

# HONG KONG PHARMACEUTICAL *JOURNAL*

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News & Short Communications

Inspirational Interview with a Macau Pharmacist

A Drug Use Evaluation of Amoxicillin/Clavulanate  
in Hospital Setting: a Focus on Prescribing Patterns  
(2 CE Units)

Functional Foods: A Paradigm Shift for Health and  
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Closing Remarks of the 2017 Hong Kong  
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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*

# Rethinking Disease Care and Health Care in today's Modern Society



It has been clearly shown that everyone wants to stay healthy or even to live eternally regardless of classes, countries or times. Throughout human history, people have put great effort into identifying and developing good food, better medicines or treatments in order to combat diseases or to maintain and promote their health. To achieve this goal, it was driven significantly by the advancement of chemistry and

biological sciences that became prosperous about two century ago, while drug research contributed more to the progress of medicine only during the past century than any other times. Within this period, hundreds of drugs have been discovered or synthesized. For examples, analogs of sulfonamide from coal-tar, morphine from opium extract, penicillin from mold, insulin from pancreas tissue, interferons from human leukocytes, monoclonal antibodies from B-leukocytes, tissue plasminogen activator from humanized recombinant cells etc are the most compelling cases of drug discovery in the last hundred years.<sup>(1)</sup>

Certainly, drugs are not food for daily consumption. They may impose some undesirable effects after taken and should be monitored closely. In this issue, we report that the European Medicines Agency has recently reminded people taking canagliflozin, dapagliflozin and empagliflozin, all of them are SGLT-2 inhibitors for treatment of type 2 diabetes to terminate the treatment if they develop significant foot complications related to infections or skin ulcers (page 4). Similarly, the Canadian Health also gave order to discontinue the use of Zydelig, an antineoplastic agent, for blood cancer patients due to reports of increased rates of serious infections or death (page 6).

On the other hand, despite the development of so many antibiotics for combating infectious diseases during the last fifty years, reports about antibiotic resistance worldwide are increasing. In a growing number of cases, many studies revealed that micro-organisms have developed resistance to these drugs and it is a global problem threatening human health because it may lead to therapeutic dead-end of some infectious diseases. Hence, World Health Organization (WHO) recently warned people that treatment options will run out soon for some multi-resistant strains of bacteria and virus (page 5). Because of this possibility, WHO compiles a list of bacteria for which new antibiotics are urgently needed and reminded people to properly use of any antibiotics. Amongst those headache bacteria are carbapenem-resistant *Pseudomonas aeruginosa*, carbapenem-resistant and ESBL-producing *Enterobacteriaceae*, vancomycin-resistant *Enterococcus faecium* and clarithromycin-resistant *Helicobacter pylori*. In order to prevent the spread of multi-drug resistant bacteria, proper use of antibiotics has been regarded as one of the main strategic approaches. And treatment of many infections associated to multidrug resistant infections requires regular evaluation of clinical efficacy of "old" drugs in combination or the development of totally novel molecules. In this current

issue, Chan and Chu provided us with a drug use evaluation (DUE) scheme recently implemented in Hong Kong Hospital for monitoring the emergence of antibacterial resistance with aims to improve patient outcomes by reducing adverse effects due to inappropriate prescribing.<sup>(2)</sup>

But health problems and diseases are not merely derived from infection. Most people have neglected lifestyle could also have great impact on their health. It is only until recently, people are moving from the idea that diseases are things, like bacteria that need to be treated with a drug, like an antibiotic, which was a wonderful paradigm for 20<sup>th</sup> century illness, but it's not a good paradigm for chronic lifestyle-driven diseases. Most people, no matter whether layman or medical professionals, looked to choose drugs over lifestyle to treat disease that are really lifestyle-driven illnesses. And historically, people just tried to find the drug for the bug or the pill for the ill instead of really finding out how to treat the body as a system. It was only until the last couple of decades that people realized many diseases develop because of unhealthy food or life habit. Nowadays, more and more people realize that choosing some good foods to eat can promote or strengthen our health. These foods, which could provide some functional benefits for preventing the occurrence of some diseases in our body, are cloned as functional foods and become more popular in these days. Cheung and Baibado have reviewed and provided us with a more detailed description of what is functional foods in this issue.<sup>(3)</sup> Readers can get a glimpse of this new trend of health care by going through the article they written. The shift of attitude from disease care to health care has great impact in individual as well as for the whole society as it can significantly reduce the cost of medical services for the long run.

Whatever new discovery, achievements or changes of our society, it is no doubt that some devoted persons are there to push or to strive for their happen. In the pharmacy practice field, the establishment of our professional is not an even path and the effort of our predecessors who have paid a great price for us to lay down the current platform for us today. Sometimes ago, we have already interviewed and reported some key figures in Hong Kong. But in this issue, we turn to Macau, a nearby city of ours, and interviewed Mr Lai Lek-Sang, who is a senior pharmacist there;<sup>(4)</sup> his struggle and efforts certainly deserve our respect and applause. His success is also a good model for our younger people who wants to become a pharmacist as their life-long career. I hope you will enjoy reading this interview and be inspired.

*Cheung Hon-Young*  
Editor-in-Chief  
20 April, 2017

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- Pharmacy Education & Practice
- Drugs & Therapeutics
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- 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.

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Prepared by: Annie Tsoi, Hercules Tse

### Tricagrelor Vs. Clopidogrel in Peripheral Artery Disease

Date: January 5, 2017

The EUCLID trial demonstrated that symptomatic peripheral artery disease, ticagrelor was not proven to be superior to clopidogrel for the reduction of cardiovascular events. Major bleeding occurred at similar rates among the patients in the two trial groups. Peripheral artery disease is a disease closely related to systemic atherosclerosis with associated adverse cardiovascular and limb events. The trial compares clopidogrel with ticagrelor, a potent antiplatelet agent, in patients with peripheral artery disease.

The study is a multinational, double-blind, event-driven trial, involving 13,885 patients with symptomatic peripheral

artery disease to receive monotherapy with ticagrelor (90 mg twice daily) or clopidogrel (75 mg once daily). Patient selection included if they had an ankle-brachial index (ABI) of 0.80 or less or had undergone previous revascularization of the lower limbs. The primary efficacy end point was a composite of adjudicated cardiovascular death, myocardial infarction, or ischemic stroke. The primary safety end point was major bleeding.

Source: <http://www.nejm.org>

### FDA Finalized the Guidance on Way of Non-proprietary Naming for Biological Products

Date: January 12, 2017

Due to the high molecular complexity of biological products, there may be subtle differences between biosimilars and the originator biological product. These differences imply that they may not be interchangeable, so it is important to distinguish between different versions of a biological product. In view of this, FDA has just finalized its guidance on nonproprietary naming of biological products.

The guidance applies to the originator biological products and the biosimilar products. It is recommended that after the core name of the originator biological product, a four-letter lowercase suffix should be attached. For example, non-proprietary names of a biological product called "replicamab" may be "replicamab-cznm" or "replicamab-hjxf". The suffix should be unique, devoid of meaning, and at least three out of the four letters should be

distinct. The suffix should not be similar to any currently marketed product, in order to prevent confusion or medical errors. According to FDA, this naming convention provides several advantages. In terms of pharmacovigilance, some side effects may be specific to the biological product from a particular manufacturer. Different names for the different products can provide better surveillance and faster problem identification. The subtle molecular differences can also give rise to different immunogenic effects. The naming system can prevent inadvertent substitution. Moreover, biosimilar products may have fewer licensed indication or route of administration than the originator product. The new naming system is believed to remind health-care professionals of their differences.

Source: [www.fda.gov](http://www.fda.gov)

### Potential Risk of Toe Amputation in Patients Taking SGLT-2 Inhibitors

Date: February 24, 2017

Information about a potential increased risk of lower limb amputation (mostly related to the toes) in patients taking SGLT-2 inhibitors has been released by the European Medicines Agency (EMA). Patients taking canagliflozin, dapagliflozin and empagliflozin for type 2 diabetes should check their feet regularly and have proper foot care. Doctors may consider treatment termination if the patient develop significant foot complications related to infections or skin ulcers.

The increased risk has been observed in two still ongoing clinical trials, CANVAS and CANVAS-R, which involve patients

at high risk of heart problems. There is an increase in lower limb amputation (mostly affecting the toes) among patients taking canagliflozin compared to placebo. No such risk increase has been noticed in studies related to dapagliflozin and empagliflozin, but with limited data to date, the risk may also apply to these two medicines in the same class. The mechanism of the increased risk of amputation is also yet to be determined.

Source: [www.ema.europa.eu](http://www.ema.europa.eu)

## Phase Two of the Colorectal Cancer Screening Pilot Scheme is now launched

Date: February 26, 2017

The Colorectal Cancer Screening Pilot Scheme has entered its second phase. In addition to the Hong Kong residents born in years from 1949 to 1951 who were already eligible in the first phase, those born in years 1946 to 1948 are now also eligible to join. The Department of Health also reminds eligible persons to enroll in the electronic Health Record Sharing System (eHRSS) before joining.

During the first three months since the launch of the scheme, 70% of the participants who underwent the colonoscopy examination were diagnosed with colorectal adenomas and had it removed during the examination. Furthermore, about 6% of the

participants were diagnosed of colorectal cancer and has been referred for further assessment and treatment.

The Colorectal Cancer Screening Pilot Scheme consists of two stages. In the first stage, eligible participants who has made an appointment with an enrolled primary care doctor will undergo the fecal immunochemical test. If the result is positive, the participant will enter the second stage and will be referred to an enrolled colonoscopy specialist to receive a colonoscopy examination. Both stages are heavily subsidized by the government.

Source: [www.info.gov.hk](http://www.info.gov.hk)

## WHO wants Antibiotics Developed for a List of Bacteria

Date: February 27, 2017

Antibiotic resistance is a global problem threatening human health. For some multi-resistant strains of bacteria, treatment options will run out soon. In February, WHO has released a list of bacteria for which new antibiotics are urgently needed.

The list, containing 12 families of bacteria, is divided into three categories according to the urgency of need for a new antibiotic: critical, high and medium priority. The critical group include the organisms that pose the most threat to hospital and nursing homes. The group includes carbapenem-resistant *Acinetobacter baumannii*, carbapenem-resistant *Pseudomonas aeruginosa* and carbapenem-resistant, ESBL-producing *Enterobacteriaceae*. As for the second and third category in the list, they include other

resistant bacteria that can cause more common diseases. Examples are vancomycin-resistant *Enterococcus faecium* and clarithromycin-resistant *Helicobacter pylori*. Tuberculosis was not included in the list because it is targeted by other dedicated programmes.

The list was developed using multiple criteria, such as the frequency and mortality of the infection, the duration of hospital stays, and the remaining treatment options. The list provides guidance to the R&D initiatives, and also reminds the public of the importance of proper antibiotic use.

Source: [www.who.int](http://www.who.int)

## Mutant H7N9 Virus shows Resistance to Tamiflu

Date: March 1, 2017

Medical experts are looking into the possibility of a mutation on the H7N9 bird flu virus in China. Recently, it is seen that the virus is growing resistant to the anti-viral, Tamiflu, a drug commonly used to treat H7N9.

According to the Nanfang Daily, two patients in Guangdong province with the new strain of the virus have failed to show efficacy to Tamiflu. The new strain was identified by the China Centre for Disease Control and Prevention.

The World Health Organisation noticed the spread of mutated virus, however it suggested that the risk of the transmission remains low amongst the population. In roughly 7 per cent of human H7N9 infections, scientists have identified genetic mutations leading to the resistance to Tamiflu. Zhong Nanshan, a respiratory expert, mentioned that most the patients are responsive to the Tamiflu treatment, therefore, it suggests that the mutant virus is not the dominant strain amongst the infected population.

Source: <http://www.scmp.com>

## First Ever Treatment for Nocturnal Polyuria Approved by FDA

Date: March 3, 2017

FDA approved the first treatment for nocturnal polyuria, a condition of overproduction of urine at night.

The treatment is Noctiva, a desmopressin nasal spray which helps to reduce the number of times the patients wake up to

urinate at night. Nocturia (wakening up for urination at night) can be caused by a wide range of conditions, such as congestive heart failure and poorly controlled diabetes mellitus. Since Noctiva is only approved for treating nocturia caused by nocturnal polyuria, healthcare professionals should confirm the condition with a 24-hour urine collection.

Noctiva is administered daily, at approximately 30 minutes before bedtime. It works by decreasing kidney water absorption, leading to less urine production. Its efficacy was demonstrated in two randomized controlled trials involving 1,045 patients with

nocturnal polyuria of age 50 or above. More subjects treated with Noctiva experienced a reduction in night-time urination.

A boxed warning was also issued by FDA due to Noctiva's effect on electrolytes. Noctiva can lead to hyponatremia, so careful monitoring is necessary. Noctiva should also be avoided in patients with symptomatic congestive heart failure and uncontrolled hypertension due to the fluid retention effect of Noctiva.

Source: [www.fda.gov](http://www.fda.gov)

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## Schizophrenia Medication Updated Indication for Maintenance Treatment

Date: March 8, 2017

The FDA has accepted a supplemental new drug application (sNDA) for Vraylar (cariprazine). The sNDA application is to expand the product's label indication, after new clinical data that evaluate the efficacy of Vraylar as a maintenance treatment for adults with schizophrenia. The clinical data were supplied from a phase 3 multinational, randomized study of the drug in adults with schizophrenia. The study reported that cariprazine significantly delayed relapse time when compared to a placebo. This indicates

that Vraylar may be an option for the maintenance treatment of schizophrenia.

In September 2015 FDA approved cariprazine for the acute treatment of manic or mixed episodes of type 1 bipolar disease and the treatment of schizophrenia in adults.

Source: <https://www.allergan.com/>

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## Long Term Efficacy of Gleevec for Patients with Chronic Myeloid Leukemia

Date: March 9, 2017

*New England Journal of Medicine* recently published a 11-year follow-up study on patient on **Gleevec** Imatinib, a selective BCR-ABL1 kinase inhibitor, for chronic myeloid leukemia. The results showed an estimated overall survival rate of 83.3 percent. 11 years of follow-up showed that the efficacy of imatinib persisted over time and that long-term administration of imatinib was not associated with unacceptable cumulative or late toxic effects.

According to the National Cancer Institute, before the approval of Gleevec by FDA in 2001, less than 1 in 3 CML patients survived

five years past diagnosis. The study enrolled 1,106 participants at 177 cancer centers in more than 16 countries. The survive rates of the patient increased greatly. The discovery of Gleevec was a milestone for personalized cancer medicine. It demonstrated that drugs can be used to shut down cells that enable cancer to grow without harming healthy ones. In addition to CML, Gleevec has proved effective against other cancers, including paediatric CML and gastrointestinal stromal tumor or GIST.

Source: [www. http://www.nejm.org/doi/](http://www.nejm.org/doi/)

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## Zydelig Infection Risk Assessments

Date: March 12, 2017

Health Canada reviewed the risk of serious infections with Zydelig due to recent clinical trial reports of increased rates of serious infections (sometimes leading to death) amongst those treated with Zydelig, versus patient who were not. In four Canadian clinical trials, involving the cancer medicine Zydelig (idelalisib) in combination with other cancer medicines, the drug is being discontinued after reports of an increased rate of serious adverse events, including deaths. Three additional trials will be amended by implementing added measures to protect participants.

