), and total plasma cholesterol.[6] Tables 1 and 2 show the list of common over-the-counter slimming agents or food supplements from common herbs (Fig. 1) including their chemical composition, mechanism of action, dosages, and adverse effects.

Figure 1: *Common herbs or vegetables with anti-obesity effects.[19] (1st top row L to R: Gymnema sylvestris; fucus vesiculosus, Gingko biloba, Laminaria digitata; 2nd middle row, L to R: Guarana antarctica, Ananas comosus, Catha edulis, Brassica olearacea; 3rd bottom row, L to R: Citrus aurantium, Plantago ovata (Psyllium), Amorphophallus Konjac, Avena sativa (oats)*

DIABETIC AND SLIMMING NON-PRESCRIPTIONAL FOOD SUPPLEMENTS

There is an issue as to whether or not food supplements for diabetics are also suitable for slimming. Diabetic products cannot be used interchangeably with slimming products because the sugars are equivalent to sucrose or glucose in terms of calories. These diabetic food supplements contain xylitol, sorbitol, and fructose. However, slimming aids (Table 3) are containing low calories and high fibers and therefore, can be a good food supplements for diabetics. A diet with high polyunsaturated fats and vegetable oils with reduced saturated fats can lead to decrease in cholesterol level.[20] Non-digestible polysaccharide fibers in the diet can result to lowering of blood sugar levels. Apples, wheat bran, nuts, and vegetables are rich in fibers. The mechanism of action of lowering of blood glucose level due to intake of fibers may be due to reduction in the total intake of calories and the viscosity effect as well.[20] Furthermore, dietary fibers can decrease and stabilize interprandial plasma glucose and insulin levels compared to diet without fiber supplements. It may also induce satiety.[21] Hydrogenated carbohydrates like polyols can be used as sugar

Table 2. Mechanistic actions and adverse effects of some substances relevant to the function of losing weight[13-18]

Components	Mechanism of Action	Side Effects
Rhubarb root	Laxative	Dehydration & electrolyte imbalance
Flaxseed	Laxative	Dehydration & electrolyte imbalance
Cascara	Laxative	Dehydration & electrolyte imbalance
Gingko biloba	Reduce stress- or depression-related eating	nausea, vomiting, diarrhea, heart palpitations and restlessness, Headaches, dizziness, possible increased risk of bleeding, gastrointestinal discomfort
St John's Wort	Reduce stress- or depression-related eating	dizziness, confusion, tiredness and sedation, drug interactions, gastrointestinal symptoms
Pantothenic acid (vitamin B_5)	Enhance fat or carbohydrate metabolism	nausea, headaches, diarrhea and a lack of energy
Hydroxycitric acid	Enhance fat or carbohydrate metabolism	Stomach pain
Green tea	Enhance fat or carbohydrate metabolism	Drug interactions, potential liver damage
Pyruvate	Enhance fat or carbohydrate metabolism	None to date
Licorice	Enhance fat or carbohydrate metabolism	Pseudoaldosteronism, hypertension and hypokalaemia
L-carnitine	Enhance fat or carbohydrate metabolism	None reported
Chromium picolinate	Enhance fat or carbohydrate metabolism	None reported
White kidney bean extract	Enhance fat or carbohydrate metabolism	None reported
Conjugated linoleic acid	Enhance fat or carbohydrate metabolism	Insulin resistance
Sodium alginate	Promotes satiety	Blockage of the throat, esophagus or intestine if taken without ~ 250 ml of water or other fluid
Guar gum	Promotes satiety	Blockage of the throat, esophagus or intestine if taken without ~ 250 ml of water or other fluid
Glucomannan (Konjac extract)	Promotes satiety	Blockage of the throat, esophagus or intestine if taken without ~ 250 ml of water or other fluid
Psyllium	Promotes satiety	Blockage of the throat, esophagus or intestine if taken without ~ 250 ml of water or other fluid
Ephedra (ma huang) or ephedrine*	Stimulants or energy enhancers	Increased heart palpitation, psychiatric, autonomic and gastrointestinal adverse effects
Caffeine, theophylline or theobromine (from kola nut, guarana or maté)	Stimulants or energy enhancers	Irritability, heart palpitations, anxiety and other central nervous system events
Bitter orange	Stimulants or energy enhancers	Increased blood pressure, possible drug interactions
Chitosan (polyglucosamine)	Block dietary fat absorption	Gastrointestinal symptoms
Orlistat (Alli)**	Reduces fat digestion & absorption due to inhibition of pancreatic lipase	Diarrhea, frequent or loose stools (fecal incontinence), gas with discharge, oily spotting, abdominal pain, sinus infection, and backpain.

*Sale prohibited in USA since 2004

**The only over-the-counter weight loss medication approved by FDA.

Table 3. Common foods in our daily consumption that may have slimming effect[23-32]

Slimming Aids	Effects
glucomannan	Forms a gel when mixed with water in the stomach and triggers feeling of fullness
Korean pine Nut Oil	Decreases appetite
Conjugated linolenic acid (CLA)	Build lean muscle and lose belly fat
Low sodium nuts	Suppresses appetite, high in fibers
Canola Oil (with omega 3)	Suppresses appetite, essential fatty acid for the body
Sunflower oil	Suppresses appetite, contains essential fatty acids
Olives and Olive Oil	Suppresses appetite, contains essential fatty acids
Safflower oil	Suppresses appetite, contains essential fatty acids
Low fat salad dressing	lessens fat intake
Low fat cheese	lessens fat intake
Natural peanut butter	Suppresses appetite, lessens fat intake
Cold water fish	Suppresses appetite
Pumpkin seeds	Suppresses appetite, lessens snacking
Sunflower seeds	Suppresses appetite, lessens snacking
Flax seed	Suppresses appetite, lessens snacking
Avocado	Suppresses appetite, contains lecithin that increases fat metabolism
Cayenne peppers (capsaicin)	Sustained fat oxidation and weight maintenance
Chewing gums	Less food craving, improves mood and lessens stress
Weight loss pills	suppress appetite, burn more fat, increase metabolism, and also increase your energy
Wheat bread	Helps in the maintenance of blood sugar, lessens fat & salt in the circulation
Oats, bran, & fibers	Lowers sugar, decreases fat storage, prevents constipation
Lemon polyphenols	suppressed body weight gain and body fat accumulation by increasing peroxisomal β-oxidation through up-regulation of the mRNA level of ACO in the liver and white adipose tissue
Spirulina	Prevents hyperlipidemia, hypertension, and diabetes mellitus
Slimming Tea *(Equisetum Debile Roxb, Pericarpium Citri Reticulatae, Fructus Hordei Gerimiatus Rhizoma Alismatis, Herba Agastachis, Fructus CrataegiSemen Raphaini, Oolong Tea, Camelia sinensis etc.)*	Lowers blood pressure and body fat, diuretic

replacers. They can lower the sugar level, non-cariogenic, lowers insulin levels, colon hydrating, laxative, and low digestible carbohydrate.[22]

ISSUES AND CONCERNS ON OVER-THE-COUNTER SLIMMING PRODUCTS AVAILABLE IN HONG KONG

There is a global concern in the prominent rates of obesity. About 1/3 of the US population is considered obese.[33] According to the Population Health Survey 2003/2004 of the Department of Health of Hong Kong, the prevalence of obesity and overweight showed increasing trends with age with the highest prevalence among those aged between 55-64 in both males and females but the prevalence decreased among those aged 75 and up that may be due to underestimation of the degree of overweight because of the reduced lean muscle mass in elderly (Fig.2).[34]

Hong Kong is ranked number 5 in the world for abusing the use of weight control drugs.[35] There are various herbal slimming products available in Hong Kong market but most of them are with

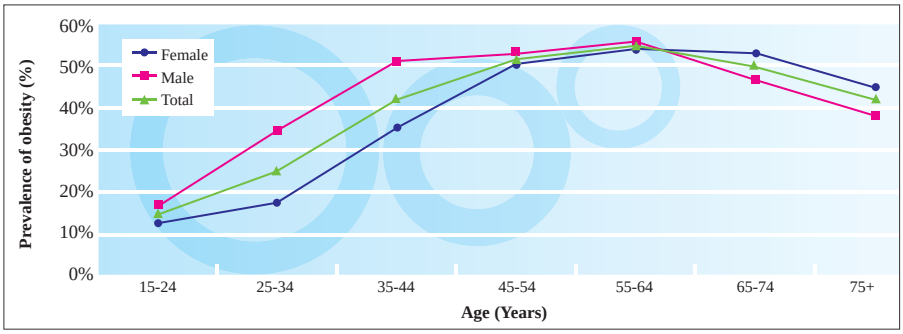

Figure 2: *Age-Sex related prevalence of obesity and overweight (BMI≥23) in Hong Kong, 2003/2004.[34]*

Table 3. Top six countries / regions that frequently abuse the slimming products[35]

Country/ Region	Daily intake (mg)/ thousand population
Brazil	12,483
Argentina	11,689
South Korea	9,838
USA	4,876
Hong Kong	4,514
Singapore	4,044

Source: International Narcotics Control Board (INCB)

minimal clinical studies. These include L-carnitine, chitosan, activated charcoal, capsaicin, caffeine, conjugated linoleic acid, hydroxycitric acid, chromium, ephedra, and spirulina.[35] Recently this year, the Department of Health of Hong Kong warned the public on slimming products with banned ingredients like sibutramine and phenolphthalein.[36] Strict medical supervision is required on the use of Orlistat (Alli) which is the only licensed drug in the treatment of obesity in Hong Kong which can be purchased over-

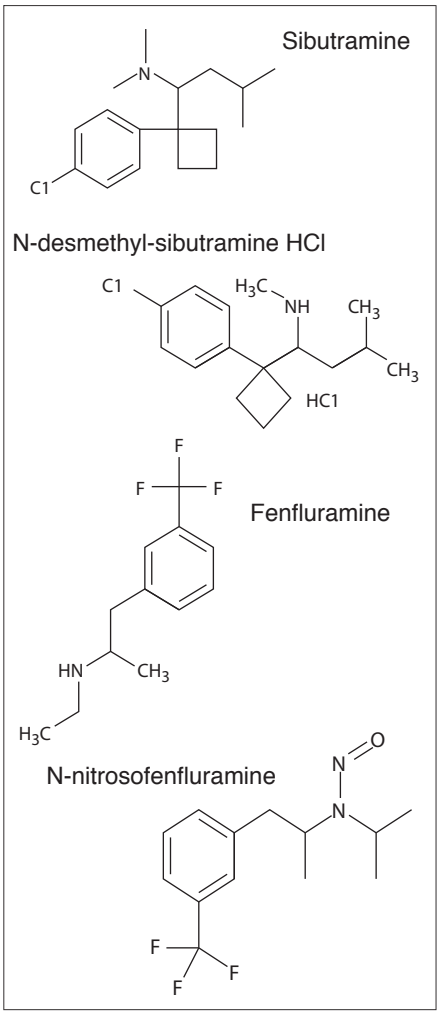

Figure 4: *Chemical structures of slimming drugs [Sibutramine & Fenfluramine] and their respective analogues [N-desmethyl-sibutramine HCl & N-nitrosofenfluramine] used as adulterants in over-the-counter slimming products.[40-44]*

the-counter.[30,37] Combination therapies are not recommended due to various contraindications.[37] Inappropriate use of drugs which are not intended for weight loss are also discouraged.[37] Adulterants were also reported to be incorporated in nonprescription slimming products which cause many adverse effects including thyrotoxicosis, gastrointestinal upset, liver toxicity, renal toxicity, carcinogenicity, cardiac malfunctions, irregularities in blood pressure, postural syncope, psychoses, insomnia, and other related complications.[37-39] Fig. 4 shows some pharmaceuticals that have been illegally added as slimming agents in OTC slimming products without disclosing their uses.[40] Analogues of sibutramine (e.g. N-desmethyl-sibutramine) and fenfluramine (e.g. N-nitrosofenfluramine) had been banned and yet were found in 2 slimming OTC products in Hong Kong. Consequently, persons were hospitalized after taking these adulterated slimming products.[40] In other extreme cases, there were reports indicating that many OTC food supplements claiming for slimming purposes had no significant effects in terms of weight loss in comparison to the placebo.[13]

CONCLUSIONS

Slimming products gain popularity worldwide. However, safety of these products is often ignored. The toxic effects and drug-drug interactions involving these agents should require rigorous clinical testing before they can be made available in the market although the effectiveness of food supplements do not have to be proven and are not subject to legislation. Health awareness related to the adverse and toxic effects are usually less emphasized. The consumers are desperately blinded by advertisements and their motives to take these slimming products for the sake of losing weight. There is inadequate public awareness related to the proper use of over-the-counter slimming aids. This is probable reason why abuse of such agents is very common. The undetectable use of analogues as adulterants to over-the-counter slimming food supplements is very harmful to the public. There is a necessity for heightened awareness among health professionals, regulatory boards, and the public consumers on this emerging health problem. Still, the least expensive and the safest management for obesity include proper diet, reduction in fat and calorie intake, high fiber diet from fresh fruits and vegetables, daily exercise, modification of lifestyle, water as fluid replacement, enough sleep, and a relaxed positive outlook in life.