Zydelig is used to treat 2 types of blood cancers: relapsed chronic lymphocytic leukemia and follicular lymphoma. Zydelig

belongs to the family of antineoplastic agents. It acts by changing the growth of cancerous white blood cells leading to cell death. This drug is commonly prescribed with rituximab for chronic lymphocytic leukemia patients that have been previous treated with other drugs. Zydelig is also used as a monotherapy for the treatment of follicular lymphoma, when the patient is not responsive to other forms for treatment. Zydelig is a drug that is currently marketed in the Hong Kong in the form of an oral tablet.

Source: <http://www.hc-sc.gc.ca>

## Inspirational Interview with a Macau Pharmacist

HAU, Melody WK; TAM, Emily YL; CHAN, Phoebe WL\*

Department of Pharmacology and Pharmacy, LKS Faculty of Medicine, University of Hong Kong

\* Corresponding author

### INTRODUCTION

Mr. Lai Iek Sang (黎奕生先生) (Figure 1), the first registered Asian pharmacist in Macau, is a renowned, knowledgeable and passionate pharmacist and he has made great contribution in the pharmacy development in Macau. The Hong Kong Pharmaceutical Journal had the pleasure in conducting an interview with Mr. Lai that he might share his inspiring stories and his pathway in the field of Pharmacy with the readers.



Figure 1. A photo of Mr. Lai Iek Sang

### THE INTERVIEW

L: Mr. Lai

I: Interviewer

**I: Greetings to you Mr. Lai, we understand that you studied Pharmacy in Taiwan. Could you tell us more about that?**

L: At that time, there was no pharmacy schools in Macau, so I went to Taiwan to study Pharmacy at the National Defense Medical Center. Reflected by the name of my university, the students there were also soldiers at the same time. Sometimes, several students had to buy food from the market for all other students, just similar to what a normal soldier would do. **Figure 2** shows me wearing a soldier uniform in the campus.



Figure 2. Mr. Lai as a student when studying in the National Defense Medical Center

**I: You mentioned that even though after graduation, you were still closely linked to Taiwan and have often been back to Taiwan. Would you share with us why?**

L: A major reason for being back to Taiwan frequently was that Pharmacy was still not popular in Macau after I graduated. Moreover, the communication at that time was not as convenient as nowadays and people still wrote letters with one another. When I was working as a pharmacist, I usually encountered a number of doubts like the use of drugs and formulations of the drugs, yet I could hardly find professionals in Macau for clarification of those doubts. Therefore, I regularly flew back to Taiwan and asked my professors and classmates.



Figure 3. Mr. Lai being the outstanding alumni of the National Defense Medical Center

**I: Have you been back to Taiwan these years?**

L: Certainly! After retirement, I have also been back to Taiwan frequently, but with a different purpose. I usually meet my schoolfellows and friends for the reunion. I would also meet my teachers. **Figure 3** reveals that I was back to Taiwan last year to receive an award from my university.

**I: You are now a registered pharmacist in Macau, but before your home-coming, have you been involved in any Pharmacy-related jobs in Taiwan after graduation?**

L: I was asked by my university to stay in Taiwan after graduation. As much as I wished to do so, it was not possible because my father past away when I was in Year Two. I am the eldest son in the family, thus I had the responsibility to look after my younger brothers and sisters. I believed that taking good care of my younger brothers and sisters also allowed them to get into the university much easier. Therefore, it is important for me to have a job in Macau rather than Taiwan after my graduation.

**I: Did you need to get a pharmacist registration certificate when you were back in Macau?**

L: At that time, Macau was ruled by Portugal and all the professional qualifications were not recognised by the Portuguese government unless you obtained the qualification in Portugal. When I handed in my certificate of the degree of Pharmacy obtained in Taiwan to the Serviços de Saúde de Macau (SSM), they told me that such situation had not been approved by laws and my Pharmacy degree would not be recognised. However, the secretary advised me to learn Portuguese so that I could communicate with the Portuguese and be able to understand the prescription written in Portuguese. The secretary also said that he would further consider my application after I had understood Portuguese. At that time, Pharmacy was developing in Hong Kong, so I decided to go to Hong Kong for starting my Pharmacist career, due to the proximity to Macau.

**I: Would you describe your career path in Hong Kong?**

L: I could have obtained the recognition of certificate for my Pharmacy profession in Hong Kong with a completion of 1000 practical hours in Queen Mary Hospital (QMH) and a pass in a registration exam. At that time, QMH offered me around HKD\$200 per month as the transportation cost. However, we all know the expensive transportation cost in Hong Kong, the expenditure in housing in Hong Kong was also a great concern for me. At the same time, my secondary school in Macau needed teachers to teach Physics, Chemistry and Biology and they invited me to teach these subjects. Owing to these reasons, I accepted the invitation from my secondary school and became a science teacher first, even though the QMH officially offered me an internship after.

**I: So did you finally come back to Macau? Or did you stay in Hong Kong?**

L: Owing to the reasons I have just mentioned, I stayed in Macau at last and became a science teacher in my secondary school in Macau at that time. One month later, I received an official offer of doing an internship at QMH. However, I still decided to turn down the offer from the hospital because I had already accepted that from my school.

**I: Then how did you become a registered pharmacist in Macau later? It seems that there was not a great linkage between a science teacher and a pharmacist.**

L: At that time, there was a Portuguese teacher in the secondary school and he promised to help me learn Portuguese. Every day after school, I would go to his house and learn Portuguese, and I had been doing this for two years. Thanks to the teacher, I was able to communicate in Portuguese, as well as understand Portuguese prescriptions and document. Therefore, I handed in the pharmacist registration application to the SSM. I could communicate with the secretary in Portuguese, in spite of a number of grammatical mistakes. As Portuguese was very difficult to learn and I appeared to have such great enthusiasm in being a pharmacist, the secretary eventually approved my application. Thus, I obtained the recognition of my professional qualification in 1973, becoming the first Chinese pharmacist and the second Portuguese-citizen pharmacist in Macau. You can see that my pathway in becoming a registered pharmacist was quite difficult because I obtained my professional qualification in Taiwan rather than Portugal, so I expressed my concern to the secretary about the difficulties in getting the recognition after graduating from overseas universities. As an overseas Pharmacy graduate, I was the pioneer of obtaining recognition of qualification that opened the door so that students getting their certificate of the Pharmacy diploma abroad could apply to be a registered pharmacist in Macau much easier.

**I: After being a registered pharmacist in Macau, how was your career path?**

L: At that time, Pharmacy was not developed in Macau and many registered pharmacists could not find a Pharmacy-related job. For me, I have tried to apply for a job in different dispensaries. However, all the dispensaries rejected my application and they mentioned that the presence of pharmacists in the dispensaries was not mandatory by the laws. The owners of the dispensaries also thought that hiring a pharmacist would increase their monthly operational cost, which the business owners would have no choice but to increment the retail price of medications to the customers in compensation. As a result, I could only remain as a science teacher. Similar situations also happened to other registered pharmacists, some of which became a teacher just like me, some continued their Pharmacy career in Hong Kong or Taiwan and some opted to further their studies in the United States. At that time, nobody stayed in Macau to be a pharmacist despite the obtainment of the recognition of their qualifications.

**I: Then when did you start your Pharmacy career in Pharmacy-related fields such as the dispensaries?**

L: Speaking of this, I would like to thank Farmacia Popular, which was the first-ever pharmacy in Macau, for giving me the opportunity to work for them. At that moment, the pharmacy was in need of a pharmacist, however, the Portuguese pharmacists were reluctant in working in Macau due to the Motim 1-2-3.<sup>(1)</sup> Owing to these reasons, the owner of Farmacia Popular visited me and invited me to be the pharmacist. I was thrilled with the invitation and thought that I could practice as a real pharmacist at last. The excitement was slightly dampened when I learned that I was only hired as a part-time pharmacist, simply allowed to sign for poison prescriptions and to remain in the dispensary for a short period each day, without the permission to take charge of the dispensary.



### I: When did Pharmacy start to develop?

L: This needs to trace back to 1989 when the Portuguese government realised the need for the separation of prescribing from dispensing of drugs. In order to foster such separation, the government specified that each registered pharmacy premise should be staffed with a duty pharmacist in the shop. No other pharmacies were allowed within 300m of the registered pharmacy premise to minimise competitions. The government would also subsidize the medication cost of the patients if they collect their medicines from community pharmacies instead of hospitals. With these regulations, community pharmacy service started to blossom. Nowadays, there have been already 538 registered pharmacists, 280 registered pharmacies and 263 drug stores in Macau.

### I: We heard that Mr. Lai has open a drug company before. How was the exact progress?

L: I have set up two drug companies in total. The first one does not turn out well. I have started up my first drug company with a doctor in 1947 (**Figure 4**) but our first company was closed within a year because of the limited support and resources from the government. Around 1989, I set up my second drug company in Macau and participated in this field again since the immigration to the United States in 1980. I was in charge of the whole company at that time, from drug manufacturing to administrative work. I have learned the techniques and knowledge of drug formulations from a senior, whom I am still very thankful for. Later, I managed to make different dosage forms like tablets, suspensions, ointments and creams. My second drug company was more successful as the government decided to stock my products for hospitals' use. The business of making generic products started to soar in Macau since then. I am so glad that the second trial of my drug company turned out quite well and I always wanted to thank those who have helped me, taught me and gave me advice during that period.



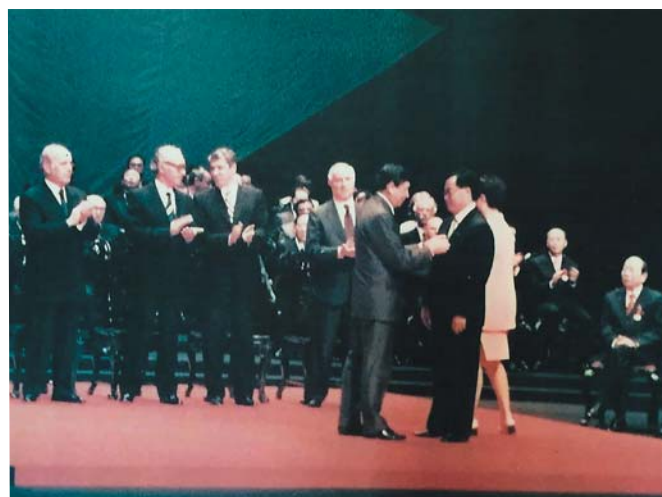
**Figure 4.** The license of the first drug company set up by Mr. Lai in 1974

### I: How do the role of pharmacist help you in setting up the drug company?

L: Being in charge of a drug company can use up most of my learnt knowledge especially pharmaceuticals and drug formulations. My knowledge grows the most when I was running my drug company. Asking questions is one of the best ways to learn. Do not be afraid of asking others, do not frown upon any opportunity to learn. On top of drug formulations, drug storage is also very important as a manufacturer because we usually buy relatively large lots of raw materials each time and they all require to be stored in appropriate conditions. Moreover, I was also involved in the administrative work of a drug company such as buying raw materials and applying for the product patents. I got involved in many aspects related to drugs and safety. Being the person in charge of the drug company actually exhibits the role of a pharmacist the most to me.

### I: We also heard that Mr. Lai has been a consultant for the Serviços de Saúde de Macau. What post(s) did you get involved in?

L: I have a close affiliation with the current and the former chief of the Serviços de Saúde de Macau (SSM). Since 1987, I was constantly in contact with the staffs of the SSM. I was invited by them to help monitor the quality of the manufacturing materials, check the herbal formulations and provide advice on some health policies. Upon the Macau hand-over, I was given a Medal of Honour, in recognition of my dedication to the health development in Macau (**Figure 5**). In 1999, I became the senior pharmacy consultant of the SSM. During my term at the post, I have assisted in some law enforcement and also fostering the establishment of Drug and Poison board in Macau. During that period, the pharmacy profession is rapidly developing and has created many opportunities for many pharmacists. Many pharmacy-related associations and societies were established since then and I was currently the president of over 20 associations, namely Pharmacist Association of Macau (the founder), Association of Macau Pharmaceutical Products Manufacturer (the founder), Macau Pharmacies Association (the founder), to name but a few.



**Figure 5.** Mr. Lai receiving the honour in the recognition of his contribution to the pharmacy development in Macau

**I: How do you think is the social status of pharmacists in Macau nowadays?**

L: With the ever-advancing development of Pharmacy, the social status of pharmacists has also been increasing with time. Nowadays, I think the supply and demand of pharmacists have already reached an equilibrium. Pharmacists have been widely accepted by the general public and this can be reflected from better monthly salaries and benefits received at their posts. I could say that pharmacist is “one of the best professionals nowadays”.

**I: How do you feel about the future development of the pharmacy profession in Macau? Is there any potential for the development of further pharmacy services?**

L: Undoubtedly yes. There is a sufficient supply of pharmacists in the hospital and community pharmacies currently in Macau. However, there is still room for further development in this field. First, I think the development in the roles of clinical pharmacists in the hospital can be considered as one of the potential developments because there are no pharmacists doing ward rounds with the doctors currently in Macau. On top of that, the Macau government can also help train qualified clinical pharmacists by providing a course in which the pharmacy students can spend an extra year to acquire the clinical pharmacy certification. Secondly, I would also like to further promote the community drug safety, targeting the high-risk groups such as the elderly. Providing detailed drug consultation to the elderly is particularly important. Some information such as side effects and the expected duration of the therapy are some of the important information in avoiding the misuse of drug and ensuring good treatment outcome. Therefore, I think that these two areas do have the potential for further pharmaceutical development to improve the well-being of the general public.

**I: Now you have retired already, what are the reasons that drive you to continue to be active in current pharmacy-related activities?**

L: Retiring does not mean leaving the pharmacy profession, I am always active in many kinds of pharmacy-related activities. Firstly, I would like to be the role model for the young pharmacists. Not only will I share my experience and inspire the young pharmacists to develop their potential, but I will also try my best to help the current pharmacists. I will give advice on the activities but I would not interfere with their decisions. I think that I have the responsibility to take care of the young pharmacists. Therefore, I will try my best to participate in any pharmacy-related events including annual dinners, talks etc. On top of that, I also engage in some community-related activities such as visiting the elderly.

**I: Have you ever regret in being a pharmacist?**

L: I am not regret in being a pharmacist. I have been through the thick and thin of the profession, after all, I did enjoy myself throughout my journey and it has always been an inspiring one that I get to know many nice people and all of these encounters all bring me fruitful experiences. Despite of going

through a tough time in running my first company, I think that it is also an important milestone for my journey as a pharmacist. I felt frustrated when my first drug company did not succeed, but fortunately, my second drug company turned out quite successful. When I was running my second drug company, I have also taken up the post as a science teacher to help me make a living for 8 years while I was also working as a part-time community pharmacist. Until this day, I am still bonded with my former students and have very good relationships with them. I am so blessed that Macau has provided me such a great platform to explore and develop the profession of pharmacy. My passion for pharmacy never dies. Therefore, I would like to express my deepest gratitude to the Macau government and every people that I crossed path with in my life, thanking for all their advice and supports.

**I: What qualities you think that a pharmacist should possess? Do you have any word that you want to tell the young pharmacists?**

L: Being a pharmacist is not just about oneself, but it also means so much to society. Firstly, we should always update ourselves with the drug knowledge as there are new medications and new treatment choices coming out every day. Continuous learning is always a golden rule in medical field. Secondly, pharmacists should always be aware that we are the safeguard of the public health. We should proactively take up the roles of detecting any misuse or incorrect use of the drugs and improve the well-being of the general public. We serve the citizens and we are very crucial in the healthcare system. Always should we bear in mind our responsibilities and serve everyone with heart and care. Working with passion and learning continuously to broaden our vision are the essential elements in a pharmacist. I sincerely look forward to a better healthcare system with many professional, energetic and passionate pharmacists in the future.

**I: Thank you very much Mr. Lai for your precious time in talking to us. It is a very inspiring story and we are very sure that your experience will be a valuable lesson and encouragement to the readers. Thank you.**

**Author's background**

**Ms. HAU, MELODY WING KEI** is currently a Third year Bachelor of Pharmacy student of the University of Hong Kong. Her email address: [u3518225@connect.hku.hk](mailto:u3518225@connect.hku.hk)

**Ms. TAM, EMILY YUK LAM** is currently a Third year Bachelor of Pharmacy student of the University of Hong Kong. Her email address: [u3518094@connect.hku.hk](mailto:u3518094@connect.hku.hk)

**Ms. CHAN, PHOEBE WING LAM** is currently a lecturer at the University of Hong Kong. She graduated from the London School of Pharmacy (now UCL School of Pharmacy) and obtained her license in the United Kingdom. Her email address: [pwlchan@hku.hk](mailto:pwlchan@hku.hk)

**References**

1. A riot happened on 3<sup>rd</sup> December, 1966 in Macau. The incident arose from a conflict between the residents of Taipa Island and the Portuguese government regarding the delay of the permission to build a private school on November. During the riot, there were 8 people killed by the police and 212 people injured.

# A Drug Use Evaluation of Amoxicillin/Clavulanate in Hospital Setting: a Focus on Prescribing Patterns

CHAN, Pauline TY; CHU, Jody KP\*

Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China (\* Corresponding author)

### ABSTRACT

Emergence of antibacterial resistance is recognised as an alarming global public health issue by the World Health Organisation (WHO), which is accelerated by the inappropriate use of antibiotics. Due to the faltering development of new antibiotics, the efficacy of currently available antibiotics must be preserved to prevent compromised patient outcomes and increased healthcare expenditure resulting from the failure of response to standard treatment. To promote judicious antibiotic use through antibiotic stewardship programmes (ASP), it is necessary to characterise current prescribing pattern and to identify existing problems associated with drug use. This drug use evaluation (DUE) aims to identify the prescribing patterns of amoxicillin/clavulanate in a tertiary hospital in Hong Kong. A total of 52 in-patient amoxicillin/clavulanate prescriptions were reviewed retrospectively over a 7-month period. The mean age of patients was  $80.6 \pm 12$  and 57.7% were male. 98.1% of patients had at least one comorbidity, such as hypertension and diabetes. All antibiotic uses were empirical and 40.4% of prescriptions were indicated for community-acquired pneumonia. 50% of patients had prior amoxicillin/clavulanate exposure within 6 months and 24.4% of the antibiotics were prescribed for an inappropriate indication. There were 8 different amoxicillin/clavulanate dosing regimens but in 35.6% of the cases, doses were not adjusted according to patients' renal function. Base on this DUE, patient's gender, comorbidities, availability of culture and sensitivity results and convenience of dosing may influence antibiotic prescribing. They can be targeted in newly developed ASP aiming to optimise antibiotic use. Non-clinical factors, such as physicians' experience and drug cost, may also affect antibiotic prescribing so further investigation on the use of amoxicillin/clavulanate in Hong Kong is warranted.

**Keywords:** antibacterial resistance, amoxicillin/clavulanate, drug use evaluation, antibiotic stewardship programmes, prescribing patterns

### INTRODUCTION

Amoxicillin/clavulanate is a combined formulation of amoxicillin, which is an antibacterial agent in the penicillin class, with clavulanic acid, which is a beta-lactamase inhibitor. Being introduced in the 1970s,<sup>(1)</sup> amoxicillin inherits activity against a wide range of microorganisms such as *Streptococcus pneumoniae* and *Staphylococcus aureus* which are Gram-positive; and *Haemophilus influenzae* and *Escherichia coli* which are Gram-negative.<sup>(2)</sup> Despite its broad spectrum of activity, the use of amoxicillin was challenged by the emergence

of resistance. It was found that some microorganisms could produce beta-lactamases to hydrolyse and inactivate amoxicillin.<sup>(1)</sup> In light of this discovery, clavulanic acid was identified and used in combination with amoxicillin as a beta-lactamase inhibitor. It inhibits the inactivation of amoxicillin, therefore extending the spectrum of activity to beta-lactamases producing strains, such as in *Klebsiella pneumoniae*, *Moraxella catarrhalis*, and *Bacteroides fragilis* which is an anaerobic bacterium.<sup>(3,4)</sup> Amoxicillin/clavulanate is recommended in many infection treatments because of its broad spectrum of activity and good safety profile.<sup>(5-9)</sup> In Hong Kong, amoxicillin/clavulanate is recommended by the Hong Kong Interhospital Multi-disciplinary Programme on Antimicrobial Chemotherapy 2012 (4<sup>th</sup> Edition) (HKIMPACT) guideline for the treatment of some bacterial skin and soft tissue infections, intra-abdominal and gastrointestinal system infections, upper and lower respiratory tract infections.<sup>(10)</sup>

Globally, an escalated use of penicillins has been observed and several articles suggested the need for further evaluation on antibiotic use.<sup>(11-13)</sup> Excessive and inappropriate use of antibiotics is a concern worldwide because evidence aggregated from different studies demonstrated that the use of antibiotics is linked with acquired antibacterial resistance in the community as well as in hospitals.<sup>(14)</sup> This poses a challenge onto the treatment of infectious diseases because the emergence of resistance leaves limited choices of agents that remain effective. Besides, the development of novel antibiotics has declined partly because of scientific challenges in discovering new agents and also because new antibiotics are economically unattractive to pharmaceutical companies.<sup>(15)</sup> Antibiotic treatment is usually sold at low cost for a short course, yielding a low margin of profit compared to more long-term treatments such as chronic medications and chemotherapy.<sup>(16)</sup> When infections are becoming harder to treat, patients are more susceptible to poor clinical outcomes and increased healthcare expenditure arisen from lengthened treatment duration.<sup>(17,18)</sup> Regarding such threat to the global public health, prudent use of antibiotics is highly emphasised in all healthcare settings.

### Antibiotic stewardship and drug use evaluation

The aim of antibiotic stewardship is to preserve the efficacy of currently available antibiotics against the emergence of antibacterial resistance<sup>(19)</sup> and to improve patient outcomes by reducing adverse effects brought from inappropriate prescribing.<sup>(20)</sup> Any strategies and interventions that aim to improve the appropriateness of antibiotic use are essentially components in an antibiotic stewardship programme (ASP) which needs to be tailored to the local practice and resistance pattern that differ from region to region.<sup>(21)</sup> Also, ASP is a multidisciplinary programme, involving physicians, nurses, clinical microbiologists, clinical pharmacists and administrative

personnel, that requires clear commitment from the healthcare professionals in order to run and sustain the ASP.<sup>(20)</sup> Antibiotic stewardship is not a new concept and it is emerging, in fact some countries have already been implementing antibiotic stewardship measures. Sweden has launched the Strategic Programme for the Rational Use of Antimicrobial Agents and Surveillance of Resistance (STRAMA) in 1995 that successfully reduced the amount of antibiotic used as well as the antimicrobial resistance rate over 10 years.<sup>(22)</sup> The most frequently used strategies in ASPs are prospective audit and feedback interventions.<sup>(19)</sup> A systematic review published in the United Kingdom in 2011 reflected that general practitioners can identify areas where they need to improve in antibiotic prescribing through prescribing feedback programmes and it is considered an acceptable way to influence their prescribing practices.<sup>(23)</sup> Furthermore, passive strategies such as formulary restriction and guideline development are also well known approaches in ASPs.<sup>(19,20)</sup> In France, new recommendations were made in 2011 on antibiotic prescription for acute otitis media in infants aiming to reduce the consumption of broad-spectrum antibiotics.<sup>(24)</sup> China has also issued guidelines to promote prudent use of antibiotics and the percentage of antibiotic use dropped from 57.2% to 41.8% in three years after the implementation of the 'guidelines for clinical use of antimicrobials' in 2004.<sup>(11)</sup>

The Hospital Authority (HA) in Hong Kong has implemented an ASP to optimise antibiotic use and influence physicians to prescribe antibiotics prudently in hospital settings. One of the strategies is the antibiotic monitoring program that consists of the monitoring of 'big gun' antibiotic use and intravenous to oral switch of certain antibiotics.<sup>(25)</sup> However, amoxicillin/clavulanate is not one of the antibiotics that are under the surveillance of the ASP. Thus, the prescribing pattern of amoxicillin/clavulanate in Hong Kong has not been extensively studied, and yet some small observational studies revealed that antibiotics were frequently prescribed.<sup>(26-28)</sup> Despite not considered a 'big gun', amoxicillin/clavulanate is one of the oral antibiotics that has the broadest spectrum of activity against bacteria. The emergence of resistance against amoxicillin/clavulanate and its extensive use warrant the review of its use. Either being a prospective or retrospective audit, a drug use evaluation (DUE) can be performed on amoxicillin/clavulanate, after which feedback and recommendations can be made if the drug is found inappropriately used. DUE is a systematic approach that serves to review the current practice of drug utilisation in order to identify problems with drug use.<sup>(29,30)</sup> By reviewing cases with amoxicillin/clavulanate prescriptions, the appropriateness of antibiotic use can be determined in terms of indications, dosage, frequency and duration of therapy. Meanwhile, physicians' antibiotic prescribing patterns can be revealed which may be helpful in explaining improper drug use. Thus, corresponding strategies can be taken place to solve the issues. In this study, a retrospective DUE focusing on prescribing patterns of amoxicillin/clavulanate was carried out in a tertiary hospital in Hong Kong. The objective of this study is to identify factors that may affect physicians' decisions when prescribing this agent.

## MATERIALS AND METHODS

### Study approval

The study was conducted in a 7-month period between September 2014 to March 2015 before which the ethics approval was obtained from the Institutional Review Board of the University of Hong Kong/ Hospital Authority Hong Kong

West Cluster (HKU/HA HKW IRB). A written patient consent was not required for patient enrolment in the study because patient data were reviewed retrospectively without having direct patient contact. Throughout the study, patient anonymity was strictly maintained.

### Data collection

Patients over the age of 18, who received amoxicillin/clavulanate between February 2014 and July 2014 during their admission in the medical ward of Queen Mary Hospital (QMH), Hong Kong, were eligible to be included in this study. Those patients were captured from a computerised database named Clinical Data Analysis Reporting System (CDARS) and 52 patients were randomly selected by using a simple random sampling method conducted by SAS version 9.3. The hand-written case notes were requested and the Electronic Patient Record (EPR) system was used in order to review patients' profiles. Patient data regarding the particular admission were collected according to the data collection form which was also approved by the HKU/HA HKW IRB. From the EPR system, data collected included patient demographics, presenting complaints, principal diagnosis, past medical histories, medication histories, prescribed medications, justification of antibiotic use, organs and systems involved, prior antibiotics exposure, laboratory data including microbiology results, review of therapy, adverse effects, and final outcome of the patient. More details on the justification of antibiotic use as well as the dosing regimens (dosage, frequency, duration) of antibiotics were captured from the case notes.

### Statistical analysis

Qualitative analysis was performed in this study as this is a descriptive study. Since a patient might be prescribed with amoxicillin/clavulanate more than once during the specified period for different admissions, the data were reviewed by case of admission rather than by patient. Data were tabulated and analysed using the number of cases with available data as the denominator. The appropriateness of prescribing was analysed based on a pre-defined DUE criteria generated from the Sanford Guide to Antimicrobial Therapy 2014 (44<sup>th</sup> Edition) (Sanford),<sup>(8)</sup> Clinical practice guidelines by the Infectious Diseases Society of America (IDSA),<sup>(5-7,9,31-35)</sup> European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines<sup>(36,37)</sup> and also the HKIMPACT.<sup>(10)</sup> Guideline recommendations of indications, dosage, route of administration, frequency and duration of treatment were included in the DUE criteria. The prescriptions of amoxicillin/clavulanate were assessed according to these components and prescriptions that were not in accordance with the DUE criteria would be considered inappropriate.

## RESULTS

### Patient demographics

A total of 52 cases were reviewed and the patient demographics were shown in **Table 1**. The mean age of patients was 80.6 ± 12 (range 34-103) with 57.7% male and 42.3% female. 90.4% of patients had no known drug allergy (NKDA) while drug allergies were reported for 5 cases that included rash resulted from aspirin, rash resulted from private cough mixture and angioedema resulted from ramipril. The majority of patients (98.1%) had at least one comorbidity which included hypertension (55.8%), diabetes mellitus (42.3%), dementia

(30.8%), history of stroke (28.8%), chronic obstructive pulmonary disease (COPD) (17.3%), coronary heart disease (17.3%), dyslipidaemia (13.5%), chronic kidney disease (9.6%) and asthma (1.9%).

	n (%)
<b>Age</b>	
< 80 years of age	19 (36.5)
≥ 80 years of age	33 (63.5)
<b>Gender</b>	
Male	30 (57.7)
Female	22 (42.3)
<b>Drug Allergy</b>	
NKDA	47 (90.4)
Yes	5 (9.6)
<b>Co-morbidities</b>	
Hypertension	29 (55.8)
Diabetes Mellitus	22 (42.3)
Dementia	16 (30.8)
History of Stroke	15 (28.8)
Coronary Heart Disease	9 (17.3)
COPD	9 (17.3)
Dyslipidaemia	7 (13.5)
Chronic Kidney Disease	5 (9.6)
Asthma	1 (1.9)

### Indications for antibiotic use

When patients were admitted to the hospital, their presenting complaints included shortness of breath (48.1%), fever (46.2%), cough (30.1%), increased sputum (30.1%), decreased in general condition (7.7%) and others (15.4%). Amoxicillin/clavulanate was frequently indicated for community-acquired pneumonia (CAP) and acute exacerbation of COPD representing 40.4% and 17.3% of the total number of cases respectively. They are followed by urinary tract infection (UTI) (11.5%), bacteraemia (7.7%), aspiration pneumonia (5.8%), upper respiratory tract infection (URTI) (5.8%) and infective exacerbation of bronchiectasis (1.9%). 9.6% of cases were diagnosed with other disease conditions. Furthermore, half of the patients (50%) had prior amoxicillin/clavulanate exposure within 6 months before their hospital admission. Patients in 5 cases had received treatments of other antibiotics within 6 months and prior antibiotic exposures of 12 cases were unknown. A summary of the indications for antibiotic use is displayed in Table 2.

### Antibiotic use

Table 3 shows the distribution of amoxicillin/clavulanate regimens. Since a patient could receive more than one regimen of amoxicillin/clavulanate during an admission, the total number of amoxicillin/clavulanate prescription order was 64 and they were prescribed in 8 different dosing regimens with 1.2gram intravenously (IV) every 8 hours being the most frequent regimen (46.9%) followed by 1gram orally (PO) every 12 hours (17.2%). 60.9% of amoxicillin/clavulanate were prescribed in intravenous formulations and 39.1% were prescribed in oral formulations.