Author's background

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Biochemical- and Biological-Based Studies of Abri Herba (雞骨草)

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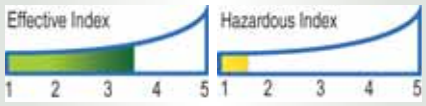
Botanical Name: *Abrus cantoniensis* Hance, *Abrus mollis* Hance, *Abrus pulchellus* Wal1, *Abrus precatorius* Linn
Family: Leguminosae
Common names/other names:
Indonesian: Saga (Indonesia)
Malaysia: saga negri, akar kachang inai (Peninsular)
Thailand: ma klam phueak (Chiang Mai), kho kiu (Chanthaburi), ma khaam yaan (Trang)
Vietnam: Kê cốt thảo
Chinese: Huang tou cao, Da huang cao, Jia niu gan zi , Hong mu ji cao, Zhu yao cao, Huang shi cao, Xiao ye long ling cao
Chinese Name: 雞骨草(Jigucao)
Part Usually Used: Whole plant except seeds
Common Uses: Cleanse damp heat, remove toxicity, dissipate blood stasis, ameliorate fatty liver, and relieve pain

ABSTRACT

Abri Herba is derived from the dried plants of *Abrus* species. *Abrus cantoniensis* Hance is the main constituent of a popular herbal tea in southern China, which contains alkaloid, hydroxylanthraquinone, sapogenol, saponins and other bioactive compounds. Biologically, the herb is hepatoprotective, and acts as an anti-cancer, anti-oxidative, anti-mutagenic, anti-inflammatory, anti-diabetic, anti-hyperlipidemia, anti-bacterial agent and has immuno-protective effects. Among the compounds that are isolated and identified from this herb are saponin compounds such as soyasaponin I and kaikasaponin III that are regarded as the main constituents responsible for the biological effects listed above. The toxic protein abrin, which has potent antitumor affects, is mainly concentrated in the seeds and can be easily removed during processing of the herbal material. According to clinical trials, extract of *A. cantoniensis* has also been shown to have positive effects on acute hepatitis and ABO incompatibility patients. Given this, the therapeutic potential of *A. cantoniensis* in treating hepatic-related diseases is envisioned in the future.

Keywords: *Abrus cantoniensis Hance, abrin, soyasaponin, kaikasponin, hepatoprotective, anticancer, antioxidant*



Contraindications

No report has been focused on the harmful effect of Abri Herba although their seeds contain toxalbumin abrin that might cause severe diarrhea, gastroenteritis with vomiting and abdominal pain after accidental intake. The seeds should be removed while ultilization.

Undesirable Effects

No undesirable effect of Abri has been reported. However, their seeds show toxic effect on organs and cells according to *in vivo* and *in vitro* studies.

Interaction with Conventional Drugs

The abrin has strong anti-platelet properties and can interact additively with anti-platelet drugs like aspirin, naproxen and warfarin.[120] Abrin can also interact with anti-hypertensive drugs and nephrotoxic drugs. Care should be taken when *A. precatorus* and *Cassia senna* were taken in combination, symptoms of weight loss, organ lesions and anemia might be observed.[123]

INTRRODUCTION

Abri cantoniensis Herba is the dried whole plant of *Abrus cantoniensis* Hance, which belongs to the *Abrus* genus in the Leguminosae family.[1] Out of the 12 species worldwide, four are found in China: *Abrus cantoniensis* Hance, *A. mollis* Hance, *A. pulchellus* Wal1, *A. precatorius* Linn. The morphology of the former two plants is similar and they are believed to have the same pharmacological effects.[2] *A. cantoniensis* and *A. mollis* are widely grown in Guangdong, Guangxi, Fujian, Guizhou, Yunnan provinces in China. Some can be found in southern east countries such as Thailand and Malaysia as well.

The dried whole plant of both *A. cantoniensis* Hance and *A. mollis* Hance are well-known in Chinese folk medicine and they have been used for clearing damp heat, removing toxicity, dissipating blood stasis, ameliorating fatty liver and relieving pain.[3] Additionally, they have been utilized for the treatment of liver-related disease (jaundice, acute or chronic hepatitis, cirrhosis with ascites), cholecystitis, mastitis, stomachache, rheumatism, thanatophidia bite injury, and urinary system infections.[1, 4, 5] *A. cantoniensis* is also a major component of the hepatitis therapy drug "Jigucao Capsule".

DESCRIPTION AND IDENTIFICATION

The morphologies of *A. cantoniensis* and *A. mollis* are similar and the latter is regarded as a confused species.[2]

Macroscopic appearance

A. cantoniensis Hance is a climbing liana with height of 1-2 m. The branches are slender, smooth, while leaflets are oblong or obovate-oblong in shape (Fig. 1). The leaves are 0.5-1.5 cm long and 0.3-0.6 cm wide. The backs of the leaves are strigose and pilose. Flowers are approximately 6 mm long with fascicled short rachis and short pedicel. The color of the corolla is either purple-red or light purple. The legumes are flat and beaked with 4 or 5 black-brown colored seeds at the apex. The florescence and fruiting period start between June and August. The root is grayish-brown and is coarse with fine longitudinal wrinkles. The grayish-brown colored stem is extremely thin and is covered with sparse, short pubescence. The herb has slight fragrance and is bitter in taste.[1]

A. mollis Hance is a climbing liana as well. The root is grayish-brown with developed lateral roots. None or as few as one to two branches are observed near the rhizome. The stem is about 2 mm in diameter, which is larger than that of *A. cantoniensis*. The surface of stem is velvety with yellowish-green color twigs. The size of the leaves is 1.0-2.5 x 0.5-1.0 cm with about 9-16 pairs of leaflets. The upper epidermis of the leaves is puberulous while the lower is white pilose. The vein of the leaves is not obvious (Fig. 2).

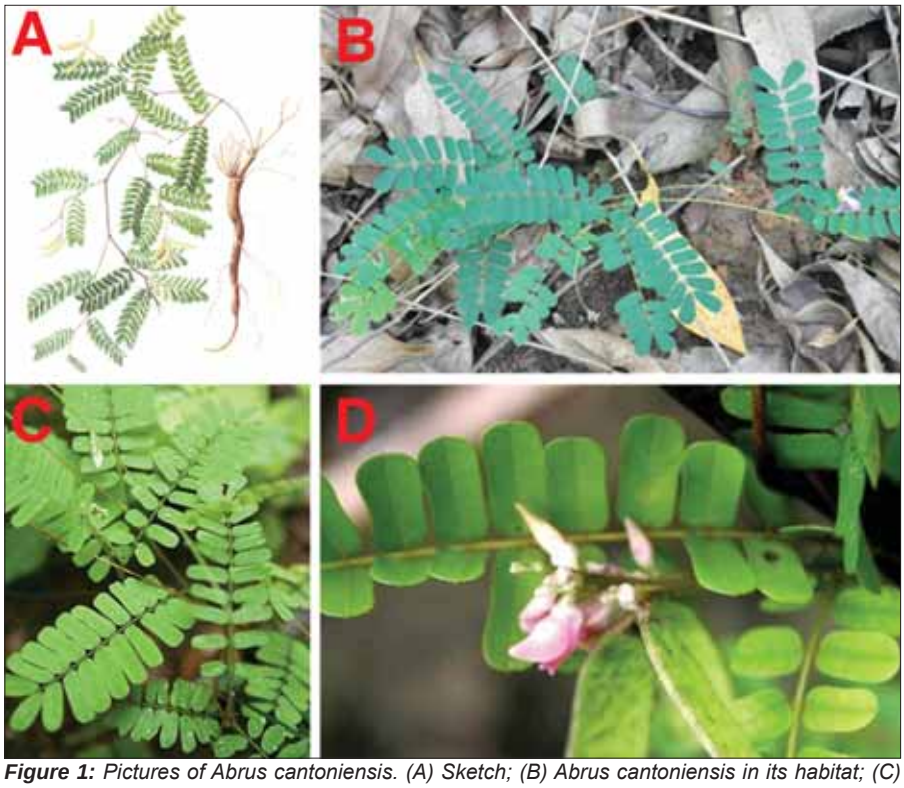


Figure 1: *Pictures of Abrus cantoniensis. (A) Sketch; (B) Abrus cantoniensis in its habitat; (C) Leaf; (D) Enlarged view of flower and fruit (adopted from http://www.hkwildlife.net/viewthread.php?tid=22775)*

Figure 2: *Morphological appearance of Abrus Cantoniensis Herba (A) and Abrus Mollis Herba (B), root of A. cantoniensis (C1), root of A. mollis (D1), stem of A. cantoniensis (C2), stem of A. mollis (D2), leaves of A. cantoniensis (C3), leaves of A. mollis (D3).*

Microscopic description

Root

The cork of the brownish root of *A. cantoniensis* consists of several layers of subsquare or rectangular shaped cells. The cortex is narrow with stone cells and prisms of calcium oxalate arranged in a cycle. The phloem is relatively thin and the cambium is formed in a cycle. The xylem has scattered vessels and is radially arranged. The width of xylem ray is about 2 to several rows of cell width (Fig. 3).

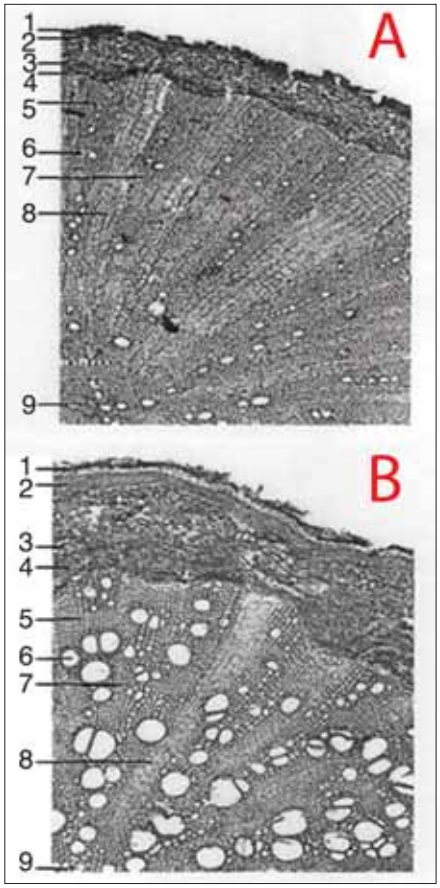


Figure 3: *The root transverse section of Abrus cantoniensis (A) and Abrus mollis (B) (10× magnification) (Cited from Liu et al. 2008)[124] 1 epidermis, 2 cortex, 3 bast fibre, 4 phloeom, 5 secondary xylem, 6 secondary eylem vessel, 7 xylogen, 8 wood ray, 9 primary xylem vessel*

Stem

The cork of the stem of *A. cantoniensis* also contains several layers of subsquare or rectangular shaped cells. The cortex is relatively thin and has visible prisms of calcium oxalate and stone cells. The stem contains numerous phloem fibers which are arranged in a circle. The xylem is relatively broad and the vessels are radially distributed. The pith of stem is broad which is generally broken and hollow in mid-part. The parenchymatous cells have subrounded shapes (Fig. 4).

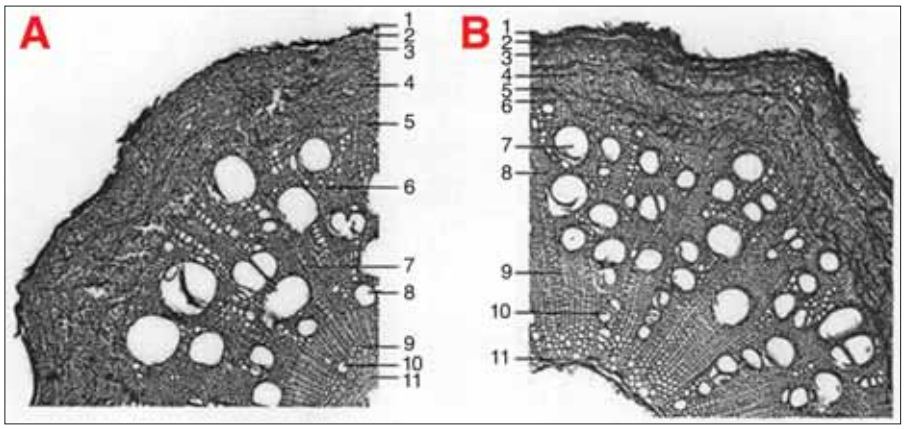


Figure 4: *The stem transverse section of Abrus cantoniensis (A) and Abrus mollis (B) (10× magnification) (Cited from Liu et al. 2008)* [124] *1=epidermis, 2=cortex, 3=bast fibre, 4=phloeom, 5=cambium, 6=xylogen, 7=wood, 8=secondary xylem vessel, 9=primary xylem, 10=primary xylem vessel, 11=marrow*

Leaf

The upper epidermis of leaves contains one layer of subsquare or rectangular shaped cells. The prisms of calcium oxalate are occasionally observed under the epidermal cells. The palisade tissue of leaves consists of two layers of palisade cells. Cells in the spongy tissue have subrounded shapes and are loosely distributed. The vascular bundles are collateral and the xylem vessels are radially distributed. Abounding fibers are observed around the vascular bundles (Fig. 5).