Dosage	1.2g Q8H	1.2g Q12H	600mg Q8H	600mg Q12H	1g Q12H	375mg Q8H	375mg Q12H	457mg/5mL, 10mL Q12H	Total
Route of administration	IV	IV	IV	IV	PO	PO	PO	PO	
Number of prescription									
n	30	4	1	4	11	7	2	5	64
%	46.9	6.3	1.6	6.3	17.2	10.9	3.1	7.8	100

Q8H = every 8 hours; Q12H = every 12 hours

	n (%)
<b>Principal diagnosis</b>	
CAP	21 (40.4)
Acute exacerbation of COPD	9 (17.3)
UTI	6 (11.5)
Bacteraemia	4 (7.7)
Aspiration pneumonia	3 (5.8)
URTI	3 (5.8)
Infective exacerbation of bronchiectasis	1 (1.9)
Other	5 (9.6)
<b>Organs or systems involved</b>	
Respiratory	37 (71.2)
Urinary	9 (17.3)
Other	6 (11.5)
<b>Prior antibiotic exposure</b>	
<i>Amoxicillin/clavulanate</i>	
Within 6 months	26 (50)
Longer than 6 months	6 (11.5)
<i>Other antibiotics</i>	
Within 6 months	5 (9.6)
Longer than 6 months	3 (5.8)
<i>Unknown</i>	12 (23.1)

### Microbiology results

All amoxicillin/clavulanate regimens were started empirically before microbiology results, if any, were available. 48 (92.3%) cases had microbiology culture obtained and 29 of them had more than one culture sample taken. As illustrated in Table 4, the two most common types of culture samples obtained were midstream urine and nasopharyngeal aspirate. Among all microbiology results, *E. coli* was cultured in 6 midstream urine samples and 1 catheterised urine sample with 2 of the strains being extended-spectrum beta-lactamase (ESBL) producing *E. coli*. The sensitivity reports showed that all *E. coli* cultured were sensitive to amoxicillin/clavulanate. In a catheterised urine culture, *Pseudomonas aeruginosa* that was not sensitive to amoxicillin/clavulanate was grown. Besides, microorganisms in the *Enterococcus* species, *Klebsiella* species and the *Proteus* species were cultured in a midstream urine sample, a sputum sample and a catheterised urine sample respectively. Viruses were found in 6 nasopharyngeal aspirate cultures in which 4 of them were influenza A viruses.

	n (%)	Remarks
<b>Culture</b>		
Obtained	48 (92.3)	
Not obtained	4 (7.7)	
<b>Types of sample</b>		
Midstream urine	22 (42.3)	1 out of 6 <i>E. coli</i> cultures obtained ESBL <i>E. coli</i> .
Nasopharyngeal aspirate	21 (40.4)	Viruses found included respiratory syncytial virus and influenza A
Blood	16 (30.8)	No microorganisms was found
Sputum	15 (28.8)	Microorganisms found included acid fast bacilli, <i>Candida albicans</i> , <i>Klebsiella</i> species
Catheterised urine	11 (21.2)	Microorganisms found included ESBL <i>E. coli</i> , <i>P. aeruginosa</i> , <i>Candida glabrata</i> , <i>Proteus</i> species

## Treatment outcomes

Case notes of 7 out of 52 cases were not available and it was difficult to conclude the treatment outcomes of those patients without reviewing the progress notes and the drug charts. As a result, only 45 cases were investigated. The average length of hospital stay in QMH was 4.7 days  $\pm$  4.0 days and the average duration of inpatient antibiotic therapy was 4.8 days  $\pm$  2.9 days. No rash or gastrointestinal discomfort was reported after the administration of amoxicillin/clavulanate. However, elevation of both aspartate transaminase (AST) and alanine transaminase (ALT) were observed in 3 cases whereas an AST elevation was observed in 1 case and an ALT elevation in another. The causality of amoxicillin/clavulanate use and such observation was not determined. The courses of amoxicillin/clavulanate were completed in 33 (73.3%) cases within which intravenous to oral switches were performed in 13 cases. 10 out of 45 (22.2%) amoxicillin/clavulanate treatments were not successful and required changes of antibacterial agents. 37 cases (82.2%) were finally treated and 16 cases were transferred to another hospital for further recovery. Unfortunately, one patient passed away despite multiple antibiotic treatments.

### Appropriateness of the use of amoxicillin/clavulanate

Similar to the assessment of treatment outcomes, the missing case notes lacked the information regarding the justification of antibiotic prescription and medication dosing regimens. Thus the appropriateness of amoxicillin/clavulanate use could only be assessed in 45 cases. The assessment of prescriptions against the DUE criteria was divided into two levels: a) against treatment guidelines combined and; b) against individual treatment guidelines. The percentage appropriateness of amoxicillin/clavulanate use assessed against treatment guidelines combined is shown in **Table 5**. Overall, the majority of prescriptions were appropriately prescribed but 24.4% were inappropriately prescribed for septic patients with prior exposure to amoxicillin/clavulanate and patients with URTI. Some of the URTIs were caused by viruses but amoxicillin/clavulanate might have been prescribed for the coverage of potential bacterial URTI. Among those appropriate prescriptions, 8 cases were treated for an inappropriate duration. The appropriateness of therapy duration for 2 cases of aspiration pneumonia could not be assessed because the recommended treatment duration was neither specified in ESCMID guidelines nor HKIMPACT. In terms of dosage, the prescriptions were assessed against Sanford. 35.6% of the prescriptions were not adjusted for the renal function of the patients and therefore, those prescriptions were considered inappropriate. **Table 6** shows the percentage appropriateness according to individual guidelines. 33.3% of the prescriptions were compliant to Sanford, 42.2% were compliant to clinical practice guidelines of IDSA, 64.4% were compliant to ESCMID guidelines and 68.9% were compliant to HKIMPACT.

	Appropriate	Inappropriate
Indication	34 (75.6%)	11 (24.4%)
Duration of therapy	24	8
Dosage	29 (64.4%)	16 (35.6%)

	Appropriate, n (%)	Inappropriate, n (%)
Sanford	15 (33.3)	30 (66.7)
IDSA	19 (42.2)	26 (57.8)
ESCMID	29 (64.4)	16 (35.6)
HKIMPACT	31 (68.9)	14 (31.1)

## DISCUSSION

In a DUE, the assessment of appropriate drug use is a very important component but in this evaluation, the focus would be placed on the prescribing pattern of amoxicillin/clavulanate in a hospital setting. Physicians' antibiotic prescribing behaviours contribute to the trend of antibiotic use which is now increasing worldwide. By identifying the pattern of prescribing, factors that may affect physician's decision in antibiotic use can be targeted in newly developed interventions aiming to optimise antibiotic use.<sup>(38)</sup>

### Age

Results showed that amoxicillin/clavulanate was prescribed to patients over the age of 80 more than patients under the age of 80. Elderly people are often associated with vulnerability and susceptibility to diseases, complicating the management of infections. This suggested that patients' age may be a factor that can affect antibiotic prescribing. However, this result is not consistent with the literature. In a Swiss study of antibiotic prescribing patterns for UTI, the authors did not observe patient age as a factor to influence the choice of antibiotics.<sup>(39)</sup> Besides, no differences was found between age groups in antibiotic use or duration of treatment in *Clostridium difficile* infections in Korea.<sup>(40)</sup> Moreover, in a study conducted in Belgium, a stable proportion of amoxicillin/clavulanate was observed over the lifespan of patients enrolled in that analysis.<sup>(41)</sup> As a result, further investigation in the relationship between patient age and prescribing behaviours is needed.

### Gender

On the other hand, in the same Belgian study, the authors found that females were more likely than males to be prescribed amoxicillin in comparison with amoxicillin/clavulanate suggesting that physicians tend to treat female patients less intensively with antibiotics.<sup>(41)</sup> Bassetti et al.<sup>(42)</sup> investigated the prescription behaviours for tigecycline and it was found in five observational studies that more male patients were prescribed with tigecycline than female patients. There were more male patients enrolled in this DUE, but a distinctive difference in the proportion of amoxicillin/clavulanate use between male and female patients was not observed. Therefore, it was hard to conclude that patient gender is a definite factor that can affect physicians' prescribing behaviours. Further investigation will be useful in better understanding this potential association.

### Comorbidity

In most of the cases in this study, patients suffered from more than one comorbid condition with hypertension being the most frequent comorbidity. It can be explained by the old age (mean age 80.3  $\pm$  12.5) of enrolled patients as the number of

comorbidities tends to increase with age. A similar observation was found in a descriptive study of antibiotic prescribing in Italy. The increased severity of health status was found to be correlated with antibiotic use because increased comorbid conditions of patients may raise the physicians' awareness leading them to prescribe antibiotics for treatment.<sup>(43)</sup> In addition, there is literature suggesting that the level of C-reactive protein (CRP) in the body may have an association with increased blood pressure.<sup>(44)</sup> A cross-sectional study even suggested that CRP level may be a risk factor for developing hypertension.<sup>(45)</sup> Since CRP levels are often elevated during infections, physicians may tend to prescribe antibiotics to hypertensive patients to avoid their blood pressure to increase further. On the other hand, diabetes mellitus was the second most common comorbidity in this study. In patients with diabetes, there are defects in the complement system, low production of inflammatory cytokines, impaired antioxidant mechanisms and glycosylation of antibodies which render diabetic individuals more susceptible to infections.<sup>(46)</sup> Despite inconsistent data regarding the causal relation between diabetes mellitus and infections, diabetic patients are at higher risk of contracting common infections, such as skin and mucous membrane infections, respiratory tract infections and UTIs.<sup>(46,47)</sup> Patients with diabetes were also found to have increased staphylococcal carriage that contributed to skin infections and pneumonia while asymptomatic bacteriuria is also frequently observed in diabetic patients possibly because glycosuria enhances the growth of bacteria.<sup>(48)</sup> These pathological reasons may explain the higher level of antibiotic prescriptions for diabetic patients.

### Indication of antibiotic use

CAP was the most frequent indication of which amoxicillin/clavulanate was prescribed followed by acute exacerbation of COPD and UTI. It may be because of adequate evidence-based treatment guidelines available rendering physicians more confident in prescribing amoxicillin/clavulanate instead of other agents especially when guidelines adherence is very much emphasised nowadays. Sanford, clinical practice guidelines of IDSA, ESCMID guidelines and HKIMPACT all provide guidance to the treatment of CAP with comprehensive treatment outline covering monitor parameters and intravenous to oral switch.<sup>(7,8,10,36)</sup> Guidelines for the treatment of acute exacerbation of COPD and UTI are also included in 3 out of 4 guidelines used in the DUE criteria. However, for infections that are not as common, there may not be sufficient evidence to support certain treatment regimen. This may result in improper prescribing because physicians do not have adequate knowledge of treatments for certain diseases. It was proposed that lack of expertise of healthcare professionals may be one of the contributors to the over and inappropriate prescriptions of antibiotics in China.<sup>(49)</sup>

### Prior antibiotic exposure

Overuse of antibiotics results in antibacterial resistance even on an individual level because it is related to the bacterial gene pool of an individual.<sup>(50,51)</sup> Literature suggested that if an antibiotic treatment is necessary for a patient with prior antibiotic exposure within 12 months, a different agent should be considered.<sup>(51)</sup> Additionally, treatments recommended by Sanford for patients with acute otitis media, who has received

antibiotics in the prior month, and patients with CAP, who had received antibiotics within 3 months, are different from those who has not received antibiotics within the specified period.<sup>(8)</sup> The incorporation of this criterion into clinical guidelines indicates the level of evidence supporting this phenomenon. Gathering information from the literature, a 6-month period before admission was considered to be more critical in this study. However, previous antibiotic exposure within 6 months seemed not to be affecting amoxicillin/clavulanate prescribing in this study. It was because 26 cases (50%) of patients who have had amoxicillin/clavulanate exposure in the previous 6 months, received amoxicillin/clavulanate treatment again instead of different agents during the study period. Therefore, previous antibiotic exposure was not a factor affecting antibiotic use in this study but such finding warrants interventions to emphasise on the relationship between antibiotic consumption and emergence of resistance.

### Microbiology results

A total of 100% empirical treatment with amoxicillin/clavulanate in this study strongly implied that this antibiotic is mostly used in a lot of infectious conditions before microbiology results are available. Furthermore, all *E.coli* cultures plus a culture of *Klebsiella* species were reported sensitive to amoxicillin/clavulanate. The susceptibility reporting of antibiotics was found to be able to affect antibiotic prescribing in a study in the United Kingdom. The prescriptions of amoxicillin/clavulanate fell by more than 50% after the intervention of replacing this agent with cephalexin, a first generation cephalosporin, in culture reports.<sup>(52)</sup> Physicians may tend to prescribe amoxicillin/clavulanate empirically because microorganisms were frequently reported to be sensitive to it.

### Convenient dosing

Apart from its broad spectrum of activity, preparations of amoxicillin/clavulanate are available in different strengths that facilitate the administration of many different dosing regimens. Convenient dosing was suggested to contribute to the popularity of fluoroquinolones in the treatment of CAP in adults in the USA.<sup>(53)</sup> Amoxicillin/clavulanate is available as a 1.2g vial, 1g tablet, 375mg tablet, 457mg/5mL syrup and 156mg/5mL syrup. By using these preparations in various frequencies, the dosage can be adjusted for patients of different disease severity, age, size, renal function and co-existing conditions.

### Adherence to guidelines

Last but not least, it was observed that the prescriptions were compliant to HKIMPACT the most among the four treatment guidelines in the DUE criteria. The assessment of antibiotic use was performed against individual guidelines because differences in recommendations among guidelines exist. For example, the use of amoxicillin/clavulanate in cystitis is recommended in Sanford<sup>(8)</sup> and HKIMPACT<sup>(10)</sup> but it is a non-first-line treatment which should only be used when other agents are not appropriate according to the clinical guideline of IDSA.<sup>(32)</sup> Differences in local resistance patterns can cause inconsistency among guidelines. One of the reasons for guidelines non-adherence in Europe is the discrepancy between local flora and international guideline recommendations.<sup>(54)</sup> Additionally, from the physicians' perspective, guidelines are

not always applicable to individual patients and physicians' knowledge, attitude and experience can override guideline recommendations.<sup>(65)</sup> On top of that, physicians may not accept the validity of the guidelines issued by certain organisations which can also lead to non-adherence.<sup>(66,67)</sup> HKIMPACT was written by a team of healthcare professionals in Hong Kong aiming to produce guidance to antibiotic use that is suitable and applicable in Hong Kong. Hence, physicians may be more convinced to comply with a local guideline than with a guideline of other countries. With regard to clinical practice guideline, changes in susceptibility and resistance rates of bacteria shape the local resistance pattern which is one of the largest considerations in developing guidelines on antibiotic use. Therefore, guidelines should be reviewed and updated frequently to reflect the current local resistance pattern to better guide appropriate antibiotics use.

### Other non-clinical factors

Although not investigated in this DUE, financial consideration, patients' expectations for antibiotics and consultation time are some non-biomedical factors that may affect the prescribing behaviours of physicians.<sup>(58-61)</sup> Another critical determinant that can affect antibiotic use is the prescribing style of a physician. The tendency to prescribe or not to prescribe certain antibiotics can be affected by the physician's experience in antibiotic use, and perceptions of the importance of antibacterial resistance.<sup>(62)</sup>

### Limitations of study

This retrospective study on antibiotic use consisted of only a small number of subjects and essential information for appropriateness assessment of 7 cases was missing. During data collection, a complete medication history could not be retrieved from the EPR system and case notes as the system only consisted of prescriptions record within HA. The lack of direct contact with the patient also did not allow us to obtain information such as whether any additional private medications such as antibiotics, over-the-counter medications and healthcare supplements were used by the patients. For the assessment of antibiotic usage, most of the justification for antibiotic used could not be found in the progress notes and often there was no reason stated for antibiotic change. They were assumed to be changed due to culture results if a microorganism was cultured or treatment failure. Furthermore, the assessment of treatment efficacy, adverse effects and treatment duration and outcomes of antibiotics was difficult due to transfer of patients to another hospital for convalescence.

### Future direction

In order to better evaluate the prescribing patterns of amoxicillin/clavulanate in Hong Kong, more DUE and investigations should be conducted. Factors identified in this study that may affect physicians' prescribing practice need to be confirmed by more association studies and it will be extremely useful if future interventions in the ASP can target on specific areas where antibiotic prescribing behaviours can be changed and improved. Apart from clinical factors, non-clinical factors are

also worth investigating when studying the prescribing patterns of this antibiotic.

## CONCLUSIONS

In conclusion, amoxicillin/clavulanate is a very frequently prescribed antibiotic that is not under the surveillance of ASP in Hong Kong. This DUE aimed to identify determining factors that may influence physicians' practice in antibiotic prescription through evaluating the current prescribing pattern. This can help future antibiotic stewardship interventions to target on areas that can be improved for drug use optimisation. From this study it was found that patient gender and comorbid conditions, frequency of susceptible results and convenient dosing of the medication are possible factors that can influence physicians' decision in antibiotic prescribing whereas the association between patient age and prescribing behaviour is inconclusive. Besides, prior antibiotic exposure of patients did not seem to affect antibiotic prescribing. Evidence-based guidelines are helpful to physicians but they may not be completely adherent to guidelines as every physician has his or her own prescribing style that may be affected by various non-clinical factors. There were limitations in this retrospective analysis but its purpose was to provide a snapshot of the current prescribing pattern of amoxicillin/clavulanate in Hong Kong. Further investigation will be beneficial in identifying more prescribing determinants of antibiotics so that strategies can be developed to improve antibiotic prescribing by changing behaviour.

**Table 7. Potential factors that may affect antibiotic prescribing**

Potential factor	Possible explanation
Patient gender	Physicians tend to treat females less intensively with broad-spectrum antibiotics than males. <sup>(41)</sup>
Hypertension	Infection may aggravate hypertension. Control of infection by antibiotics may prevent further blood pressure elevation. <sup>(44)</sup>
Diabetes mellitus	Immune systems of diabetic patients are impaired rendering them more vulnerable against infections. <sup>(46)</sup>
Community-acquired pneumonia	There are adequate evidence-base treatment guidelines published, so physicians are more confident in prescribing antibiotics.
Microbiology results	Sensitivity to an antibiotic frequently reported in microbiology results promotes empirical prescribing. <sup>(52)</sup>
Convenient dosing <sup>(53)</sup>	Different strengths of preparation available allow easy dosage adjustment.

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### Author's background

**Miss CHAN, Pauline TY** is currently a resident pharmacist at Queen Elizabeth Hospital. Her email address: [cty434@ha.org.hk](mailto:cty434@ha.org.hk). **CHU, Jody KP** is currently a Lecturer at the Department of Pharmacology and Pharmacy, the University of Hong Kong. Her email address: [chukpj@hku.hk](mailto:chukpj@hku.hk).



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# Questions for Pharmacy Central Continuing Education Committee Program

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

**1) Which of the following statement regarding amoxicillin/clavulanate is incorrect?**

- a) Amoxicillin/clavulanate is an antibiotic in the penicillins group.
- b) A wide range of microorganisms, except beta-lactamases producing strains, are susceptible to amoxicillin/clavulanate.
- c) Amoxicillin/clavulanate is one of the antibiotics that is under the surveillance of antibiotic stewardship programme in the Hospital Authority in Hong Kong.
- d) Amoxicillin/clavulanate is being heavily used in Hong Kong.



**2** CE Units

**A Drug Use Evaluation of Amoxicillin/Clavulanate in Hospital Setting: a Focus on Prescribing Patterns**

**2) What are the consequences of excessive and inappropriate antibiotic use?**

- i) Emergence of antibacterial resistance
  - ii) Infections become harder to treat
  - iii) Promote development of novel antibacterial agents
  - iv) Reduced healthcare expenditure
- a) i and ii and iii
  - b) ii and iii and iv
  - c) i and ii
  - d) i and iv

**3) Which of the following statement regarding novel antibiotics is correct?**

- a) The increased in demand for antibiotics to combat antibacterial resistance fosters the development of novel antibiotics.
- b) Pharmaceutical companies are willing to develop novel antibiotics to combat antibacterial resistance.
- c) Pharmaceutical companies are reluctant to develop new antibiotics because of low market demand.
- d) The development of novel antibiotics has declined due to scientific challenges and low margin of profit.

**4) Which of the following statement regarding antibiotic stewardship programme (ASP) is correct?**

- a) It is a multidisciplinary programme that solely aims to reduce the use of antibiotics.
- b) The Hospital Authority in Hong Kong has implemented ASP aiming to improve appropriate antibiotic use.
- c) Antibiotic stewardship programme was first introduced in the United Kingdom.
- d) The percentage of antibiotic use has increased in China after implementing the 'guidelines for clinical use of antimicrobials' in 2004.

**5) Which of the following are considered useful approaches in ASPs?**

- a) Guideline development
- b) Formulary restriction
- c) Prospective audit and feedback intervention
- d) All of the above

**Question 6 to 8 refer to this drug use evaluation (DUE).**

**6) Which of the following condition was amoxicillin/clavulanate mostly indicated for?**

- a) Urinary tract infection
- b) Community-acquired pneumonia
- c) Soft tissue infection
- d) Abdominal infection

**7) Which of the following factors was not found to be associated with increased antibiotic prescribing?**

- a) Gender
- b) Diabetes Mellitus
- c) Microbiological results
- d) Cost

**8) Which of the following are proposed explanations for increased antibiotic prescription in patients with comorbidities?**

- i. Blood pressure further increases in hypertensive patients during infection due to increased level of C-reactive protein (CRP).
  - ii. The use of antibiotics can reduce the risk of hypoglycemia in diabetic patients during infection.
  - iii. Diabetic patients are more susceptible to infections.
  - iv. Patients with hypertension are more responsive to antibiotics.
- a) i and ii
  - b) i and iii
  - c) i and iv
  - d) ii and iii and iv

**9) Why is amoxicillin/clavulanate frequently used for treating infection?**

- a) Microorganisms are frequently reported to be sensitive to this broad spectrum antibiotic.
- b) Amoxicillin/clavulanate is available as tablet, syrup and injection forms that can facilitate dosing and administration.
- c) The use of amoxicillin/clavulanate is recommended in various infections by HKIMPACT.
- d) All of the above

**10) Which of the following is a non-clinical factor that can also affect antibiotic prescribing?**

- a) Prescribing style of physicians
- b) Social status of patients
- c) Geographical location of antibiotic use
- d) Season and climate

**Answers will be released in the next issue of HKPJ.**

**CE Questions Answer for 234(D&T)**

**Current and Alternative Uses of Oral Vitamin D in the Pediatric Population**

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

## Functional Foods: A Paradigm Shift for Health and Disease

CHEUNG, Hon-Yeung\*; BAIBADO, Joewel Tarra

Research Group for Bioactive Products, Department of Biomedical Sciences,  
City University of Hong Kong, 83 Tat Chee Avenue, Kowloon Tong, Hong Kong SAR, China  
(\*Corresponding author. E-Mail: cheung.honyeung@cityu.edu.hk Tel.: +852 3442-7746; Fax: +852 3442-0522.)

### ABSTRACT

Functional foods are a group of naturally nutrient-rich foods that enhance a person's health better than conventional foods. Functional foods have gained popularity and played a vital role even in disease prevention and improvement of quality of life. This is a shift from the traditional concept that food is merely for growth and development. However, health claims of functional foods should be supported by solid scientific evidence. There are some foods which are considered functional foods but lack approved health claims from designated authorities. The various types and sources of functional foods and the corresponding scientific evidence of their health claims are discussed and reviewed in this article. In addition, various challenges and opportunities in the production of functional foods are also considered. Although functional foods are known to have a variety of health claims, it must be understood that they are not meant to be an elixir. It is only one of many factors that contribute to a healthy life.

**Keywords:** functional foods; health claims; bioactive compounds; lifestyle

### INTRODUCTION

Functional food is a food that improves the well-being of an individual and is a part of the normal food pattern giving targeted functions to the body.<sup>(1)</sup> To avoid confusion, the term "functional" does not refer to the physico-chemical properties of food ingredients (functionality). Rather, it refers to the health benefits it provides over and above its nutritive value.<sup>(2,3)</sup> Due to various cultural perceptions, it is often used interchangeably with terms like health foods, nutraceuticals, dietary supplements, designer foods, pharma-foods, and even herbal or natural medicine.<sup>(3)</sup> However, the European Commission Concerted Action on Functional Food Science in Europe differentiates it from the rest by describing it to be not in the form of a capsule, a pill, or any dietary supplement.<sup>(1)</sup> To distinguish functional food from dietary supplement, the 1994 Dietary Supplement Health and Education Act (DSHEA) in the US, defines the latter as "a product (other than tobacco) that is intended to supplement the diet and that bears or contains one or more of the following dietary ingredients: a vitamin, a mineral, an herb or other botanical, an amino acid, a dietary substance for use by man to supplement the diet by increasing the total daily intake, or a concentrate, metabolite, constituent, extract or combinations of these ingredients." It may be in the form of a capsule, tablet or a pill. It is usually labeled as a dietary supplement and is not intended for use as a conventional food or as the main component of the diet.<sup>(4)</sup>

### Lifestyle Diseases associated with Diet

Nowadays, there is an increasing awareness in the relationship between food and health. A healthy lifestyle plays a key role in the reduction of the risk of developing a disease or illness. Urbanization, economic improvement, westernization of diet, and opulence can be associated to lifestyle diseases due to less physical activity and greater access to unhealthy foods. Obesity is one of the clustering risk factors associated with metabolic syndrome. Besides obesity, other risk factors for metabolic syndrome include atherogenic dyslipidemia, hypertension, insulin resistance, and hyperglycemia.<sup>(5,6)</sup> Lifestyle risk factors have to be identified, modified, and reduced to prevent most cases of diabetes, Coronary Artery Disease, stroke, and many cancers not only among high-income populations but also from low-risk migrating populations.<sup>(7-9)</sup>

### POTENTIAL SOURCES AND HEALTH BENEFITS OF BIOACTIVE CONSTITUENTS IN FUNCTIONAL FOODS

It has been proven that some foods and their inherent constituents can reduce the risk of diseases. Biologically active peptides possess diverse functions such as antioxidants, immune modulation, cholesterol lowering, antimicrobial, and anti-hypertension.<sup>(10)</sup> It has been shown in *in vivo* and *in vitro* conditions that milk protein-derived peptides especially from fermented dairy products like cheese and yoghurt perform a number of bioactive effects in the body. Reduction of mild hypertension is one of the clinical benefits of these products.<sup>(11)</sup> In fact, daily consumption of powdered fermented milk with *Lactobacillus helveticus* CM4 showed significant decline in elevated blood pressure without any adverse effects.<sup>(12)</sup> Bioactive peptides obtained from marine organisms were also reported to have bioactive functions incorporated in functional foods.<sup>(13)</sup> Angiotensin converting enzyme (ACE) inhibitory peptides were generated and incorporated in functional foods to potentiate vasodilatory effects of bradykinin and inhibit effects of angiotensin II, thereby, regulating blood pressure.<sup>(14)</sup> In another study, functionality of egg proteins has been studied to promote human health.<sup>(15,16)</sup> Besides egg proteins, artichoke leaf extracts could be used as a raw material for the production of food additives and nutraceuticals.<sup>(17)</sup>

Dietary fibers also known as roughage or ruffage are plant components that are either soluble or insoluble in water that are known to improve gastrointestinal functions. Soluble fibers may absorb water to become a gelatinous or viscous substance. They undergo fermentation easily upon transit in the colon through bacterial action, thereby, producing physiologically active substances and gases. Insoluble fiber may act as prebiotic fibers which can be metabolically fermented in the

colon similar to soluble fibers. Besides being a prebiotic, insoluble fiber also function as bulking fibers absorbing water as they pass through the digestive tract facilitating regularity of bowel evacuation and a smooth defecation process.<sup>(18)</sup> The beneficial effects of soluble fibers include alleviating the symptoms of irritable bowel syndrome and inflammatory bowel disease through anti-inflammatory functions of the short chain fatty acids which are byproducts of fermentation of soluble fibers in the colon.<sup>(19-24)</sup>

The U.S. Institute of Medicine (IOM) Panel on the Definition of Dietary Fibers proposed two definitions for functional and dietary fibers. Functional fiber refers to isolated, nondigestible carbohydrates that have beneficial physiological effects in humans while dietary fiber refers to nondigestible carbohydrates and lignin that are intrinsic and intact in plants.<sup>(25)</sup> A daily fiber intake of 38 grams for adult men and 25 grams for adult women has been recommended by the National Academy of Sciences of the Institute of Medicine within the United States. A minimum fiber intake of 18 g/day for healthy adults has been recommended by the British Nutrition Foundation. However, many countries around the world recommended 25-30 grams for their populations. The US Department of Agriculture adopted functional fibers to be included in the diet. It includes non-starch polysaccharides such as cellulose, beta-glucans, arabinoxylans, oligosaccharides, inulin, pectins, lignin, chitins, waxes, resistant dextrins, and resistant starch.<sup>(18)</sup> Resistant starch (**Table 1**) is a starch derived product that is resistant to digestion and acts as a dietary fiber in the colon.<sup>(26)</sup> It is considered as both a dietary supplement and a functional fiber depending on whether it is inherent or an additive.<sup>(27)</sup>

Table 1. Categories of Resistant Starch.		
Category	Feature	Sources
RS1	Physically inaccessible or digestible resistant starch	seeds or legumes and unprocessed whole grains
RS2	occurs in its natural granular form	uncooked potato, green banana flour <sup>(28)</sup> and high amylose corn
RS3	formed when starch-containing foods are cooked and cooled	legumes, <sup>(29)</sup> bread, cornflakes and cooked-and-chilled potatoes, pasta salad or sushi rice
RS4	chemically modified to resist digestion	wide variety of structures and are not found in nature

There are different proposed health benefits of resistant starch. According to Slavin 2005, it can help in weight management through its ability to increase satiety and decrease appetite.<sup>(30)</sup> Hence, it is a valuable tool for formulators of reduced-calorie foods.<sup>(31,32)</sup> It is also reported to be involved in fatty acid metabolism through lipid oxidation and adipocyte differentiation.<sup>(33-35)</sup> In addition, it is also believed to be involved in glycemic management through decreased glycemic response and increased insulin sensitivity in both healthy and diabetic individuals.<sup>(34,36-41)</sup> It also plays a role in reducing the risk of developing cardiovascular diseases.<sup>(42)</sup>

In the digestive tract, resistant starch performs different functions. It functions as a mild laxative due to increase microbial activity in the colon.<sup>(43)</sup> It can also induce apoptosis in human colonic cancer cells.<sup>(44,45)</sup> In fact, resistant starch combined with wheat bran can be beneficial in the prevention of colorectal cancer.<sup>(46)</sup> Another study suggested that rats would be less likely to develop manifestations of age related macular degeneration upon treatment of high amylose corn resistant starch.<sup>(47,48)</sup> It can also be used as an effective treatment for diarrhea in combination with an oral rehydration solution.<sup>(49,50)</sup>

$\beta$ -glucans are components of mycetes' cell walls besides chitin.  $\beta$ -1,3-D-glucans and  $\beta$ -1,6-D-glucans isolated from some basidiomycetes have been found to have a high level of biological efficiency. They possess anti-allergic effects by increasing the number of Th1 lymphocytes. Anticarcinogenic activity has been shown by a number of beta-glucans [i.e. pleuran from Oyster mushrooms (*Pleurotus* spp.) or lentinan from Shiitake (*Lentinus edodes*) mushrooms]. In addition,  $\beta$ -glucans may participate in fat metabolism besides having an immunity-stimulating effect. They are also associated with anti-obesity effects.<sup>(51,52)</sup> The data presented by Hong *et al.*, 2004, indicated that barley  $\beta$ -1,3; 1,4-glucan given orally, similarly potentiated the activity of antitumor monoclonal antibody (mAb), leading to enhanced tumor regression and survival. This investigation showed that orally administered yeast  $\beta$ -1,3; 1,6-glucan functioned similarly to barley  $\beta$ -1,3;1,4-glucan with antitumor mAb.<sup>(53)</sup>