BIOACTIVE COMPOUNDS

Abrus Cantoniensis Herba

Several types of bioactive compounds have been isolated and identified in *A. cantoniensis* Herba: alkaloids, hydroxyanthraquinones, sapogenols, saponins, flavonoids and more. Chemical structures are shown in Fig. 6.

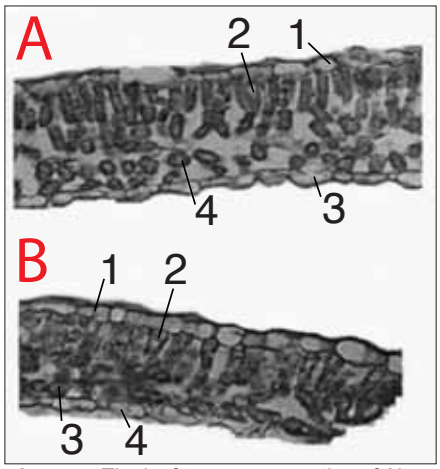


Figure 5: *The leaf transverse section of Abrus cantoniensis (A) and Abrus mollis (B) (20× magnification) (Cited from Liu et al. 2008)*[124] *1=upper epidermis, 2=palisade tissue, 3=lower epidermis, 4=spongy tissue*

Abrin

Abrin is a toxalbumin found in the seeds of *A. cantoniensis* Hance, and *A. precatorius* (rosary pea). The toxic glycoprotein consists of abrin A, B, C, D and abrus agglutinin.[6] The molecular mass of abrins A, B, C, D range from 63 to 67 kDa, while that of abrus agglutinin is 34.9 kDa.[7] Abrin A is a heterodimeric glycoprotein that belongs to the type II ribosome inactivating proteins family. It consists of two chains A and B which are connected with a single disulfide bond. The former has N-glycosidase activity and is responsible for protein synthesis inhibition, while the latter is a lectin-like chain that can bind with cell-surface receptors and penetrate into the cells.[8]

Alkaloid

Abrine, hypaphorine and choline are the main alkaloids of *A. cantoniensis*.[9,10] Abrine (N-methyl-L-tryptophan) is a bioactive indole alkaloid found in the *Abrus* genus of the Leguminosae family.[11]

Hydroxyanthraquinone

Chrysophanol (1,8-dihydroxy-3-methyl-anthraquinone) and physcion (1,8-dihydroxy-3-methoxy-6-methyl-anthraquinone) are the main hydroxyanthraqinones which have a anthraquinone ring structure.[12]

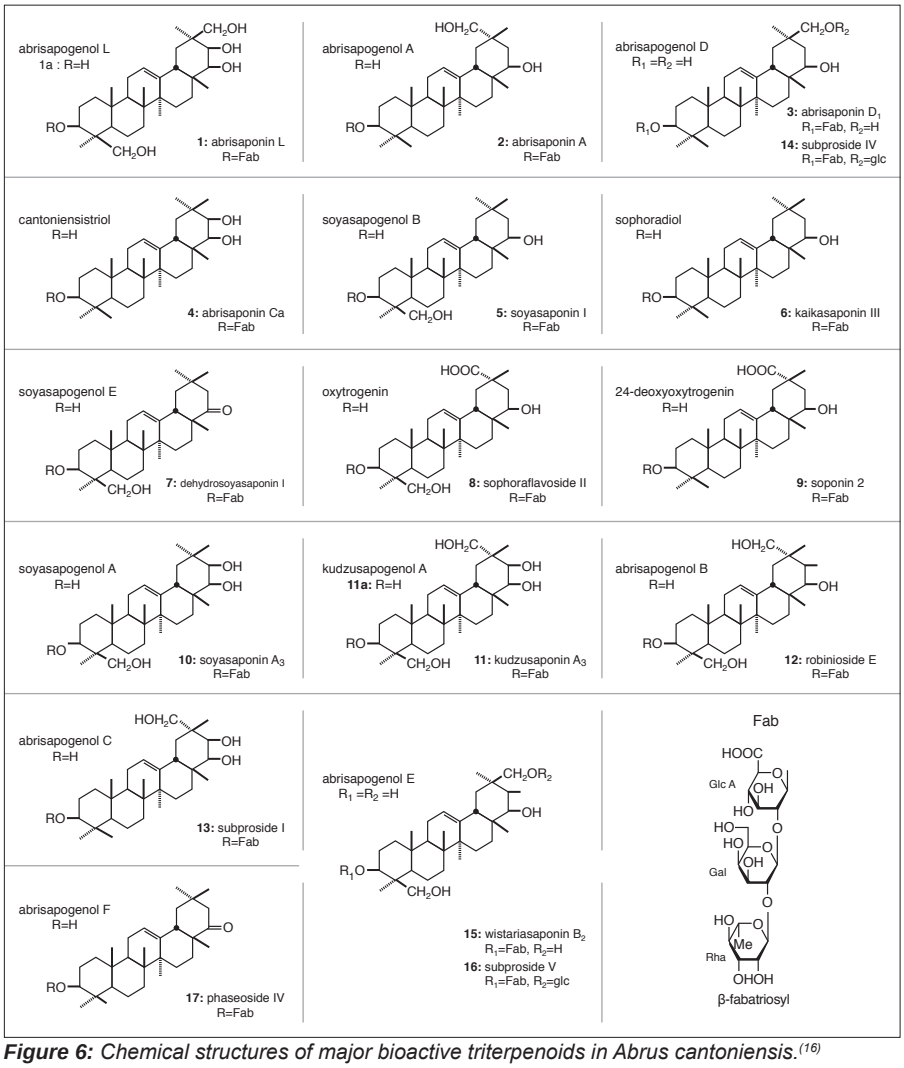


Figure 6: *Chemical structures of major bioactive triterpenoids in Abrus cantoniensis.*[16]

Sapogenol

Sapogenols have a oleanene-type structure with different functional groups. Cantoniensistriol, sophoradiol, soyasapogenols A, soyasapogenols B were isolated from the hydrolysate of the crude saponins of *A. cantoniensis*.[13] Abrisapogenol A-H, I (3-O-[α-L-rhamnopyranosyl-(1→2)-β-D-galactopyranosy-(1→2)-β-D-glucuronopyranosyl]), glycyrrhetinic acid, glabrolide, kdzusapogenol A have been identified in the hydrolysate of the crude saponins as well.[14, 15] Recently, a new sapogenol called abrisapogenol L was isolated and characterized by Miyao *et al*.[16]

Triterpene saponin

Triterpene saponin is a chemical compound that contains a olean-12-ene type triterpene structure and a branch sugar chain connected with the C-3 position of ring A. Abrisaponins A, Ca, D_1-D_3, F, I, L, So_1-So_2, SB, soyasaponin I, kaikasaponin III, dehydrosoyasaponin I, saponin 2, soyasaponin A_3, kudzusaponin A_3, robinioside E, subproside I, subproside IV, subproside V, wistariasaponin B2, phaseoside IV have been isolated and purified from *A. cantoniensis*.[14,16-18]

Other compounds

β-sitosterol, stigmasterol, tannins, anthraquinone glycosides and saponins were obtained from the methanol extract of roots by Wong *et al*.[19] Additionally, ursolic acid, 4′-methoxy-2′-hydroxychalcone and 2′,4′-dihydroxychalcone were isolated from the ethyl acetate fraction of the aerial part of *A. cantoniensis*.[20] Lupeol, ethyl protocatechuate, daucosterol, protocatechuic acid, quebrachitol, 7, 3′, 4′-trihydroxy-flavone, adenine, adenosine, biflorin, isobiflorin, N, N, N-trimethyl tryptophan, betulinic acid were isolated from *A. cantoniensis* as well.[21]

Abrus Mollis Herba

The constituents of *A. mollis* Herba are similar to those of *A. cantoniensis* Herba.[20] Betulinic acid, vanilic acid, inositol methyl ether, soyasaponin I, kaikasaponin III, dehydrosoyasaponin I, β-sitosterol, stigmasterol, nonacosanyl caffeate, daucosterol, sucrose, lupeol, ursolic acid, oleanolic acid, 7,4'-dihydroxy-8-methoxyisoflavone have been identified in *A. Mollis*.[11, 22]

Abrus Precatorius Herba

Three triterpenoids namely abruslactone A, methyl abrusgenate, and abrusgenic acid were isolated from A. precatorius Linn.[23] Moreover, four sweet-tasting triterpene glycosides, abrusosides A, B, C, D were isolated and identified from the leaves of *A. precatorius*.[24,25] 3-*O*-g-d-glucuronopyranosylsophoradiol methyl ester, (20S,22S)-3g,22-dihydroxycucurbita -5(10),24 -diene-26,29-dioic acid i-lactone, 3-*O*-[6'-methyl-g-d-glucuronopyranosyl]-3g,22g -dihydroxyolean-12-en-29-oic acid methyl ester and sophoradiol were isolated from the acid hydrolyzed methanol-soluble extract of the leaves as well.[26] The latest report highlighted the identification of a new triterpenoid saponin, 3-*O*-*β*-D-glucopyranosyl-(1→2)-*β*-D-glucopyranosyl subprogenin D and subprogenin D, triptotriterpenic acid B, abrusogenin in the leaves and stems.[27]

ISOLATION, PURIFICATION AND IDENTIFICATION OF THE CHEMICAL COMPOUNDS

Alkaloid

Abrine and hypaphorine are major alkaloids of *A. cantoniensis* that can be extracted within 10 minutes using microware digestion with 25% methanol as solvent, solid and liquid ratio of 1:10 at 50°C.[28]

Previously reported HPLC analysis of abrine and hypaphorine used isocratic elution as a separation method, with combined mobile phase of methanol, acetonitrile, water, acetic acid and triethylamine.[29-31] Abrine and hypaphorine can be successfully separated with gradient elution within 52 minutes.[28, 32]

Anthraquinone

Chrysophanol and physcion were obtained from the crude acidic aglycones through silica gel chromatography, petroleum ether and ethyl acetate (4:6) elution and recrystallization.[12]

Sapogenol

Sophoridiol, cantoniensistriol, soyasapogenol A and B were obtained from the n-Butanol extracted crude saponins. The crude saponins were further hydrolyzed and detected through TLC. The neutral sapogenols were chromatographed though Si-gel and were eluted with solvents with different polarity. Fractions in the same solvents were subjected to crystallization which gave the above four compounds.[13]

Saponin

Miyao *et al.* (1996) have separated approximately 17 compounds from the methanol extract of *A. cantoniensis* Herba. More specifically, methanol extracts were partitioned subsequently with n-hexane, 80% MeOH, 40% MeOH, and ethyl acetate. The fraction residue was subjected to MCI gel CHP 20P column chromatography which gave 7 fractions. Different fractions were further subjected to a Sephadex LH-20 column, preparative HPLC and silica gel. Furthermore, IR spectra, 1H- and 13C-NMR spectra, and FAB-MS were performed to identify all the compounds.[16]

The HPLC profile of hepatoprotective oleanene glucuronide (OG) of the Pueraria Thomsonii Flos containing sayasaponin I, kaikasaponin III has been reported. Water added with 0.05% trifluoroacetic acid (TFA) was prepared as mobile phase solvent A, while acetonitrile, water and TFA with a ratio of 60:40:0.05 (v/v) were prepared as solvent B. The gradient elution program was as follows: 0- 30 min, 0-83% of solvent B; 30-35 min, 83% solvent B; 35-40 min, 83-100% solvent B; 40-45 min, 100% solvent B. The flow rate was 1 mL/min with column temperature of 40°C. The constituents were detected with a UV detector at 205 nm wavelength.[33]

BIOLOGICAL EFFECTS

Liver-related diseases

The hepatoprotective effects of *A. cantoniensis* and relevant constituents have been widely reported.

Symptoms and therapies of various kinds of liver-related disease
Infectious hepatitis

Hepatitis is a disease condition caused by a viral infection that causes inflammation of the liver. Hepatitis A, B and C are the top three common types of hepatitis. Each is associated with different causes and symptoms.

Hepatitis A: Hepatitis A is an acute liver disease caused by the infection from the hepatitis A virus. The patient's condition is often dependent on the age. Hepatitis A is commonly asymptomatic in young

patients while aged patients experience jaundice as a common symptom. The onset of the disease is very sudden and is followed by jaundice and dark colored urine. Routine laboratory tests show elevated levels of serum alanine and aspartate aminotransferase, which decline rapidly each week. Serum bilirubin levels also rise following the elevation of serum alanine concentration. However, it has been shown that the symptoms of jaundice cease after approximately 2 weeks. The serum alanine and bilirubin concentrations also return to normal within 6 months from the onset of the disease.[34] The diagnosis involves the detection of immunoglobin M antibodies of hepatitis A virus or elevated serum aminotransferase levels in blood work. Occasionally, a hepatitis A infection from contaminated food by digestion occurs without a detectable elevated level of serum aminotransferase.[34]

Hepatitis B: Symptoms of hepatitis B are similar to that of hepatitis A. However, hepatitis B tends to cause more chronic damage to the liver and puts the patients at high risk for irreversible damage without proper treatment. Chronic hepatitis B infection may lead to more serious conditions such as liver cirrhosis or liver cancer in the long term. The most common route of infection is through the exchange of body fluids with an infected individual. Similar to hepatitis A, patients with hepatitis B infection experience no symptoms or mild symptoms such as flu, nausea or jaundice. Herbal remedies such as phyllantus amarus has been shown to be effective in treating chronic hepatitis B.[35]

Hepatitis C: The major route of transmission is through the exchange of body fluids between two individuals. Also, 90% of the individuals taking drugs intravenously are at high risk. Other common routes of transmission are during dental or surgical treatments, circumcision and ear piercing.[36] Studies show that hepatitis C may lead to the development of cirrhosis 20 years after the preliminary infection.[37] The baseline diagnosis involves detection of anti hepatitis C virus. Another option is liver biopsy in patients with a more serious infection. Herbal medicines serve as an important method of treatment. For example, laccase, extracted from oyster mushroom *(Pleurotus ostreatus)* has been shown to slow down the replication rate of hepatitis C virus. However, the mechanism under this remedy is unknown as of now.

Fatty liver disease

Fatty liver disease is a condition where excess fat molecules accumulate in the liver through the process of steatosis. This condition commonly occurs in patients suffering from obesity or alcohol dependence. Also, the fatty liver disease is observed to be present in obese patients without the contribution of alcohol. Based on a study done by Koebnick *et al.* (2009),[38] nonalcoholic fatty liver disease (NAFLD) hospitalizations in children have been steadily increasing since 1986 in USA. Moreover, 20 years of data show that obesity discharges have been increasing in parallel with NAFLD.[38] NAFLD is common in patients with central obesity rather than overall obesity. Besides obesity, NAFLD is associated with other health conditions such as type 2 diabetes mellitus, glucose intolerance and hyperglycemia.[39] Patients have nonspecific symptoms and sometimes experience upper quadrant pain. However, NAFLD is asymptomatic in patients for the majority of the time. Blood work tends to show mildly elevated levels of aspartate aminotransferase and alanine amino-transferase. The most accurate diagnosis is obtained by liver biopsy. Although it is an invasive method, it is the most reliable method of determining the patient's condition. Patients are strongly encouraged to undergo weight loss and lifestyle modification, including diet. It is important to note that rapid weight reduction was reported to worsen the liver condition. Therefore, gradual weight loss of less than 1.6 kg per week is recommended.[40]

Acute liver failure

Acute liver failure is a rare condition where the patient, without previous history of liver disease, experiences abrupt loss of hepatic function. The major cause of acute liver failure is from the use of acetaminophen. Patients who have taken acetaminophen in conjunction with alcohol consumption, have poor nutritional support and taken drugs containing CYP450 inducers, are at highest risk.[41] Diagnosis involves routine laboratory works including complete blood count, viral hepatitis serology and urinalysis. There are specific therapies for patients depending on the cause of acute liver failure. With acetaminophen induced acute liver failure, administration of oral N-acetylcysteine (NAC) is suggested. For acute liver injuries associated with hepatitis B virus, intake of entecavir is recommended.[41] Proper nutritional support and serum glucose maintenance are important as well. Glucose should be monitored and infused accordingly. Patients in serious conditions should be considered for liver transplantation. It has been shown that herbal medicines such as salvianolic acid B extracted from Radix Salviae miltiorrhizae has clinical roles in improving acute liver injuries. In a laboratory experiment, rat models had significantly reduced serum alanine aminotransferase and aspartate aminotransferase following the injection of salvianolic acid B.[42]

Liver cirrhosis

Cirrhosis of the liver is a permanent damage of the liver, where blood flow to the liver becomes blocked. The major causes of liver cirrhosis include diabetes, chronic alcohol consumption, viral infections such as hepatitis B and C.[43] During the early stages, there are rarely any noticeable symptoms. Patients gradually feel weak and lose appetite as the scar tissues build up. As the condition progresses, patients may vomit blood and experience delayed gastric emptying. Patients with a serious condition usually need to undergo liver transplantation. However, Nagata *et al.* (2003) proposed hepatocyte transplantation as an alternative method of treatment.[44] After experimentally inducing liver cirrhosis with phenobarbital and carbon tetrachloride in rats, porcine hepatocytes were transplanted. The results showed that the rats had prolonged survival, implying that transplanted hepatocytes may alleviate liver failure in cirrhotic rats and patients in the future. Herbal remedies such as tetrandrine derived from the Chinese medicine Stephania tetrandra has been shown to treat portal hypertension which commonly leads to upper gastrointestinal hemorrhage in patients with liver cirrhosis.[42] This highlights the therapeutic potential herbal remedies may bring to treating chronic liver diseases such as cirrhosis.

Liver fibrosis

Liver fibrosis is a condition where excess extracellular matrix proteins such as collagen accumulate in liver. Late stage liver fibrosis may lead to liver cirrhosis and portal hypertention and patients often require liver transplantation for survival. The progression of liver fibrosis to cirrhosis takes approximately 15 to 20 years, after which patients experience renal failure and variceal bleeding.[45] The main causes of liver fibrosis are chronic alcohol intake, hepatitis C virus infections and nonalcoholic steatohepatitis.[45] The most accurate method of assessment is serial liver biopsy. However, liver biopsy is an invasive procedure that patients preferentially want to avoid. Therefore, simpler and noninvasive method of assessments involving laboratory tests such as platelet count

and serum aminotransferase levels have been used. Other methods such as ultrasonography and MRI have been proposed which cost less and are less invasive. Treatment options include the usage of anti-inflammatory drugs given that inflammation occurs before and after the development of liver fibrosis.[45] Compounds derived from medicinal herbs such as glycyrrhizin and oxymatrine have been shown to have antifibrotic values.[42]

Liver carcinoma

The main cause of liver carcinoma is cirrhosis, which stems from the infection by hepatitis B and C viruses. The prognosis of hepatocellular cancer is dependent on the tumor stage, patient's condition and the remaining functional ability of the liver.[46] Patients develop symptoms only at the advanced stages of cancer. At the early stage, patients are commonly asymptomatic and can undergo resection and liver transplantation as treatment options.[46] Lencioni *et al.* (2004) proposed percutaneous ablation as the best available option for treating patients at the early stage of cancer, who are not potential candidates for resection or liver transplantation.[47] Patients who show cancer-related symptoms, such as pain and physical weakness are classified as advanced stage. These patients have approximately a 3 year survival rate, subject to receiving a liver transplantation. Glycyrrhizin, the active component of Chinese medicine, Glycyrrhizia uralensis has been used as a remedy for hepatocellular carcinoma. It has been shown that glycyrrhizin has anti-cancer properties in promoting antibody production and antioxidative activities.[42]

Antihepatotoxic activity

The antihepatotoxic activities of *A. cantoniensis* capsule (which contains A. cantoniensis Herba, Virgate wormwood Herb, Cape jasmine fruit, Pseudo-ginseng, Bezoar, Radix Paeoniae Alba) were studied. Results indicated that the herbal extract capsule has potent effects in decreasing the activities of serum alanine aminotransferase and aspartate aminotransferase in carbon tetrachloride (CCl_4) and D-Galactosamine induced acute liver injuries in mice, at doses of 14.47 g/kg body weight and 12.96 g/kg body weight, respectively. No histopathological damage was observed.[48] In CCl_4 and naphthyl isothiocyanate induced acute liver injury mice model, administration of the major alkaloid abrine, significantly decreased the activities of serum alanine aminotransferase and aspartate aminotransferase as well as total bilirubin (TBIL) content at high and low concentration.[49]

As reported by Nohara *et al.* (1999), the crude saponin fraction had over 70% inhibitory effects on CCl_4 induced liver injury in the mice model. The saponin fraction contains about 15 sapogenols including abrisapogenols, all of which have a methyl group at C-17 position and several oxygen functions on the E-ring. Moreover, about 23 oleanene glycosides with glucuronic acid in the *endo*-sugar chain were isolated from these fractions.[5] Soyasaponin I and kaikasaponin III were the representative oleanene glycosides of the fraction that showed potent hepatoprotective effects. Both of them protected primary rat hepatocytes against CCl_4 (5mM)-induced acute cytotoxicity, by inhibiting the elevation of glutamic pyruvic transaminase (GPT) and glutamic oxaloacetic transaminase (GOT). The kaikasaponin III was far more effective than the soyasaponin I and glycyrrhizin (positive control), and the most effective activity was obtained at a dose of 50 µg/ml. However, soyasaponin I and kaikasaponin III showed increased toxicity at a high dose (500 µg/ml) (Fig. 7).[18] Furthermore, the monoglucuronide of soyasapogenol B and sophoradiol were also reported to have potent anti-hepatotoxic effect on *tert*-butyl hydroperoxide (t-BuOOH) induced cytotoxicity in human-liver-derived HepG2 cell lines. Moreover, soyasaponin I, kaikasaponin III and monoglucuronide of sophoradiol increased the cytotoxicity of *t*-BuOOH in HepG2 cell lines.[50]

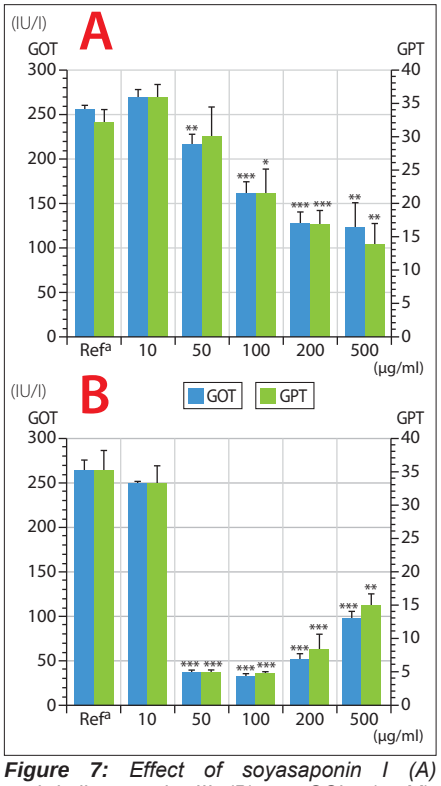


Figure 7: *Effect of soyasaponin I (A) and kaikasaponin III (B) on CCl4 (5mM)-induced cytotoxicity in primary cultured rat hepatocytes.*[18]

18β-glycyrrhetinic acid (GA), the aglycone of glycyrrhizin (GL), showed protective activities on CCl_4-induced hepatotoxicity in mice models. The hepatoprotective activities are associated with potent free radical scavenging activities and the inhibition of cytochrome P450 2E1 expression. Before the administration of CCl_4, mice were pretreated with GA at doses of 10, 50 and100 mg/kg body weight. Results showed that the activities of serum ALT and AST, peroxidation of hepatic lipid, and depletion of hepatic cellular glutathione (GSH) significantly decreased at a dose of 50 mg/kg. However, mice treated with GA alone did not exhibit increased GSH contents and glutathione-*S*-transferase (GST) activities in the liver.[51] GSH is a peptide that consists of glutamate, cysteine and glycine that acts as the major antioxidant in liver.[52] GSH is a unique substrate of GSH peroxidase and GST which takes part in the microsomal peroxidase and free radical scavenging reactions.[53] Cytochrome P450 2E1 is the primary human isozyme that is responsible for CCl_4 bioactivation and an efficient catalysis of reductive reactions.[54-56] The demethylation of N,N-dimethylnitrosamine and the hydroxylation of *p*-nitrophenol and chlorzoxazone are the most effective reactions for detecting the content of P450 2E1.[57] Jeong *et al.* (2002) have shown that GA pretreated t-BuOOH-toxic mice have decreased hepatic microsomal *p*-nitrophenol and aniline hydroxylation activities, along with reduced expression of P450 2E1 protein.[51]

Anti-hepatitis B virus effect

More than 500 million people worldwide suffer from viral hepatitis, where hepatitis B and hepatitis C are the most prevalent infections.[58] Hepatitis B is an infectious disease which results in symptoms of liver inflammatory lesion, and is mainly induced by hepatitis B virus (HBV) infection. The detection of hepatitis B surface antigen (HBsAg) and hepatitis B e antigen (HBeAg) in serum are indicators of HBV infection.[59] Hepatitis B virus deoxyribonucleic acid (HBV DNA) is the genetic material that carries the blueprint of the virus.[60] It sensitively indicates how rapidly the virus is replicating in the liver even if the patient is HbeAg-negative.[61,62] Thus, high levels

of HBV DNA indicates a high rate of HBV replication. The common therapies of HBV mainly involve antivirus antibodies and cytotoxic T lymphocytes.[63, 64] However, the reactivation of the HBV replication was observed in patients undergoing cytotoxic therapy. The HBV is shown to persist for a long time even after the patient recovers from acute viral hepatitis, although an active maintenance of a cytotoxic T lymphocyte response was observed.[65,66] For this, hepatitis B therapy has long been recognized as a tough research and clinical problem.