According to Lo *et al.*, 2006, several fungal  $\beta$ -glucans may induce hypoglycemic effects after eating, possibly by slowing down stomach emptying so that dietary glucose is absorbed more gradually.<sup>(54)</sup> In the study of Kiho *et al.*, 1995, acidic polysaccharides and fruiting bodies of *Tremella mesenterica* and *T. aurantia* can both reduce blood glucose concentrations in induced diabetic rats.<sup>(55)</sup> However, they found out later that it was not  $\beta$ -glucan.<sup>(56)</sup> In another study of Kim *et al.*, 2005, a  $\beta$ -glucan prepared by hot water extraction of *Agaricus blazei* basidiocarps showed anti-hyperglycemic, anti-hypertriglyceridemic, anti-hypercholesterolemic and anti-arteriosclerotic activity in diabetic rats, although the active component was not identified. They found that anti-diabetic activities doubled when these preparations were digested by an endo  $\beta$ -(1 $\rightarrow$ 6)-glucanase from *Bacillus megaterium*.<sup>(57)</sup> A thorough study on the structural features of  $\beta$ -glucan is needed to clarify whether  $\beta$ -glucans or their derived oligosaccharides are the effective agents.<sup>(58)</sup>

Chan *et al.*, 2009 and Chen and Seviour, 2007 summarized the pitfalls in  $\beta$ -glucans research. According to them, no  $\beta$ -glucan control standard with specific molecular weight and branches is available. Usually, most of the  $\beta$ -glucans used is zymosan, which is a mixture of cell wall particles,  $\beta$ -glucans, and chitosan. In herbal research, most of the utilized  $\beta$ -glucans are based on extracts rather than purified  $\beta$ -glucans. Qualitative or quantitative characterization methods are not well established for comparing and assessing  $\beta$ -glucans from different sources. The translational approaches to apply knowledge of receptor and signal pathways of  $\beta$ -glucan to animal studies or the clinical trials are lacking. Furthermore, there is a need to specify or define the exact immunological actions and signaling pathways induced by  $\beta$ -glucan especially in cancer research.<sup>(58,59)</sup>

Glucosinolates (GSL) are bioactive compounds found in plants mostly in Family Brassicaceae containing sulfur and nitrogen and are derived from glucose and amino acids.<sup>(60)</sup> Upon activation of the enzyme myrosinase in the presence of water, the glucose breaks away from the molecule resulting in the formation of isothiocyanate. They are responsible for plant immunity in response to injury and infection.<sup>(61)</sup> Glucosinolates and their derivatives also play a biological role in human health.<sup>(62)</sup> For instance, recent studies about sulforaphane, an isothiocyanate from broccoli, showed its potential cytoprotective properties and other health benefits in humans.<sup>(63)</sup> Green vegetable isothiocyanates are known to have anti-cancer properties by inducing apoptosis.<sup>(64)</sup> Bhattacharya *et al.*, 2010 found that allyl isothiocyanate (AITC)-

rich mustard seed powder inhibits bladder cancer growth and muscle invasion.<sup>(65)</sup> Also, benzyl isothiocyanate (BITC) can trigger elevated basal lipolysis at 1 and 100 µmol/L in adipocyte tissues *in vitro*.<sup>(66)</sup> Okulicz and Hertig, 2012 also found that total thyroxine and triiodothyronine decreased after a two-week oral administration of BITC *in vivo*.<sup>(66)</sup> The possible sources and the nutritional benefits of some bioactive constituents of functional foods are shown in **Table 2**.

## ASIAN HERBS USED AS FUNCTIONAL FOODS AND MEDICINES

### Chinese Functional Foods and Medicines

As part of Asian culture, and stemming from the influence of ancient Traditional Chinese Medicine (TCM), food is commonly used to prevent or even cure diseases. Besides being used for therapeutic purposes, TCM is commonly used as dietary supplements, functional foods, or medicinal foods (*Yao Shan*). *Yao Shan* is believed to maintain well-being such as balancing the *Yin* and *Yang*, improving blood circulation, boosting immunity, controlling aging, preventing disease, and many other health benefits. The formulations of various TCM's are recorded in Food Recipe and Chinese Materia Medica books [i.e. *Pen Tsao*

*Ching*, The Book of Herbs by Shen Nung; *Huang Ti Nei Ching*, The Yellow Emperor's Classic on Internal Medicine; *Shang Han Tsa Ping Lun*, Treatise on Febrile and Miscellaneous Diseases]. Herbal properties and effects differ in each herb. These include flavors (pungent, sweet, sour, salty, bitter); direction of actions (floating, sinking, ascending, descending); effects (synergistic, antagonistic, single, additive, opposite, inhibitive, destructive); and essences (cold, cool drugs for *Yang* diseases, warm, hot drugs for *Yin* diseases). There are four categories of herbs in TCM formulation: (1) *Imperial herb* which is the chief herb in a formula; (2) *Ministerial herb* which is ancillary to the imperial herb, augmenting and promoting the action of the chief herbs; (3) *Assistant herb* reduces the side effects of the imperial herb; (4) *Servant herb* harmonizes or coordinates the actions of other herbs.<sup>(67)</sup> Herbs can also be classified as upper, middle, and lower classes according to Shen Nung (**Table 3**).<sup>(68)</sup> The *upper class herbs* serve as the main constituent of dietary supplements and functional/medicinal foods (*Yao Shan*) and can be taken continuously for life. They are rejuvenating and non-toxic. The *middle class herbs* may have either toxic or non-toxic effects and can promote mental alertness and stability. *Lower class herbs* have toxic properties and should be taken in mild concentrations in TCM formulations. They cannot be taken over a long time.<sup>(68)</sup>

Table 2. Possible Sources of Functional Food Components and their Health Benefits <sup>(67)</sup>		
Possible sources	Functional components	Potential Health Benefits
<b>Dietary fibers</b>		
Psyllium <sup>(68)</sup>	Soluble fibers	Lower Low Density Lipoprotein (LDL) and total cholesterol; protect against heart disease and some cancers; reduce risk of cardiovascular disease.
Oats, barley <sup>(69)</sup>	Beta-Glucans	Lower LDL and total cholesterol; reduce risk of cardiovascular disease; protect against heart disease and some cancers
Wheat Bran	Insoluble Fibers	Decrease risk of breast or colon cancer
<b>Soy Phytoestrogens</b>		
Soybeans and soy-based foods <sup>(70)</sup>	Daidzein, Genistein, Isoflavones	Protect against heart disease and some cancers; menopause symptoms, such as hot flashes lower LDL and total cholesterol
<b>Sterols</b>		
Corn, soy, wheat, wood oils <sup>(71)</sup>	Stanol Ester	Lower blood cholesterol levels by inhibiting cholesterol absorption
<b>Carotenoids</b>		
Tomato products (ketchup, sauces) <sup>(72)</sup>	Lycopene	Reduce the risk of prostate cancer
Green vegetables <sup>(73)</sup>	Lutein	Reduce the risk of macular degeneration
Carrots, Fruits, Vegetables	Alpha-carotene/Beta-carotene	Neutralize free radicals, which may cause damage to cells
<b>Phenolics</b>		
Flax, rye, vegetables <sup>(74,75)</sup>	Lignans	Prevention of cancer, renal failure
Citrus	Flavonones	Neutralize free radicals; reduce risk of cancer
Cranberries, Cranberry products, cocoa, chocolate <sup>(76,77)</sup>	Tannins (proanthocyanidines)	Improve urinary tract health; reduce risk of cardiovascular disease
Tea <sup>(78,79)</sup>	Catechins	Neutralize free radicals; reduce risk of cancer
Grape fruits, red wine <sup>(80-81)</sup>	Anthocyanidins	Neutralize free radicals; reduce risk of cancer; reduce platelet aggregation; reduce risk of heart disease
Fruits/vegetables	Flavones	reduce risk of cancer; neutralize free radicals
<b>Prebiotics<sup>(82)</sup></b>		
Jerusalem artichokes, shallots, onion powder	Fructo-oligosaccharides (FOS)	Gastrointestinal health; improve quality of intestinal microflora
<b>Probiotics<sup>(82)</sup></b>		
Yogurt, Other dairy	Lactobacillus	gastrointestinal health; improve quality of intestinal microflora
<b>Fatty Acids</b>		
Cheese, meat products	Conjugated Linoleic Acid (CLA) <sup>(83)</sup>	Improve body composition; decrease risk of certain cancers; anti-obesity
Salmon and other fish oils <sup>(84-86)</sup>	Long chain omega-3 Fatty Acids Docosahexaenoic acid (DHA) Eicosapentaenoic acid (EPA) N-3-Polyunsaturated Fatty Acids (PUFA)	Reduce risk of cardiovascular disease. Improve mental, visual functions; enhance bone growth

Source: International Food Information Council

**Table 3. Common Oriental Herbs used as Functional Foods and Medicines.**

Oriental Herbs/Medicinal foods/Beverages	Folkloric use	Chemical composition	Pharmacological properties	Classification
<b><i>Ganoderma lucidum</i></b> ( <i>Ling Chih</i> , <i>Reishi</i> mushroom or spirit plant)	Medicinal mushroom, Tonic, sedative, treatment for hyperlipidemia, chronic bronchitis, angina pectoris, hepatitis, autoimmune disease, leukopenia; used as beverage	ganoderic acid A, methyl ganoderate A, methyl ganoderate B, ganoderic acid C2, ganoderic acid G, ergosta-7, 22-diene-3beta, 5alpha, 6beta-triol, ergosterol peroxide and ergosta-7, 22-diene-3beta-yl pentadecanoate; <sup>(69)</sup> <i>Ganoderma lucidum</i> polysaccharide (GI-BSP); <sup>(90)</sup> Ethanol-soluble and acidic component (ESAC); <sup>(91)</sup> $\beta$ -glucan (Curdran); <sup>(92)</sup> ganoderic acid derivatives; <sup>(93)</sup> <i>Ganoderma lucidum</i> polysaccharide (GI-PS) <sup>(94)</sup>	Anti-tumor; immunomodulatory; <sup>(90)</sup> induces G1 cell cycle arrest, and apoptosis in human breast cancer cells; <sup>(91)</sup> induction of Th17 cells; <sup>(92)</sup> Cytotoxic and pro-apoptotic effects of novel ganoderic acid derivatives on human cervical cancer cells; <sup>(93)</sup> wound healing <sup>(94)</sup>	Upper class
<b><i>Lentinus edodes</i></b> ( <i>Hsian ku</i> in China/ <i>Shiitake</i> in Japan)	Edible medicinal mushroom; antitumor	polysaccharide	Induce apoptosis <sup>(95)</sup>	Upper class
<b><i>Agaricus blazei</i></b> ( <i>Shen ku</i> in China/ <i>Hime Matsutake</i> in Japan)	Edible medicinal mushroom	B-glucan polysaccharides <sup>(96)</sup>	Anti-tumor, infection, allergy, inflammation <sup>(96)</sup>	Upper class
<b><i>Coriolus versicolor</i></b> ( <i>Yun-Chih</i> )	Edible medicinal mushroom	Protein-bound polysaccharide (PSK)	Induce apoptosis, inhibits proliferation of tumor <sup>(97)</sup>	Upper class
<b><i>Panax ginseng</i></b> ( <i>Asian Ginseng</i> )	Tonic, regenerating, rejuvenating, treat diabetes, calm nerves, normal pulse, remedy collapse body fluid production, healthy spleen and liver; used as beverage	Ginsenosides <sup>(98)</sup>	Anti-diabetic; <sup>(99)</sup> promotes cholesterol metabolism; <sup>(100)</sup> apoptosis induction <sup>(101)</sup>	Upper class
<b><i>Panax notoginseng</i></b> ( <i>Sanchi ginseng</i> )	Used as tea, pain reliever, remove blood clots, increased cardiac flow, decrease blood pressure	Ginsenoside Rb1 and Rg1 ( $\alpha$ -L-Rha $\rightarrow$ $\beta$ -D-Glc glycoside) <sup>(102)</sup>	Anti-aging, antihypertension <sup>(103)</sup>	Upper class
<b><i>Lycium barbarum</i></b> ( <i>Kou Chi Tzu</i> , <i>Go ji</i> ); <b><i>L. chinense</i></b> ( <i>Go ji</i> )	Used in soup or as a tea; goji berry juice; eaten as dried fruit; supplement for liver and kidney; diabetes, cough, weakness, vertigo, improve eyesight	<i>Lycium barbarum</i> polysaccharides (LBP); <sup>(104)</sup> Lyciumin; <sup>(105)</sup> stigmast-5-en-3 $\beta$ -ol-3-O- $\beta$ -D-(2'-n-triacontanoyl) glucopyranoside and 19,21-dimethyl triacont-17,22,24,26,28-pentaene-1-oic acid <sup>(106)</sup>	Antioxidant; hepatoprotective, antidiabetic, atherosclerosis, anti-proliferation; diabetic retinopathy; <sup>(107-109)</sup> neuroprotective effects in learning and memory deficits; <sup>(110)</sup> hepatoprotective; <sup>(111)</sup>	Upper class
<b><i>Salvia miltiorrhiza</i></b> ( <i>Tan Shen</i> or <i>Dan Shen</i> / Sage)	Coronary artery diseases;	Tanshinone IIA; Salvianolic acids <sup>(112)</sup>	Anti-anginal drug and treatment of myocardial infarction, ischemia; protects liver injury due to iron overload <sup>(112,113)</sup>	Upper class
<b><i>Zizipus jujube</i></b> ( <i>Zizipus</i> )	Tonify the spleen and stomach, moisten heart and lungs, harmonize drugs; hypotensive effects (roots); anti-obesity (leaves)	Phenolics <sup>(114)</sup>	Antioxidant <sup>(114)</sup>	Upper class
<b><i>Cordyceps sinensis</i></b> ( <i>Tung Chung Hsia Tsao</i> )	Chronic cough, asthma, impotence, relieve exhaustion, athletic strength, entomogenous fungi; tonic food & medicine	cordysinins A-E (1-5) <sup>(115)</sup>	Renal injury <sup>(116)</sup>	Upper class
<b><i>Coix lachryma-jobi</i></b> ( <i>Coix seeds</i> )	Arthritis, diarrhea, edema, cancer, indigestion	Coix polysaccharides <sup>(117)</sup>	Apoptosis; <sup>(117)</sup> gastroprotective <sup>(118)</sup>	Upper class
<b><i>Astragalus membranaceus</i></b> ( <i>Astragalus</i> or <i>Huang-qi</i> )	Antioxidant, immune-stimulant, shortness of breath, chronic nephritis, rectal and uterine prolapse, antiviral, antitumor, night sweats, sores and wounds	Astragalus polysaccharide (APS) <sup>(119)</sup>	Hypoglycemic effects; <sup>(119)</sup> enhance immune responses <sup>(120)</sup>	Upper class
<b><i>Schisandra chinensis</i></b> <b><i>S. spenantha</i></b> ( <i>Wu Wei Tzu</i> )	Dyspnea, cough, diaphoresis, insomnia, night sweats, amnesia, dry mouth and thirst	Gomisin A	Antitumor; <sup>(121)</sup> anti-HIV (Human Immunodeficiency Virus) <sup>(122)</sup>	Upper class
<b><i>Eucommia ulmoides</i></b> ( <i>Tu Chung</i> )	Leaves & bark can be used as tea; strengthened muscles and bones, stabilize fetus, supplements for liver and kidney	geniposide and genipin; <sup>(123)</sup> Ursane-Type Nor-Triterpenoid <sup>(124)</sup>	Renal injury protection <sup>(123)</sup>	Upper class
<b><i>Pueraria lobata</i></b> ( <i>Ko Ken</i> )	Cardiovascular disease, angina pectoris, hypertension, sunlight Yang diseases,	Puerarin mixed in Kudzu diet <sup>(125)</sup>	Ameliorates glucose or lipid metabolism <sup>(125)</sup>	Middle class
<b><i>Allium sativum</i></b> ( <i>Ta Suan</i> or <i>garlic</i> )	Lowers blood lipids, fatigues, headaches, weakness, fatigues, sores, tumors, infection, inhibits platelet aggregation	S-allyl cysteine <sup>(126)</sup>	Lowers blood pressure <sup>(127)</sup>	Middle class
<b><i>Zingiber officinale</i></b> ( <i>Ginger</i> )	Antiemetic, dyspepsia, and anti-nausea	[6]-gingerol and [6]-shogaol; O-methyldehydrogingerol <sup>(128)</sup>	amelioration of fructose-induced fatty liver and hypertriglyceridemia; <sup>(129)</sup> cytotoxic, toxicity, anti-cancer; <sup>(130)</sup> antiplatelet aggregation and vasorelaxing effects <sup>(128)</sup>	Middle class
<b><i>Angelica sinensis</i></b> ( <i>Tang Kuei</i> or <i>Dong Quai</i> )	Regulates menstruation, activate blood circulation, pain reliever, anti-anemia, arthralgia, traumatic injuries	ferulic acid, Z-ligustilide, butylidenephthalide and various polysaccharides <sup>(131)</sup>	Estrogenic activity; <sup>(132)</sup> ameliorates menopausal symptoms; <sup>(133)</sup> anti-inflammatory and immunostimulatory; anti-cancer, neuroprotective and anti-hepatotoxic effects; anti-cardiovascular effects. <sup>(131)</sup>	Middle class