Effects of TCMs on this disease have been evaluated by various researchers.[67-69] Wang *et al.* (2002) reported that the herbs *Phyllanthus amarus, P. niruri, P. urninaria,* and constituent oxymatrine can significantly inhibit about 45% of the serum conversion rate for HBeAg and HBV DNA. Compound 861 from *Salvia miltiorrhiza* and 9 other herbs significantly increased collagen degradation, suppressed tissue inhibitor of metalloproteinase (TIMP) expression and showed potent inhibitory activity against fibrogenesis. Double liver biopsies in 107 patients with HBV-related diseases showed high fibrosis reversal rates after half a year's administration with compound 861.[70]

The inhibitory effects of hepatitis B virus were also obtained in the ethanol extract of *A. cantoniensis* Herba and *A. Mollis* Herba in vitro. The serum of patients infected with hepatitis B virus was incubated with ethanol extracts of *A. cantoniensis* at 37ºC for 8 hours. The activities of HBsAg and HBeAg were detected using the enzyme-linked immuno sorbent assay (ELISA) method. Results indicated that the ethanol extracts of *A. cantoniensis* can significantly suppress the activities of HBsAg and the HBeAg in serum at concentrations of 96 and 48 g/L. The inhibitory rates on HBsAg were 94.7% and 88.8%, while those on HBeAg were 73.2% and 87.2%, respectively.[71] The same effects were observed in the ethanol extracts of *A. mollis*. The inhibitory ratio on HBsAg were 23.1%, 16.8% at concentrations of 96 and 48 g/L, while the ratio was 19.6%, 17.2% on HBeAg at the same concentration, respectively.[72] Further research by Chen *et al.* (2011) indicated that ethanol extracts of *A. mollis* can inhibit the secretion of HBsAg and HBeAg in HBV-producing cell line HepG2 2.15 cell, at concentration of 4 g/L. The highest inhibitory ratio was 27.9%, 36.3% after 72 hours of incubation, respectively.[73]

Anticancer effects

Sathish *et al.* (2010) showed cytotoxic effects of chloroform and ethanol extract of the leaves of *A. precatorius* Linn on various kinds of human cancer cell lines, such as A549 lung cancer cell lines, HepG2 liver cancer cell lines, HCT116 colon cancer cell lines, Hela cervical cancer cell lines. Ethanol extracts showed more potent cytotoxic effects than chloroform extracts with IC_{50} values of <31.2 µg/mL. Moreover, ethanol extract of leaves showed strongest inhibitory effects on the growth of HepG2 liver cancer cells, with IC_{50} of 18.6 µg/mL.[74] Two constituents, abruslactone A and abrusogenin, isolated from the leaves and stems of *A. precatorius,* showed moderate growth inhibitory effects on MCF-7 human breast cancer cell lines, SW1990 human pancreatic adenocarcinoma cell lines, Hela cervical cancer cell lines and Du-145 prostate cancer cell lines. The latter compound had IC_{50} value of about 2-4 µg/mL against MCF-7, SW1990 and Du-145 cancer cells.[27]

The cytotoxicity of abrin has been widely reported. The A chain of abrin has *N*-glycosidase activity and is responsible for protein synthesis inhibition, while the B chain is a lectin-like chain that can bind with cell-surface receptors and penetrate the molecule.[75] Various reports showed that abrin can induce cell apoptosis by binding to a 30k D thiol-specific antioxidant protein (AOP-1) and attenuate the antioxidant activities of AOP-1, which lead to the elevation of intracellular ROS and the release of cytochrome *c*. Then this can trigger the activities of caspase-9 and caspase-3.[76-78]

Abrine exerts effects on human tumor cell proliferation by acting on tryptophan metabolism. In primary brain tumor, high uptake α-[^{11}C] methyl- L-tryptophan (AMT) is due to the increased metabolism of tryptophan, which indicates the activation of the kynurenine pathway that regulates tumor cell growth.[79, 80] Enzyme indoleamine2,3-dioxygenase (IDO) helps to convert the amino acid tryptophan into *N*-formylkynurenine during the kynurenine pathway of tryptophan metabolism.[81] It also promotes the acquirement of tumor antigen tolerance. The L form abrine is shown to be a potent inhibitor of IDO activity in Hela cell–based studies[82,83] which can significantly reduce tumor size in animal experiments.[84]

Physcion isolated from the aerial parts of *Rumex acetosa* was subjected to cytotoxicity assay against five human tumor cell lines, including non-small cell lung A549 cell lines, ovary SK-OV-3 cell lines, melanoma SK-MEL-2 cell lines, central nerve system XF498 cell lines and colon HCY15 cell lines. MTT assay showed moderate inhibitory action against five human cancer cells with IC_{50} values of approximately 22.41-26.88 µg/mL.[85] Moreover, physcion which originates from the wood of *Millettia leucantha* exhibited potent cytostatic effects on human small cell lung carcinoma cell line NCI.H187 with IC_{50} values of 4.30 µg/mL.[86] The potent cytotoxic effects of chrysophanol were observed in human ovary cancer cell SK-OV-3 and melanoma cancer cell SK-MEL-2, with IC_{50} values of 7.28 and 5.83 µg/mL, respectively.[85] Moreover, hydroxyanthraquinone compounds can also induce dose and time dependent necrotic cell death in J5 human liver cancer cells, by suppressing adenosine triphosphate (ATP) levels and increasing lactate dehydrogenase activity.[87]

In the human hepatocellular carcinoma HepG2 cell line, soyasapogenol A and B obtained from crude methanol extract of soy flour had inhibitory effects on HepG2 proliferation after 72 hours of treatment. The IC_{50} values obtained from the MTT assay were 52 µg/ml and 128 µg/ml, respectively. Cell cycle analysis with a flow cytometer indicated increased proportion of sub-G1 phase cells (Fig. 8), and confocal laser scanning microscopy showed typical morphological changes such as nuclear condensation and fragmentation.[88] The apoptosis induction effects were also observed in group B oleanane triterpenoid extract which mainly contains soyasaponin I (62%) and III (29%) with LC50 of 389 ± 0.02 µg/mL. The cell cycle analysis indicated 17.67% apoptotic cell accumulation in sub-G1 phase, multi-caspase assay showed 6.97% mid apoptotic and 12.87% late apoptotic, while TUNEL confirmed the apoptosis cell death with 40.45% proportion.[89] Accumulation of cell cycle proportion in sub-G1 phase indicates apoptotic cells with DNA content less than 2*n*.[90] Altered sialyltransferase (ST) expression is closely related to the process of oncogenesis, tumor progression, and lymph node metastases.[91] According to

Wang *et al.* (2004), soyasaponins I is a potent anti-ST reagent which modifies migration and adhesion behavior of cancer cells.[92] However, soyasaponin I does not inhibit cell growth o fcolorectal carcinoma HT-29 cell.[93]

Glycyrrhetinic acid (GA) showed cytostatic effects on the human hepatoma HepG2cell lines and arrested the cell cycle in the G1-phase. The apoptosis-induction effect is related to the activation of caspase-8 and the suppression of anti-apoptotic proteins such as Bcl-2 and Bcl-xL. However, the pro-apoptotic proteins Bax and Bak were not attacked.[94]

Antimutagenic effect

According to the research of Lee *et al.* (2005), physcion (0.1 mg/plate) efficiently protected 35.7% and 44.7% of the *Salmonella typhimurium* strains TA98 and TA100 against sodium azide (NaN_3) induced mutagenicity, respectively.[85] Park *et al.* (2002) demonstrated the antimutagenic effect of kaikasaponin III on aflatoxin B1-induced mutagenicity of *S. typhymurium* TA100. The number of revertants induced by AFB1 was decreased by 99%, while that of N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) was 75% at a dose of 1 mg/plate. This indicates that the compound can suppress the metabolic activation of AFB_1 and scavenge electrophilic intermediate capable of mutation.[95]

Anti-inflammatory effect

The anti-inflammatory activities of ethanol extract of the seed of *A. precatorius* Linn. were studied in a carrageenan induced inflammatory animal method. Administration of 375 mg/kg resulted in 62.68% inhibition of edema in an animal paw.[96]

Anti-inflammation activities of abrine were studied with the ear swelling animal method. Results showed a significant decrease in ear weights of mice.[49] In the carrageenan-induced rat-paw oedema model, administration of physcion resulted in a 65-68% decrease of edema volume at a dose of 40 mg/kg. In lipopolysaccharide (LPS)/IFN-γ activated murine peritoneal macrophage cultures, levels of nitric oxide (NO) radical and inducible nitric oxide synthase (iNOS) as well as cyclooxygenase (COX)-2 were decreased. This shows that physcion has anti-inflammatory effects against macrophages via the suppression of iNOS and COX-2 protein expressions in the NF-κB pathway.[97] Moreover, chrysophanol was able to inhibit the LPS-induced inflammatory responses in mouse peritoneal macrophages through the suppression of NF-κB and caspase-1 activation (Fig.9).[98]

Anti-inflammation effects of soyasaponin I were also elucidated. Soyasaponin I can attenuate lipopolysaccharide (LPS)-stimulated rat peritoneal macrophages colitis by inhibiting the NF-κB pathway. Soyasaponin I suppresses the production of: a) proinflammatory cytokines such as tumor necrosis factor (TNF)-α and interleukin (IL)-1β, b) inflammatory mediators like NO and prostaglandin E-2 (PGE-2), inflammatory enzymes such as COX-2 and iNOS. It also inhibits the phosphorylation of IκB-α, the nuclear translocation of NF-κB. On the other hand, in trinitro-benzene-sulfonic acid (TNBS)-treated colitic mice, soyasaponin I decreased the inflammatory markers, colon length, myeloperoidase, lipid peroxide (malondialdehyde and 4-hydroxy-2-nonenal), proinflammatory cytokines and NF-κB activation in the colon. Moreover, the glutathione content, superoxide dismutase, and catalase activity were elevated (Fig. 10).[99]

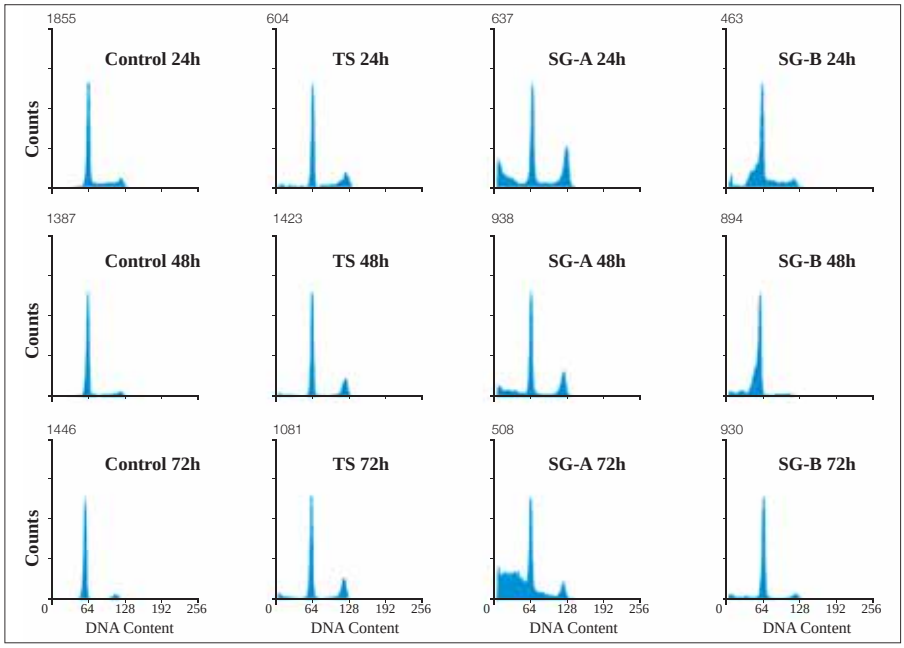


Figure 8: *DNA cell-cycle analysis of control cells, total saponin- (TS), sapogenol A- (SG-A) and sapogenol B- (SG-B) treated cells after 24, 48 and 72 h, respectively.*[88]

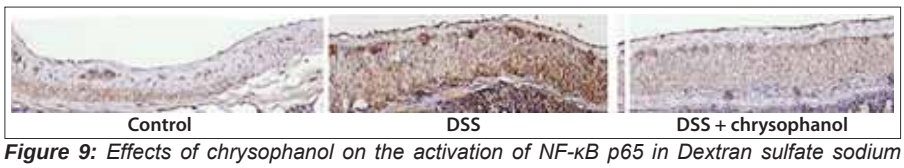


Figure 9: *Effects of chrysophanol on the activation of NF-κB p65 in Dextran sulfate sodium (DSS)-treated mice colon tissue. Colon was removed and the sections were stained with anti-NF-κB.*[98]

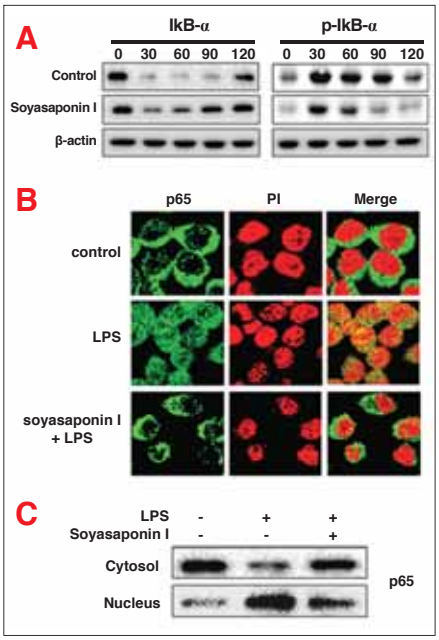


Figure 10: *Effects of soyasaponin I on IκB-adegradation and NF-κB activation in the peritoneal macrophages of LPS-induced colitic mice. (A). Time course of the degradation and phosphorylation of IκB. (B). Nuclear translocation of NF-κB by confocal analysis with p65 subunit antibody. (C). Immunoblot analysis of NF-κB activation.*[99]

Although the complement system functions as the key effector of the humoral immunity, excessively activated complement system produces active peptides and protein complex that leads to various diseases, especially the inflammatory diseases. The anti-complementary activities of sophradiol, soyasapogenol B, kaikasaponin III and soyasaponin I originating from *Pueraria lobata* have been studied. In vitro complement hemolysis assay indicated negative effects of sophradiol and soyasapogenol B. However potent anti-complementary activities were observed in kaikasaponin III and soyasaponin I with IC_{50} values of 54±1.5 and 61±6.3 μM, respectively. It was also shown that the free acid forms (-COOH) of glucuronic acid in saponins exhibit most potent anti-complementary activities, followed by the sodium salt forms ($-COO^-Na^+$) or methyl ester forms ($-COOCH_3$), and the reduced forms ($-CH_2OH$).[100]

Antioxidative effect

Relevant research on the antioxidative activities of extract of *A. cantoniensis* and *A. mollis* are relatively scarce. However, there are a few studies on the activities of their bioactive compounds isolated from other herbs. According to reports of Cai *et al.* (2004) and Krenn *et al.* (2003), chrysophanol and physcion have weak antioxidant activities against ABTS radicals, while being inactive towards DPPH radicals.[101,102] However, low antioxidant activities were observed against DPPH radicals in a report by Miura *et al.* (2002).[103]

The effect of soyasaponin I on the oxidation of corn oil and lard were investigated by Rigby *et al.* (1987). Despite the reaction of soyasaponin I with corn oil and lard, no antioxidative effects were observed according to the measurement of the levels of conjugated diene hydroperoxide, thiobarbituric acid and unsaturated fatty acids.[104] In a recent study, soyasaponin I was shown to have scavenging activities against the DPPH radical with IC_{50} value of 70.2 μM in vitro. Moreover, a potent inhibitory effect on lipid peroxidation was observed with 19.5 μM IC50 value (Lee *et al.* 2010).[99] The anti-lipid peroxidative actions of kaikasaponin III were reported by Park *et al.* (2002). Administration of 20 mg/kg kaikasaponin III inhibited 35% of lipid peroxidation in bromobenzene-treated rat model, which involves the prevention of malondialdehyde (MDA) formation caused by bromobenzene.[95] Moreover, the inhibitory effect of kaikasaponin III on the formation of malondialdehyde (MDA) and hydroxy radicals were obtained in serum and liver of the streptozotocin-induced diabetic rat. This indicates that kaikasaponin III can efficiently inhibit phase I enzyme activities given the low MDA content, xanthine oxidase and aldehyde oxidase activities. On the other hand, it can increase the activities of phase II enzymes like superoxide dismutase (SOD), glutathione peroxidase and catalase.[105]

Antidiabetic effect

The hypoglycemic and hypolipidemic influences of kaikasaponin III on streptozotocin-induced diabetic rats have been elucidated. Kaikasaponin III was intraperitoneally administrated at doses of 5 and 10 mg/kg body weight for one week. In comparison with the control group, blood glucose of the rats decreased about 39 and 43% at doses of 5 and 10 mg/kg, respectively. The body weights were increased 36 and 48%, accompanied with decreased total cholesterol, LDL- and VLDL-cholesterol and triglyceride levels. It indicated that the alleviation effect of kaikasaponin III was attributed to its antioxidative activities.[106] Further research of Choi *et al.* (2004) indicated the hypoglycemic and hypolipidemic effects of kaikasaponin III extract as well.[105]

Antihyperlipidemia effect

The hypolipidemic effect of decoction extract of *A. mollis* Hance have been studied through high-fat emulsion induced hyperlipidemia the rat model. Hyperlipidemia rats were administrated with 10, 20 and 30 g/kg body weight herbal extract for three weeks. The total blood glycerin and total cholesterol contents were significantly decreased, while high density lipoproteins (HDL) were elevated. Moreover, administration of *A. mollis* decoction ameliorated hemorrheological conditions caused by hyperlipidemia. Parameters of whole blood viscosity such as whole blood reduced viscosity (WRV), cassion viscosity, red blood cell aggregation index and red blood cell rigidity index etc. were decreased.[107]

Antithrombosis activity

Choi *et al.* (2004) showed that kaikasaponin III isolated from Puerariae Flos significantly increased the bleeding time, plasma clotting time and the tissue factor (TF) activity in streptozotocin (STZ)-toxiced rats. This indicates the anti-thrombosis effect of kaikasaponin III in STZ-treated rats.[105]

Antibacterial activity

Antibacterial activities of ethanol extract of *A. cantoniensis* on *Escherichia coli, Pseudomonas aeruginosas, Staphylococcus aurums* and *Klebsielia pneumoniae* were tested. Results showed that ethanol extract has antibacterial effects on the former two bacteria. For *P. aeruginosas*, the inhibition diameter was approximately 20.5 mm, while that of E. coli was approximately-17.5 mm. Effect of 1 g/ml ethanol extract was similar to 0.1 mg/ml tetracycline hydrochloride acid on *P. aeruginosas.*[108]

Immunoprotective effect

The ameliorative effects of abrine on experimental asthma and allergic shock were observed in a geunea pig model. Abrine administration caused inhibition of histamine phosphate induced dermovascular permeability elevation. However, no influences on the bronchial smooth muscles were observed.[109] Effects of abrine on immune organs were investigated as well. Administration of abrine increased in the weights of major immune organs thymus and spleen and elevated the secretion of haemolysin.[49]

The effects of oleanane-type triterpenoids on the expression of intercellular adhesion molecule (ICAM-1) on THP-1 human monocytic leukemia cells models were evaluated. Abrisaponin A, abrisaponin SB, abrisapogenol E and soyasapogenols B efficiently suppressed the expression of ICAM-1,[110] which participates in phorbol ester-stimulated adhesion reactions of B lymphocyte and myeloid cell lines and T lymphocyte blasts.[111, 112]

Other effects

The *A. cantoniensis* extract caused increase activity of rabbit intestine smooth muscle both *in vitro* and *in vivo*. Moreover, administration of *A. cantoniensis* also increased the swimming exhaustion time and endurance in mice models.[113] *A. precatorius* Linn is recognized as a potent herbal medicine for the therapy of coughs and catarrhal infections due to the glycyrrhizin detected in the leaves and roots.[74]

CLINICAL APPLCATIONS

Anti-acute hepatitis activity

In a clinical trial, 125 patients with acute hepatitis were randomly divided into a control group and a *A. cantoniensis* capsule administration group. The control group was only treated according to the occurrence of symptoms, while the experimental group consumed *A. cantoniensis* capsules on a regular basis. Results showed that *A. cantoniensis* capsules exhibited a total effective rate of 95.38% in 65 patients with acute hepatitis.[114]

ABO incompatibility

A medicinal soup containing *A. cantoniensis* Hance, Linearstripe Rabdosia Herb (xihuangcao), Indian Buead (fulin), Japanese farfugium herb (lianpeng), Glycyrrhiza (gancao) has been found to be effective for treating ABO incompatibility. Total efficient rate was 91.43%.[115]

SIDE EFFECTS / TOXICITIES

Poisoning

Saponin is a kind of chemical compound that is widely found in natural plant species, including *A. cantoniensis.* Although saponins have therapeutic values in enhancing nutrient absorption, it is a toxin with a bitter taste. If taken in large amounts, it is potentially toxic. In an experiment with rat liver cells, it was shown that soyasaponin I and kaikasaponin III exerted toxicity at the highest dose (500 μg/mL).[18] However, there is only a limited risk for experiencing toxicity with A. cantoniensis intake at a therapeutic dose as saponins cannot be absorbed by the human body. Also, the majority of the saponin content is removed during cooking processes so the harmful effects are generally not common.

Gastrointestinal

Abrin is a highly toxic protein concentrated in the Abrus seeds. It has caused death after accidental intake in the past. The lethal dose of abrin in animals is approximately 0.01 mg/kg body weight and the estimated lethal dose for humans is 0.1-1 μg/kg.[116] The most common abrin-induced damage is gastrointestinal toxicity. Symptoms of poisoning include severe diarrhea, gastroenteritis with vomiting and abdominal pain.[117] However, it has been shown that vaccination with abrin toxoid can help avoid abrin poisoning. Moreover, abrin also causes cell death by inhibiting protein synthesis.[118] Abrin-induced cell damage is shown to cause an increase in capillary permeability, which ultimately leads to tissue edema or vascular leak syndrome. However, the dangers of abrin intake can be avoided relatively easily through the extraction of the legume at a low cost.

An experiment done by Liu *et al.* (1990) showed that the activity of *A. cantoniensis* differs in different animal species.[113] In the experiment, administration of *A. cantoniensis* on rats enhanced the activity of intestine smooth muscles. However, when administered on guinea pigs, the effects were opposite and the activities of smooth muscles were directly inhibited.

Hepatic

When ingested, abrin may cause liver damage through the necrotizing action of the toxin. The serum level of hepatic enzymes such as aspartate transferase, alanine transferase and lactic dehydrogenase greatly elevate following ingestion. Laboratory tests will show increased level of bilirubin, which is indicative of lesions to the liver.[117]

Urinary

Abrin can cause hypotension or acute renal failure as a result of damage to tubular cells. This may lead to oliguria and anuria. The tubules may become blocked due to hemolysed red blood cells and cause renal failure.[117]

Contact dermatitis and local effects

Skin contact may cause irritation and give rise to allergic reactions. Early effects on eyes involve retinal haemorrhage. As the condition progresses, symptoms such as disorientation, impaired vision and swelling may occur.[117]

DRUG INTERACTION

The toxic protein contained in the *A. precatorius* seeds, abrin has strong anti-platelet properties. *In vitro* studies show that abrin can interact additively with anti-platelet drugs.[119] Common anticoagulant and anti-platelet drugs include aspirin, naproxen and warfarin.[120] One case report demonstrated that the hypertensive properties of Abrus seeds may interact with anti-hypertensive drugs.[121] Care should be taken when ingesting hepatotoxic drugs with Abrus seeds as the additive effects of the drugs can cause hepatocyte necrosis.[122] Similarly, animal studies report the additive effects of Abrus seeds with nephrotoxic drugs, which may lead to necrosis of renal convoluted tubules and cause changes in renal function tests.[122]

A study done by Omer *et al.* (1992) highlighted severe toxicological interactions of *A. precatorus* and *Cassia senna* when taken in combination.[123] Symptoms of weight loss, organ lesions and anemia were observed when a combination of Abrus and Senna was given to Lohmann boiler chicks.

CONCLUSION

Abri herba have been reported to exert various biological effects based on animal, cell model and even clinical trials. Saponegnols and saponins are the major bioactive compounds that contribute to hepatoprotective, anticancer and antioxidative effects. Although the biological effects are well-established, underlying molecular mechanisms are still not fully understood. Therefore, it is suggested to study effects of *Abrus* extract on liver-related diseases such as fatty liver disease, liver cirrhosis, and liver fibrosis in the future.