Oriental Herbs/Medicinal foods/Beverages	Folkloric use	Chemical composition	Pharmacological properties	Classification
<i>Cnidium officinale</i> (Chuan Chung)	Abdominal pain headache, amenorrhea, arthralgia, promotes flow of Qi, female genito-inflammatory disorder, menstrual disorders	falcarindiol, 6-hydroxy-7-methoxy-dihydrologustilide, ligustilidol, and senkyunolide H <sup>(134)</sup>	Anti-inflammatory & anti-cancer effects <sup>(134)</sup>	Middle class
<i>Punica granatum</i> (Shi Liu Pi/ pomegranate)	Anticancer, menopausal disorders, fertility, antiseptic, anti-parasitic	Polyphenolics <sup>(135)</sup>	Anti-breast cancer <sup>(135)</sup>	Middle class
<i>Thea sinensis</i> or <i>Camellia sinensis</i> (Green tea)	Antioxidant, anticancer, antibiotics	(-)-gallocatechin, (-)-epigallocatechin, (-)-epigallocatechin gallate, caffeine, (-)-epicatechin, gallocatechin gallate, and (-)-epicatechin gallate <sup>(136)</sup>	Antioxidant <sup>(137)</sup>	Middle class
<i>Euphorbia Kansui</i> (Kansui); <i>Euphorbia hirta</i> (Tawa-tawa or gatas-gatas in Philippines; <i>Feiyangcao</i> in China)	Anti-cancer, anti-leukemia, melanoma, ascites; mouth sores, antipyretic, immune-boosters, anti-dengue hemorrhagic fever; used as decoction	kansuinine A, kansuinine B, kansuinine C, kansuiphorin C, 3-O-(2'E,4'Z-decadienoyl)-20-O-acetylingenol, 3-O-(2'E,4'Z-decadienoyl)-20-O-acetylingenol, 3-O-(2'E,4'Z-decadienoyl)-20-deoxyingenol, 3-O-benzoyl-20-deoxyingenol, 5-O-benzoyl-20-deoxyingenol, kansenone, epi-kansenone, euphol; <sup>(138)</sup> gallic acid, quercitrin, myricitrin, 3,4-di-O-galloylquinic acid, 2,4,6-tri-O-galloyl-D-glucose and 1,2,3,4,6-penta-O-galloyl-beta-D-glucose <sup>(139)</sup>	Interferon- $\gamma$ (IFN- $\gamma$ ) production; <sup>(140)</sup> antidiarrhoeal <sup>(141)</sup>	Lower class
<i>Podophyllum emodi</i> (Kuei Chiu)	Skin disorders, snake bites, anti-parasitic, contact cathartic, periodontitis	podophyllotoxin, deoxypodophyllotoxin, kaempferol and quercetin <sup>(142)</sup>	Apoptosis induction <sup>(143)</sup>	Lower class
<i>Prunella vulgaris</i> (Hsia Ku Tsao)	Hypertension, tinnitus, eye inflammation, eye pain, hypotension, antibacterial, anti-tumor	rosmarinic acid (RA), ursolic acid (UA) and oleanolic acid (OA) <sup>(144)</sup>	attenuates IL-1 $\beta$ -induced apoptosis and Nuclear Factor kappa- light-chain-enhancer of activated B cells (NF- $\kappa$ B) activation <sup>(145)</sup>	Lower class
<i>Catharanthus roseus</i> (Chang chun hua in China; <i>Rosas de baybayon</i> in Philippines; <i>Sadaphuli</i> in Marathi and <i>Nityhakalyani</i> in Tamil)	Anti-cancer, <sup>(146)</sup> Diabetes, Malaria, Hodgkins lymphoma, Leukemia <sup>(147)</sup>	Vinblastine, vincristine; <sup>(148)</sup> cadin-2-en-1 $\beta$ -ol-1 $\beta$ -D-glucuronopyranoside (known as CR4-1) <sup>(149)</sup>	CR4-1 reduces the invasiveness of human cancer cells by suppressing metalloproteinases-9 (MMP-9) expression through inhibition of the NF- $\kappa$ B signaling pathways <sup>(149)</sup>	Lower class
<i>Kwei Ling Ko</i> ; <i>KLK</i> ; <i>Gui-Ling-Gao</i> (Tortoise shell-Rhizome jelly; Turtle jelly)	Used as nutraceutical or functional food; Immuno-modulatory effect	Mixture of herbs and turtle shells (amino acids from turtle shells, chlorogenic acid and other bioactive compounds from component herbs) <sup>(150)</sup>	activates the Peroxisome proliferation-activated receptors (PPARs) PPARgamma pathway and down-regulates the NFkappaB activity <sup>(151)</sup>	

## Japanese Functional Foods

In 1980's, the Japanese Scientific Committee defined functional food as foods having nutritional, sensory, and physiological functions. In 1991, a regulatory system known as Foods for Specified Health Use (FOSHU) responsible for approval of food labels was formed by the Japanese Ministry of Health, Labour and Welfare (MHLW). The evaluation is based on the effectiveness and safety according to Council of Pharmaceutical Affairs and Food Hygiene. In 2001, Foods with Health Claims as a new regulatory system was enacted. It consists of the FOSHU system and the Foods with Nutrient Function Claims (FNFC) system. Scientific evidence and harmony with international standards are the bases of labeling of functional foods. The nutrient function claims of the Japanese FNFC are

in accordance with Codex Alimentarius in 1997 and Economic Union Project in 1999. The Dietary Supplement Health and Education Act in the USA in 1994 enacted the structure function claim which is similar to the enhanced function claim of the Codex Alimentarius. The nutrition function claims of the Japanese FOSHU system are similar to both nutrition claims by the Codex Alimentarius and the Dietary Supplement Health and Education Act. The FOSHU health claims are designed for the maintenance of health especially for those who want to maintain a healthy lifestyle (Table 4). The FOSHU claims however, do not include any therapeutic claim for any human ailment. These health claims should include maintenance or improvement of a functional marker which can be evaluated easily; maintain or improve physiological mechanisms and organ functions; and subjective improvement of physical condition.<sup>(152)</sup>

Functional Ingredients	Functional Products	Experimental Evidence	Approved Health Claims
Soy Protein	Soya-bean soup	Significant decline of total cholesterol value from 256 mg/dl at the initial intake to 245 mg/dl at finishing time; also, the LDL cholesterol value decreased from 172 mg/dl to 153 mg/dl <sup>(153)</sup>	Decreases serum cholesterol level
Casein Phosphopeptide (CPP)	KOTSU CALCIUM	Induction of Ca <sup>2+</sup> influx into HT-29 cells due to formation of aggregated complexes of casein phosphopeptides (CPPs) and calcium phosphate <sup>(154)</sup>	Improves calcium absorption
Casein Phosphopeptide-Amorphous Calcium Phosphate (CPP-ACP)	RECALDENT KIDS	There was no significant difference in the enamel decalcification index between the experimental group using fluor protector under dentist's guidance and the experimental group using CPP-ACP but the control group and the two experimental groups vary significantly <sup>(155)</sup>	Makes teeth healthy by reinforcing remineralization



Functional Ingredients	Functional Products	Experimental Evidence	Approved Health Claims
<b>Lacto-tripeptide</b>	CALPIS SOUR MILK' AMEAL-S'	Lactotriptides Valine-Proline-Proline (VPP) and Isoleucine-Proline-Proline (IPP) may lead to significantly reduced Systolic Blood Pressure, particularly in Asian subjects <sup>(156)</sup>	Milk recommended for those with hypertension
<b>Heme Fe</b>	FEMININA	Markedly enhanced body iron stores and reduced iron deficiency among iron depleted children <sup>(157)</sup>	Iron supplementation to alleviate mild anemia
<b>Indigestible dextrin</b>	KENJIN SARON	Maintains glucose tolerance <sup>(158)</sup>	Lowers blood sugar level by facilitating absorption of sugar
<b>Bacillus subtilis OU V23481</b>	HONE GENKI	Vitamin K2 (menaquinone-7) biosynthesis; activates osteocalcin <sup>(159,160)</sup>	Promotes bone calcification
<b>Diacylglycerol</b>	ECONA COOKING OIL	enhanced susceptibility to lipolytic stimulation <sup>(161)</sup>	Lessens accumulation of fats in the blood vessels
<b>Fructo-oligosaccharides</b>	Mei-oligo; Meiji	Stimulates growth of bifido-bacteria; modulates lipogenesis & reduced triglyceridemia; enhanced calcium absorption; inhibits development of aberrant crypt foci <sup>(162)</sup>	Maintains healthy intestinal environment

## Functional Foods in the Philippines

In the Philippines, Functional foods (**Table 5**) are viewed as conventional foods with nutrients that have potential health benefits or desirable physiological effects. It should not be confused with food supplements.<sup>(163)</sup> This is the

proposed definition from Bureau of Foods and Drugs (BFAD), Department of Health Philippines. At present, there are no specific regulations for functional foods. However, the BFAD is responsible for strict evaluation and assessment of food products that qualify as functional foods.<sup>(164)</sup>

Table 5. Common Filipino Functional Foods and their Potential Health Benefits			
Functional Foods	Bioactive Constituent	Potential Nutritional Benefits	Possible Mechanism of Action
<b>Tiki-Tiki</b> (rice bran extract) ( <i>Oryza sativa</i> ) • <b>Purple brown rice</b> (PRE)	cyanidin, peonidin, and a newly isolated compound 2-hydroxy-5-[(3S) hydroxybutyl] phenyl-β-d-glucoside (HHPG) <sup>(165)</sup>	Prevents endoplasmic reticulum stress-induced retinal damage	Suppression of tunicamycin-induced retinal ganglion cell death at least partly by inhibiting activation of caspase-3
• <b>Enzymatic Extract from Rice bran</b> (EERB)	Enzymatic extract	Antiproliferative and immunoactivatory ability to MOLT-4 cells (human T-cell acute lymphoblastic leukemia) <sup>(166)</sup>	Apoptosis induction on MOLT-4 & immunoactivatory effect on N13 microglia cells, by inducing TNF-alpha (tumour necrosis factor-α) expression
• <b>Rice bran enzymatic extract</b> (RBEE)	Phytosterols, γ-oryzanol and tococls <sup>(167)</sup>	attenuates dyslipidemia, hypertension and insulin resistance	partial restoration of adiponectin levels and a significant attenuation of pro-inflammatory values of nitrates; reduced circulating levels of triglycerides and total cholesterol, increased High Density Lipoprotein (HDL) cholesterol
• <b>Defatted Rice bran</b> (DRB)	Phenolics <sup>(168)</sup>	Antioxidant	antioxidant activity was greater based on the decline in half maximal inhibitory concentration (IC <sub>50</sub> ) from 38.8±0.4 to 27.7±0.5 μg/ml;
• <b>Black &amp; Red Rice Bran</b>	Phenolics; ferulic, vanillic and p-coumaric acids <sup>(169)</sup>	Antioxidant	antioxidant activity was determined by using 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical assay, 2,2-azino-bis-(3-ethylenebenzothiazoline-6-sulfonic acid) (ABTS) radical cation assay, reducing power, and chelating ability
• <b>Rice bran</b> (PA)	Phytic acid (PA)	Antioxidant & Cytotoxic <sup>(170)</sup>	induced marked growth inhibition in ovary, breast and liver cancer cells
<b>Virgin coconut oil</b> (VCO) ( <i>Cocos nucifera</i> )	Unsaponifiable components; <sup>(171)</sup> phenolic acids such as ferulic acid and p-coumaric acid <sup>(172)</sup>	anti-inflammatory, analgesic, antioxidant <sup>(172)</sup> and antipyretic <sup>(173)</sup>	reduction on the transudative weight, granuloma formation, and serum alkaline phosphatase activity
<b>Gata</b> (Coconut milk)	Medium chain fatty acids (MCFAs), <sup>(174)</sup> lauric acid <sup>(175)</sup>	Antithrombosis, anticancer, anti-obesity; <sup>(174,175)</sup> anti-ulcerogenic effect <sup>(176)</sup>	increases HDL cholesterol, lower linoleate levels resulting to reduced levels of linoleate derived prostaglandin, decreases free radical levels in the cells <sup>(174)</sup>
<b>Coconut flakes/flour</b>	good source of both soluble and insoluble dietary fiber	Cholesterol lowering effect <sup>(177)</sup> glycemic index lowering <sup>(178)</sup>	reduces serum total and Low Density Lipoprotein (LDL) cholesterol and serum triglycerides of humans
<b>Buko juice/ Young Coconut juice</b> (YCJ)/ <b>Coconut water</b>	sugars, vitamins, minerals, amino acids and potassium, sodium, phytohormones	Estrogen like function; antioxidant; rehydration energy drink, electrolyte balance, diuretic	reduces histopathologic changes in the brain associated with Alzheimer's disease <sup>(179,180)</sup>
<b>Nata de coco</b> (fermented coconut water)	Dietary fiber, microbial cellulose	Give boost to the diet	supported the growth, spreading, and migration of human keratinocytes, Expressions of E-cadherin and the alpha-3 chain of laminin <sup>(181)</sup>
<b>Legumes</b> (cowpeas, mung beans, pole <i>sitao</i> , chickpeas, green peas, groundnuts, pigeon peas, kidney beans, lima beans and soyabeans)	Dietary fibers, iron zinc, calcium	Hypocholesterolemic <sup>(182)</sup>	No specific mechanism of action mentioned