Author's background

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The Forbidden City International Pharmacist Forum 2012

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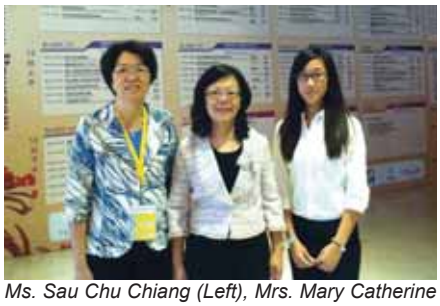
I had known I would be the only student joining the trip before I went to Beijing with Mrs. Mary Catherine Cheng, the President of the Pharmaceutical Society of Hong Kong; and Ms. Sau Chu Chiang, the Senior Pharmacist (Pharmacy Informatics and Automation Technology) at Chief Pharmacist's Office; nonetheless, I did not hesitate to participate. The experience of attending the Forbidden City International Pharmacist Forum turned out to be more rewarding than I had expected because it was not only packed with enormous amount of new pharmacy knowledge and technology information but also a lot of fun from socializing, eating and even shopping.



Ms. Sau Chu Chiang (Left), Mrs. Mary Catherine Cheng (Middle) and Anabelle Ngachung Wong (Right) at the venue of the Forbidden City International Pharmacist Forum 2012.

My first time in Beijing was before the Olympic Games; the Water Cube was not even finished at that time. Four years later, I arrived at the same city, amazed by how fast time flew. Once we stepped out of the plane, we could feel the joyful breeze. Beijing is much drier and cooler than Hong Kong; this small weather difference always reminded me that I was outside Hong Kong and it kept me staying excited. We settled in the Beijing North Star Continental Grand Hotel which was directly connected to the Forum venue. It was located right next to the Bird Nest.

The Bird Nest, situated next to the hotel and conference halls.

The Forum was held from 12 to 13 May 2012. On Saturday morning after the opening ceremony, in which Mrs. Mary Catherine Cheng was invited to give a speech, was a series of presentations under the topic 'medication safety risk, management and practice'. For instance, Mr. Thomas J. Johnson from the USA inspired us with the idea of establishing and maintaining a culture of medication safety in the pharmacy profession. Medication incidents occur usually when more than one staff is at fault therefore the culture of medication safety is important in avoiding multidisciplinary defects. The introduction of such idea tackles the drug safety problems from their roots and thus could be effective. I thought of the medication incidents in recent years and I could not help but wonder, if safety had become the principle characteristic of all healthcare providers, as it was supposed to be because no one could afford the price of an error, would Purinol incident even stand a chance? It takes efforts of all stakeholders of Hong Kong healthcare system and industry to insist on such safety culture and when it is in place, our reward shall be patients' health and safety. Mr. Shigeki Tsuda was an expert from Japan who shared with us Japan's experience in dealing with large scale and severe adverse drug reactions. His speech addressed the issue from a different angle from what I had learned in classrooms. The model of compensation and relief system set up by Japan was new to me and it surely has given me a new perspective of viewing adverse drug reactions and according procedures that a government could do. In the afternoon, presentations whose topics are 'risk of anti-infective drugs and management', 'risk management for information and medication', 'TDM, genomics and personalized medicine' and 'medication safety and management of chronic diseases' were given simultaneously in four different conference halls. I tried to run from one conference hall to another at different times so I could attend talks under all four topics. Ms. Carolina Ung brought Macao's experience in risk control of antimicrobial resistance in hospital to Beijing. My conversation with Caroline has made me realize how big a challenge it is to manage antibiotics risks because antimicrobial resistance is not a risk solely confronted by Macau but the whole China or even Asia. The problem is primarily global. In the second conference hall, I attended the talk about drug E-logistics by Mr. Zhang Jian from China. Informatics and technology are playing an increasingly important role in our healthcare system nowadays. From medication order entry at hospitals to drug information Apps developed by chain stores, electronic communication is an inevitably essential element to success. The speaker introduced the 1-D, 2-D and RFID bar code technology to us and presented clearly how warehouse management can be carried out efficiently with lowered probability to err. I went to the third conference hall and took a grasp at the development of clinical pharmacy in anticoagulant therapy in Singapore. Mr. Kong Mingchai told us, the concerned clinical pharmacy was still expanding and some Singapore-centred researches were carried out to optimize the pharmacists' clinical role in the therapy. The last conference hall

addressed issues related to chronic disease management. After listening to a detailed report on the performance of GLP-1 mimetic agent, Liraglutide, by Ms. Marianne O. Larsen Gronning from Denmark; and a thorough introduction to efficacy and safety of Statins with the latest research data by Ms. Liu Liping from China, I continued to sit in the same hall and attended the talk about improving medication adherence in chronic disease management by Mr. Joseph Dikun from the States. I was particularly interested in that topic because I believed patients' adherence and compliance could be the key to success of medication therapy, especially in chronic diseases; the speech by Mr. Joseph Dikun concurred with what I learned from my pharmacy practice lectures. I find it interesting how the same ideas repeat in the profession during different occasions; every time the information repeats, it imprints upon the deeper zone of my brain.

Ms. Chiang Sau Chu, Prof. Zhao Zhi-gang (Chairman of the Forum) and Mrs. Mary Catherine Cheng


The exhibition boards displayed the results of some latest researches done by various institutions in China.

On Sunday morning, presentations under the topics 'safety of injectable drugs and risk management', 'pharmacy college education, continuing education and assessment tools', 'drug safety evaluation and risk management' and 'education in rational drug use' were given simultaneously in four different conference halls. As the day before, I travelled from place to place without a rest to catch all the talks I wanted to listen. It was like a treasure hunt. The more moves I made, the more knowledge I collected, some into my brain, some into my notebook when my brain was overloaded. Owing to the series of reports about local paediatricians prescribing overdose medication to children in earlier times, Mr. Ian Chi Kei Wong caught me eyes with his presentation on medication safety in children. He quoted several cases in the UK in which deaths were resulted to warn pharmacists to be cautious about paediatric doses. It is again, an issue worth attention; because no one could ever imagine the victims' parents sorrow. A pharmacist has the responsibility to counter check the identity, strength and dose of a drug upon dispensing. However, there is a loop hole in local healthcare practice that hinders the safeguard of patients' health by pharmacists. Pharmacists might not be present when medications are dispensed in private clinics because prescribing and dispensing is yet to be separated in Hong Kong in all scopes of business and dispensing under the supervision of pharmacist is not a legal requirement in private clinics. That says, the lack of training and professional knowledge of personnel cannot be eliminated as the ground, other than the physicians' negligence, to overdosing children in private clinics.

Prof. Ian Chi Kei Wong educated us on "Medication Safety in Children".

The Forum was a full package of the most recent information, international experiences and insightful comments on many pharmacy related issues. It was an absolute pleasure to dive in and let myself be soaked with knowledge like a sponge; notwithstanding, the more speeches I listened to, the more I realized my ignorance. There were things that I did not understand; there were things that I had hardly heard of. I reckoned it was normal for a year two undergraduate; nonetheless I must keep myself up with my studies and do more self-learning in order to become a respectable pharmacist in the future.

The trip to Beijing was a delight because other than learning more about our profession, I also had the chance to enjoy the Beijing city with Mrs. Cheng, Ms. Chiang and her friends. Thanks to Ms. Chiang's extensive network in Beijing, we met Helen and she led us to the Beijing delicacy in a famous traditional Chinese restaurant which was a 'Siheyuan' decades ago. We were all astonished by the traditional Chinese acrobatics and other performances offered in the restaurant such as changing face and pulling tea. Another friend of Ms. Chiang's brought us to a hotel restaurant where fine buffet was served and we could dine while looking right at the glowing Water Cube. After four years, I finally see the finished Water Cube with my bare eyes! It was an invaluable opportunity to get to know many successful pharmacists such as Mr. Ivan Ng and Ms. Carolina Ung, the President and Secretary General of the Pharmaceutical Society of Macao respectively; and Mr. Ian Chi Kei Wong, Professor and Head of Pharmacy Department at the University of Hong Kong; to learn from them and to get some practice on talking with the professionals. As a pharmacist, solid science knowledge is vital but interpersonal skills are not to be overlooked. I believe I will need to talk with other professionals in addition to patients and their healthcare providers in my future career therefore experience like this would help a lot.


Beijing at night.


Traditional desserts in Beijing style.

Three days passed in no time. I could not believe the mainland China had developed so rapidly and the pharmacy profession had bloomed like after spring if I did not go and see Beijing myself. The visit has righted my biased impression and shaken me with deep reflection. Hong Kong might be proud of her developed state of healthcare and welfare system; but looking at the automation technologies and machineries displayed in the Forum, knowing that the role of clinical pharmacists in hospitals has been assured by legislation in China, what could we still boast about? Singapore has announced its effort in developing clinical pharmacists in different specialty areas; separation of prescribing and dispensing is not a goal to be reached but already plain fact in Macao. Speaking of the pharmacy profession, let us not compare with Europe and America first, but simply contrast with other Asian countries and cities, where is Hong Kong now? And where will she be in 5 years? 10 years?

While they were in Beijing, Mrs. Mary Cheng and Mr. Ivan Ng took the opportunity to meet with Ms. Ding Lixia, the new Secretary General of Chinese Pharmaceutical Association. In attendance were Ms. Li ShaoLi, Vice President, Mr. Chen Bing, Deputy Secretary General, Professor Jiang De-chun, Associate Professor of Xuanwu Hospital of Capital Medical University Department of Pharmacy and Ms. Zhang Jiang, Director of Organization Department. It was encouraging to learn that with the increasing importance of clinical pharmacists, the Chinese Pharmaceutical Association has sponsored hospital pharmacists to renowned institutions and hospitals in UK and USA to enhance their clinical skills. The meeting enabled exchange of views and better understanding of the progress of the pharmacy profession in Hong Kong, Macau and China.

(Front row from left): Ms. Chiang Sau Chu, Ms. Ding Lixia, Ms. Li ShaoLi, Mrs. Mary Cheng, Mr. Ivan Ng.
(Back row from left): Mr. Zhang Chiwah, Ms.Zhang Jiang, Ms. Caroline Ung, Mr. Chen Bing, Prof. Ian Wong, Prof Jiang De-chun

The 41st Term Practising Pharmacists Association of Hong Kong (PPAHK) General Council

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Presentation:
Pre-filled syringe for injection each 0.5 ml containing 100 or 150 mcg of corifollitropin alfa, a glycoprotein produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology.

Pharmacology:
Corifollitropin alfa is a sustained follicle stimulant with the same pharmacodynamic profile as (recombinant) Follicle Stimulating Hormone ((rec)FSH), but with a markedly prolonged duration of FSH activity.

In two randomized, double-blind, clinical trials, treatment with a single subcutaneous injection of Elonva for the first seven days of Controlled Ovarian Stimulation (COS) resulted in a significantly higher number of retrieved oocytes compared to treatment with a daily dose of (rec)FSH. Due to its ability to initiate and sustain multiple follicular growth for an entire week, a single subcutaneous injection of the recommended dose of Elonva may replace the first seven daily injections of (rec)FSH preparation in a COS treatment cycle. The long duration of FSH activity was achieved by adding the carboxy-terminal peptide of the β-subunit of human chorionic gonadotropin (hCG) to the β-chain of human FSH. Corifollitropin alfa does not display any intrinsic LH/hCG activity.

Indications:
Controlled Ovarian Stimulation (COS) in combination with a GnRH antagonist for the development of multiple follicles in women participating in an Assisted Reproductive Technology (ART) program.

Dosage and Administration:
In the absence of compatibility studies, Elonva must not be mixed with other medicinal products.

Women:
The recommended dosage, established in a treatment regimen with a Gonadotropin Releasing Hormone (GnRH) antagonist, is 100 mcg (0.5 ml) for women with a body weight ≤ 60 kg and 150 mcg (0.5 ml) for women with a body weight > 60 kg.

COS treatment cycle
- Day 1

It is administered as a single subcutaneous injection, preferably in the abdominal wall.

- Day 5 or 6

Treatment with a GnRH antagonist should be started on day 5 or day 6 depending on the ovarian response, i.e. the number and size of growing follicles and/or the amount of circulating oestradiol.

The GnRH antagonist is used to prevent premature Luteinising Hormone (LH) surges.

- Day 8

Treatment may be continued with daily injections of (rec)FSH until the criteria for triggering final oocyte maturation (3 follicles ≥ 17 mm) have been reached.

The daily dose of (rec) FSH may depend on the ovarian response. In normal responders a daily dose of 150 IU (rec)FSH is advised.

Administration of (rec) FSH on the day of human Chorionic Gonadotropin (hCG) administration can be omitted, depending on the ovarian response. In general, adequate follicular development is achieved on average by the ninth day of treatment (range 6 to 18 days).

As soon as three follicles 17 mm are observed, a single injection of 5,000 up to 10,000 IU hCG is administered the same day or the day thereafter to induce final oocyte maturation. In case of an excessive ovarian response, the risk for developing ovarian hyperstimulation syndrome (OHSS) should be minimized (see Warnings).

Children: The use of Elonva in children is not relevant within the approved indication.

Renal impairment: No clinical studies have been performed in patients with renal insufficiency. Since the elimination of corifollitropin alfa might be impaired in patients with renal insufficiency, the use of Elonva in these women is not recommended.

Hepatic impairment: Although data in hepatically impaired patients are not available, hepatic impairment is unlikely to affect the elimination of corifollitropin alfa.

Contraindications:
Patients with a history of hypersensitivity to corifollitropin alfa or to any of the excipients of Elonva.

Patients with a history of Ovarian Hyperstimulation Syndrome (OHSS).

Patients with tumours of the ovary, breast, uterus, pituitary or hypothalamus.

Patients with abnormal (not menstrual) vaginal bleeding.

Patients with primary ovarian failure, ovarian cysts or enlarged ovaries.

Patients with fibroid tumours of the uterus or malformations of the reproductive organs incompatible with pregnancy.

Warnings:
Before starting Elonva, the couple's infertility should be assessed as appropriate and putative contraindications for pregnancy evaluated. In particular, women should be evaluated for hypothyroidism, adrenocortical deficiency, hyperprolactinemia and pituitary or hypothalamic tumours, and appropriate specific treatment given.

Additional injections of Elonva should not be given within the same treatment cycle. More than one injection of Elonva within one treatment cycle or too high dose of Elonva and/or (rec)FSH are likely to increase the risk of OHSS.

In the first seven days after administration of Elonva, no (rec)FSH should be administered (see Dosage and Administration).

Limited data on the use of Elonva in combination with a GnRH agonist is available. Results of a small uncontrolled study suggest there is a higher ovarian response in combination with a GnRH antagonist. Therefore, the use of Elonva in combination with a GnRH agonist is not recommended.

Elonva has not been studied in patients with polycystic ovarian syndrome (PCOS). In these women the use of Elonva is not recommended.

The ovarian response was shown to be higher after treatment with Elonva than with daily (rec)FSH. Therefore, women with known risk factors for a high ovarian response may be especially prone to the development of OHSS during or following treatment with Elonva. For women having their first cycle of ovarian stimulation, for whom risk factors are only partially known, careful monitoring for potential ovarian hyperresponse is recommended.

Clinical signs and symptoms of mild and moderate OHSS are abdominal pain, nausea, diarrhoea, mild to moderate enlargement of ovaries and ovarian cysts. Severe OHSS may be life-threatening with large ovarian cysts (prone to rupture), acute abdominal pain, ascites, pleural effusion, haematological abnormalities and weight gain as clinical signs and symptoms.

Signs and symptoms of OHSS are stimulated by administration of human Chorionic Gonadotropin (hCG) and by pregnancy (endogenous hCG). Early OHSS usually occurs within 10 days after hCG administration and may be associated with an excessive ovarian response to gonadotropin stimulation. Usually, early OHSS resolves spontaneously with the onset of menses. Late OHSS occurs more than 10 days after hCG administration, as a consequence of (multiple) pregnancy. Because of the risk of developing OHSS, patients should be monitored for at least two weeks after hCG administration.

To minimise the risk of OHSS, ultrasonographic assesments of follicular development and/ or determination of serum oestradiol levels should be performed prior to treatment and at regular intervals during treatment. In ART there is an increased risk of OHSS with 18 or more follicles of 11 mm or more in diameter. When there are 30 or more follicles in total it is advised to withhold hCG administration. For luteal phase support, administration of hCG should be avoided. Adherence to the recommended dose and treatment regimen and careful monitoring of ovarian response is important to minimise the risk of OHSS.

Multiple pregnancies and births have been reported for all gonadotropin treatments. The woman and her partner should be advised of the potential risks for the mother (pregnancy and delivery complications) and the neonate (low birth weight) before starting treatment. In women undergoing ART procedures the risk of multiple pregnancies is mainly related to the number of embryos transferred.

Since infertile women undergoing ART, and particularly In vitro fertilization (IVF), often have tubal abnormalities, the incidence of ectopic pregnancies might be increased. It is important to have early ultrasound confirmation that a pregnancy is intrauterine, and to exclude the possibility of extrauterine pregnancy.

The incidence of congenital malformations after ART may be slightly higher than after spontaneous conceptions. This is thought to be due to differences in parental characteristics (e.g. maternal age, sperm characteristics) and the higher incidence of multiple pregnancies.

There have been reports of ovarian and other reproductive system neoplasms, both benign and malignant, in women who have undergone multiple treatment regimens for infertility treatment. It is not yet established whether or not treatment with gonadotropins increases the baseline risk of these tumours in infertile women.

In women with generally recognized risk factors for thromboembolic events, such as a personal or family history, severe obesity (Body Mass Index > 30 kg/m2) or thrombophilia, treatment with gonadotropins may further increase this risk. In these women the benefits of gonadotropin administration need to be weighed against the risks. It should be noted that pregnancy itself also carries an increased risk of thrombosis.

No studies on the ability to drive and use machines have been performed. Elonva may cause dizziness. Women should be advised that if they feel dizzy, they should not drive or use machines.

Interaction:
No interaction studies with Elonva and other medicines have been performed.

Since corifollitropin alfa is not a substrate of cytochrome P450 enzymes, no metabolic interactions with other medicinal products are anticipated.

Pregnancy and lactation:
Use in pregnancy: No teratogenic risk has been reported in clinical use with gonadotropins, following controlled ovarian stimulation. When inadvertent exposure to Elonva during pregnancy occurs, clinical data are not sufficient to exclude an adverse outcome of pregnancy. In animal studies reproductive toxicity has been observed. The use of Elonva during pregnancy is not indicated.

Use in lactation: The use of Elonva during breast-feeding is not indicated.

Side effects:
The most frequently reported adverse drug reactions during treatment with Elonva in clinical trials are Ovarian Hyper-stimulation Syndrome (OHSS), pelvic pain and discomfort.

Headache, nausea, fatigue and breast complaints (including tenderness) also occur.

The frequencies of main adverse reactions are expressed in patient-years, according to the following categories: common (≥ 1/100 to <1/10 patient-years), uncommon (≥1/1,000 to <1/100 patient-years).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.
Nervous System Disorders: Common: Headache. Uncommon: Dizziness.
Gastrointestinal Disorders: Common: Nausea. Uncommon: Abdominal pain, vomiting, diarrhoea, constipation and abdominal distension.
Reproductive System and Breast Disorders: Common: OHSS, pelvic pain and discomfort, breast complaints. Uncommon: Ovarian torsion.
General Disorders and Administration Site Conditions: Common: Fatigue.

In addition, ectopic pregnancy, miscarriage and multiple gestations have been reported. These are considered to be related to the ART procedure or subsequent pregnancy.

Forensic Classification:
P1S1S3

Visanne®
(Bayer Healthcare Ltd)

Presentation:
Each tablet contains 2 mg dienogest.

Pharmacological Properties:
Dienogest is a nortestosterone derivative with no androgenic but rather an antiandrogenic activity of approximately one third of that of cyproterone acetate. Dienogest binds to the progesterone receptor of the human uterus with only 10% of the relative affinity of progesterone. Dienogest acts on endometriosis by reducing the endogenous production of estradiol and thereby suppressing the trophic effects of estradiol on both the eutopic and ectopic endometrium. When given continuously, dienogest leads to a hypoestrogenic, hypergestagenic endocrine environment causing initial decidualization of endometrial tissue followed by atrophy of endometriotic lesions. Endogenous estrogen levels are only moderately suppressed during treatment with Visanne®.

Indications:
Treatment of endometriosis.

Dosage and Administration:
Tablet-taking can be started on any day of the menstrual cycle. The dosage is one tablet daily without any break, taken preferably at the same time each day with some liquid as needed. Tablets must be taken continuously without regard to vaginal bleeding. When a pack is finished the next one should be started without interruption. There is no experience with treatment >15 months in patients with endometriosis. The efficacy may be reduced in the event of missed tablets, vomiting and/or diarrhea (if occurring within 3-4 hours after tablet taking). In the event of missed tablet(s), the woman should take one tablet only, as soon as she remembers, and should then continue the next day to take the tablet at her usual time. A tablet not absorbed due to vomiting or diarrhea should likewise be replaced by one tablet.

Additional information on special populations
Visanne® is not indicated in children prior to menarche. The safety and efficacy in adolescents (menarche to 18 years) has not yet been established.

Contraindications:
Visanne® should not be used in the presence of any of the conditions listed below, which are partially derived from information on other progestogen-only preparations. Should any of the conditions appear during the use, treatment must be discontinued immediately.

- Active venous thromboembolic disorder
- Arterial and cardiovascular disease, present or in history (e.g. myocardial infarction, cerebrovascular accident, ischemic heart disease)
- Diabetes mellitus with vascular involvement
- Presence or history of severe hepatic disease as long as liver function values have not returned to normal
- Presence or history of liver tumors (benign or malignant)
- Known or suspected sex hormone-dependent malignancies
- Undiagnosed vaginal bleeding
- Hypersensitivity to the active substance or to any of the excipients

Precautions:
Before starting Visanne® treatment, pregnancy must be excluded. During treatment, patients are advised to use non-hormonal methods of contraception (e.g. barrier method) if contraception is required. Uterine bleeding, for example in women with adenomyosis uteri or uterine leiomyomata, may be aggravated with the use of Visanne®. If bleeding is heavy and continuous over time, this may lead to anemia (severe in some cases). Discontinuation should be considered in such cases. In patients who are at an increased risk of osteoporosis a careful risk-benefit assessment should be performed before starting Visanne because endogenous estrogen levels are moderately decreased during treatment. Patients who have a history of depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree.

Drug Interactions:
Progestogens including Dienogest are metabolized mainly by the cytochrome P450 3A4 system (CYP3A4) located both in the intestinal mucosa and in the liver. Therefore, inducers or inhibitors of CYP3A4 may affect the progestogen drug metabolism. An increased clearance of sex hormones due to enzyme induction may reduce the therapeutic effect of Visanne® and may result in undesirable effects e.g., changes in the uterine bleeding profile. A reduced clearance of sex hormones due to enzyme inhibition may increase the exposure to dienogest and may result in undesirable effects.

Side Effects:
Headache, breast discomfort, depressed mood, acne and changes in menstrual bleeding patterns

Forensic Classification:
P1S1S3

NEW PRESENTATION

ISOPTIN®
(Abbott)

Active ingredient:
Verapamil HCl

Presentation:
30 sustained release tablets 240 mg

Pharmacological Properties:
Verapamil HCl blocks the transmembrane influx of calcium ions into cardiac and muscular muscle cells. It lowers the myocardial oxygen consumption directly by intervening in energy-consuming metabolic processes in the cardiac muscle cell and indirectly by reducing the afterload

Indications:
Hypertension

Dosage and Administration:
1 tablet in the morning unless otherwise prescribed by the physician. Patients requiring particularly gradual blood pressure lowering should be started on half a tablet taken in the morning. If required, after about 2 weeks, the dose may be increased to a maximum of 2 tablets daily (additionally half to 1 tablet in the evening after an interval of about 12 hours)

Forensic Classication:
P1S1S3

nivestim™
filgrastim
Protecting patients on their journey

You plan your patients' chemotherapy. Nivestim™ protects them on their journey

- Neutropenia can disrupt your patient's chemotherapy and may compromise its outcome. Nivestim, the new daily G-CSF[1], lets you continue to treat the cancer without the diversion of neutropenia.
- Nivestim is comparable to Neupogen® in terms of safety[2], efficacy[2] and quality but has a unique combination of differentiating features*.
- Nivestim is available in a broad range of presentations and combines ease of use with an integrated needle-safe device. Nivestim can help more of your patients complete their full course of chemotherapy on time.
- There are more than 5,600 patient courses exposed to Nivestim in Europe[3].
- Biosimilars are likely to offer health economic benefits as they should be more cost-effective than the branded reference product.

References:
1. Nivestim (filgrastim) SmPC, 2010.
2. Waller et al. Onkologie 2012 33:504-511
3. Based on Periodic Safety Update Reports (PSUR), Jun-Nov 2011.

* Nivestim is available in 120ug, 300ug and 480ug pre-filled syringe form with 7 day out-of fridge stability

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Hospira
Advancing Wellness™

SHIFT the practice for heart failure

1991 SOLVD ACEI → **1999 CIBIS II β-blocker** → **2010 SHIFT Coralan**

Coralan :

further reduces 26% of heart failure mortality[1]

reverses cardiac remodeling[2]

on top of ACEI & β-blocker

1. Karl Swedberg, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomized placebo-controlled study. *Lancet*. 2010;376:875-885.
2. Tardif JC, et al. *Eur Heart J* 2011; Online August 29.

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