Functional Foods	Bioactive Constituent	Potential Nutritional Benefits	Possible Mechanism of Action
<b>Moringa oleifera</b> ( <i>Malunggay</i> )	4-( $\alpha$ -L-rhamnopyranosyloxy) benzyl isothiocyanate, methyl N-4-( $\alpha$ -L-rhamnopyranosyloxy) benzyl-carbamate, and 4-( $\beta$ -D-glucopyranosyl-1 $\rightarrow$ 4- $\alpha$ -L-rhamnopyranosyloxy)-benzyl-thiocarbamate; <sup>(183)</sup> aurantiamide acetate 4 and 1,3-dibenzyl urea; <sup>(184)</sup> quercetin and kaempferol; <sup>(185)</sup> O-ethyl-4-( $\alpha$ -L-rhamnopyranosyloxy)benzyl carbamate, 4( $\alpha$ -L-rhamnopyranosyloxy)-benzyl isothiocyanate, niazimicin, niazirin, beta-sitosterol, glycerol-1-(9-octadecanoate), 3-O-(6'-O-oleoyl-beta-D-glucopyranosyl)-beta-sitosterol, and beta-sitosterol-3-O-beta-D-glucopyranoside	Antibacterial; <sup>(183)</sup> Anti-inflammatory & analgesic; <sup>(184)</sup> Antioxidant; <sup>(185)</sup> Antitumor <sup>(186)</sup>	inhibited the production of TNF-alpha and Interleukin(IL)-2; <sup>(184)</sup> scavenging peroxy and superoxyl radicals <sup>(185)</sup>
<b>Momordica charantia</b> ( <i>Ampalaya</i> ; Bitter melon)	3-O-[6'-O-palmitoyl-beta-D-glucosyl-stigmasta-5,25(27)-dien and stearyl derivative; <sup>(186)</sup> 3 $\beta$ ,7 $\beta$ ,25-trihydroxycucurbita-5,23(E)-dien-19-al, momordicine I, momordicine II, 3-hydroxycucurbita-5,24-dien-19-al-7,23-di-O- $\beta$ -glucopyranoside, and kuguaglycoside G; <sup>(187)</sup> trans-nerolidol, apiole, cis-dihydrocarveol and germacrene D <sup>(188)</sup>	Antitumor <sup>(189)</sup> ; Antidiabetic; <sup>(187)</sup> hypoglycemic; <sup>(190)</sup> Antibacterial <sup>(188)</sup>	stimulating insulin secretion <i>in vitro</i> ; selective 11 $\beta$ -hydroxysteroid dehydrogenase type 1 (11 $\beta$ -HSD1) inhibitory activity; <sup>(190)</sup> Antibiotic property especially to <i>Staphylococcus aureus</i> but no specific mechanism of action mentioned <sup>(188)</sup>
<b>Root crops</b> (Taro, <i>Colocasia esculenta</i> ; <i>Kamoteng kahoy</i> , <i>Manihot esculenta</i> ; <i>Kamote</i> , <i>Ipomoea batatas</i> ; Yam, <i>Dioscorea alata</i> )	Resistant starch; <sup>(191)</sup> 35 kDa and 50 kDa proteins; <sup>(192)</sup> arabinogalactan-protein <sup>(193)</sup>	Hypoglycemic; <sup>(193)</sup> Cytokine-mimetic properties; <sup>(192)</sup> fibrosis antagonist <sup>(194)</sup>	Lowers glycaemic index; <sup>(191)</sup> stimulate proliferation of bone marrow cells and spleen cells; <sup>(192)</sup> regulating the Transforming Growth Factor (TGF)- $\beta$ /smad signaling pathway and modulating Epithelial Mesenchymal Transition (EMT) expression <sup>(194)</sup>
<b>Zea maize</b> (Purple & yellow corn, <i>Mais</i> )	chlorogenic acid, caffeic acid, rutin, ferulic acid, morin, quercetin, naringenin, and kaempferol; <sup>(195)</sup>	Antioxidant; <sup>(195)</sup> hypoglycemic <sup>(196)</sup>	Reducing lipid peroxidation, increasing endogenous antioxidant enzyme Catalase (CAT), Total Peroxidase (TPX) and Superoxide Dismutase (SOD) activities in isolated mouse kidney, liver, and brain; <sup>(195)</sup> $\alpha$ -glucosidase inhibitor <sup>(196)</sup>
<b>Philippine fruits</b> [Banana ( <i>Musa acuminata</i> ), Pineapple ( <i>Ananas comosus</i> ), Guava, ( <i>Psidium guajava</i> ), Mango ( <i>Mangifera indica</i> ), Papaya ( <i>Carica papaya</i> ), Guyabano ( <i>Annona muricata</i> )]	Phenolics; dietary fibers <sup>(197,198)</sup> triterpenoids <sup>(199)</sup>	Antioxidant & antiproliferative activities; <sup>(197,198,200)</sup> hypolipidemic, antidiabetic; <sup>(201)</sup> Nephroprotective; <sup>(199)</sup> antimicrobial; <sup>(202,203)</sup> anti-breast cancer, pancreatic cancer & other cancers <sup>(204,205)</sup>	Decrease levels of fasting blood glucose, significantly increase serum insulin and insulin sensitivity index; <sup>(199)</sup> activates peroxisome proliferator-activated receptor gamma (PPAR- $\gamma$ ); <sup>(204)</sup> downregulation of Epidermal Growth Factor expression; <sup>(206)</sup> downregulation of Hypoxia Inducible Factor (HIF)-1 $\alpha$ , NF- $\kappa$ B, Glucose Transporter (GLUT)1, GLUT4, Hexokinase (HK)II, and Lactate Dehydrogenase A (LDHA) <sup>(207)</sup>

## Korean Functional Foods

The Korean Food and Drug Administration (KFDA) defines Health Functional Foods as a product intended for the use of enhancing and preserving human health with one or more functional ingredients or constituents. To ensure the safety of health functional foods, the Korean Food and Drug Administration (KFDA) enacted the Health Functional Food Act in August 2002. The revised act in 2008 includes conventional foods and other diet supplements and certain products in the form of tablets, capsules, powders, granules, pastes, gells, jellies, and bars. According to the Health Functional Food act, the term Health Functional Foods means manufactured foods including processed foods with functional raw materials or ingredients useful for the human body. The term "functionality" means nutrients for the proper functioning of the structures of the human body. Unless the products receive specific recognition from KFDA, they cannot be considered as functional foods even though they are considered as such in other countries. In recent years, KFDA recognized 37 ingredients for functional food. Red Ginseng is the best-selling functional food ingredient in Korea because of its numerous health benefits. Other food ingredients which retain large market shares include omega-3 fatty acid, aloe, vitamin and mineral supplements, and glucosamine. It is known that Korean traditional medicine utilizes only natural herbal ingredients. This accounts for the increasing demands and preferences of consumers for products issuing health claims. Over the past years, the incidence of lifestyle diseases is increasing among the Korean population. Hence, functional foods that target these diseases are becoming more popular in Korea. These include functional foods with anti-aging effects, immune boosters, slimming effects, skin care enhancer and even hair growth enhancer among aging men. Energy drinks containing red ginseng entice consumers to develop a habit of drinking it, increasing its sales

in the functional food market. Food supplements containing glucosamine, aloe vera extracts, and omega-3 fatty acids are also showing increased consumption.<sup>(208)</sup>

## RECENT ADVANCEMENTS ON FUNCTIONAL FOOD RESEARCH

The interweaving of various fields such as nutrition, biochemistry, food science, chemistry, genetics and physiology results in the advancement of research findings about human diet and functional foods. In order to have a vivid picture of the biological basis of the relationship between food and health, advanced research in metabolomics, proteomics, nutrigenomics, and other disciplines is necessary. Advances in these fields of research will unravel the molecular mechanism of actions of nutrients in the human body. Various nutritional effects in different scenarios can also be recorded. The identification of various proteins and mapping of their biological functions is the concern of proteomics.<sup>(209)</sup> Metabolomics is a growing field of analytical chemistry that focuses on identifying small metabolites and has become a powerful tool in agriculture and food science.<sup>(210)</sup> The relationship of nutrition and diet to human health is the application of nutrigenomics.<sup>(211)</sup> The advancement of "Omics" technology (i.e. transcriptomics, proteomics, and metabolomics) leads to the emergence of various screening trials for human diseases that can lead to determination of metabolic signatures for various diseases. In this connection, there is also a need to find biomarkers that will identify individuals at risk of developing a certain disease in the future. This requires large scale high-throughput longitudinal studies and if the results are generalizable, then more appropriate intervention could be identified and focused on those populations most at risk.

## Foodomics

A new discipline known as *Foodomics* has been defined recently by Cifuentes 2009 and Herrero *et al.*, 2010.<sup>(212,213)</sup> It includes the concepts of nutrigenetics and nutrigenomics. Nutrigenetics entails the genetic bases of functional food, or food supplement and a dietary pattern for a certain health outcome. Nutrigenomics focuses on the interactions resulting in protein expression and metabolite generation.<sup>(214)</sup> It applies advanced Omics technologies in the study of food,

nutrition and medical research (**Table 6**).<sup>(215,216)</sup> Foodomics can facilitate biomarker identification that can help in the evaluation of the health status of an individual and provides multiparameter quantitation for nutritional effects in humans. In fact, the concepts of Systems Biology together with Omics technologies are transforming current diagnostic and therapeutic approaches to a predictive, preventive and individualized medicine.<sup>(217)</sup> These developments can be useful in the formulation of personalized therapeutic dietary regimen.<sup>(218,219)</sup>

	Omega-3 fatty acid	Genistein	Isoflavones	Polyphenols	Quercetin	Sulforaphane	Flavonoids/phenolics
<b>Beverage/ Food</b>	Fish oil	Soybean	Soya food/Soy/cereals	Grape juice/wine/green tea	Fruits & vegetables	Cruciferous vegetables	Red wine/ Tea/red grape juice
<b>Health issue</b>	Cancer prevention	cAMP signaling & cell differentiation	Vascular health/kidney function/ Atherosclerosis prevention	Inflammatory bowel disease prevention/ anti-cancer	Colorectal cancer prevention	Cancer prevention	Cardiovascular disease prevention
<b>Omics technology</b>	Transcript-omics	Transcript- omics	Proteomics/ Metabolomics/ Proteomics	Metabolomics/ Proteomics	Proteomics	Transcriptomics	Metabolomics
<b>Analytical tool</b>	DNA microarray	DNA microarray	DIGE, LC-MS/MS/ <sup>1</sup> H-NMR/2DE-MALDI-TOF-MS	<sup>1</sup> H-NMR/2DE, nLC-ESI-Q-TOF MS/MS	2DE-MALDI-TOF-MS	DNA microarray	GC-TOF-MS
<b>In vitro/ in vivo model</b>	Caco-2 cells	Peripheral lymphocytes	Human serum/ urine/ Human peripheral blood mononuclear cells	Human feces/ Human lung adenocarcinoma cells, A549 cells	Human SW480 colon carcinoma cells	Mice feces, plasma	Human urine,
<b>References</b>	(220)	(221)	(222-224)	(225,226)	(227)	(228)	(229,230)

**Abbreviations:** Deoxy Ribonucleic Acid (DNA); cyclic Adenosine Monophosphate (cAMP); Difference Gel Electrophoresis (DIGE); Liquid Chromatography-Mass Spectrometry/Tandem Mass Spectrometry (LC-MS/MS); 2D-Electrophoresis (2DE); Matrix-assisted Laser Desorption/ionization-Mass Spectrometry (MALDI-TOF-MS); Hydrogen-1-Nuclear Magnetic Resonance (<sup>1</sup>H-NMR); Nano-scale Liquid Chromatographic Electrospray Ionization Quadrupole Time-of-Flight Tandem Mass Spectrometry (nLC-ESI-Q-TOF-MS/MS); Gas Chromatography-Time of Flight Mass Spectrometry (GC-TOF-MS)

## micro-RNAs

Nowadays, the application of biotechnology to the field of nutrition is very promising. The relationship between nutrients and the genes of interests is elucidated using DNA chips and proteomics. For instance, the concept of Micro-RNAs (miRNA or miR) can be applied in the search for biomarkers to be applied to research on functional food, human health, and disease. miRs are short non-coding RNAs that bind to target mRNA and regulate specific gene expression.<sup>(231,232)</sup> They can downregulate specific gene expression by destabilization of target genes, degradation, and translational repression.<sup>(232)</sup> The diverse miR expression profile can serve as new signals in the understanding of the functions of functional foods and the molecular mechanisms affecting one's diet. For instance, there are nutraceuticals that regulate important genes to provide physiological benefits in maintenance of a healthy well-being. Takanabe *et al.*, 2008 found that miR-143 might be involved in the regulation of adipocyte gene expression in mice.<sup>(233)</sup> In another scenario, Schoonjans *et al.*, 1996 showed that the presence of fatty acids can either facilitate or inhibit the expression of adipocyte genes.<sup>(234)</sup> Thus, nutrition could be a determinant in the regulation of genes associated with obesity. Recent scientific evidences showed promising roles of miRs in the growth of organism, cell differentiation, cell proliferation, cell death, and different metabolic pathways.<sup>(235)</sup> miRs are also related to a variety of human diseases including vascular diseases, cancers, neurologic diseases, tissue diseases and metabolic diseases.<sup>(236,237)</sup> With the increasing number of discovery of miRs, more therapeutic targets for various diseases will be revealed. Thus, miRs research should be given a thorough understanding in order to target diseases with unknown effective therapies.

There are various studies confirming the roles of dietary nutrients in alleviating disease condition. In fact most of these are target specific. Some natural dietary nutrients may show enhancing, inhibiting, or synergistic effects. For instance, Bickford *et al.*, 2006 found out that catechin, carnosine, vitamin D3, green tea, and blueberry could enhance bone marrow cell growth compared with human granulocyte-colony stimulating factor (hGM-CSF) and could trigger synergistic effects upon combination which can help in the healing process.<sup>(238)</sup> Studies also show that food bioactive compounds might be responsible in apoptotic modulation (**Table 7**). This simply shows that the bioactive food nutrients may influence the cell physiology through genomic and proteomic processes.<sup>(239)</sup> Thus, modulation of miR expression may be associated with the specific roles of bioactive compounds in foods although it requires further studies about the exact mechanisms involved.

## Food Biotechnology and Genetic Engineering

The bioactivity expression of the natural food extracts depends on the chirality of biomolecules. In fact, the stereochemistry-bioactivity relationships are complicated.<sup>(257)</sup> Here, the bioactivity may not be attributable only to a single compound but also to the complexity and peculiarity of the structures involved. For instance, Guevarra *et al.*, 1990 suggested that the antimutagenic activity of *M. charantia* (Ampalaya) may reside in the peculiar lipid-like structure of the acylglucosylsterols that could adversely affect the membrane permeability towards mitomycin C and disrupting its cellular activity.<sup>(186)</sup> This could be a possible mechanism for the anticarcinogenic property of this vegetable plant. In another study, Oberlies *et al.*, 1999, studied the structure-activity relationships of diverse Annonaceous acetogenins against multidrug resistant human mammary adenocarcinoma (MCF-7/Adr) cells. They found that among

Table 7. Apoptotic Functions of Food Bioactive compounds.	
Food Bioactive Compounds	Apoptotic Functions
<b>Via Intrinsic pathway (Mitochondrial-mediated apoptosis)</b>	
a) Genistein	up-regulation of miR-34a, resulting in the down-regulation of Notch-1 signaling pathway <sup>(240)</sup>
b) Ellagitannins/punicalagins/urolithins	Inhibition of 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD)-induced cytochrome (CYP)1-mediated 7-ethoxyresorufin-O-deethylase (EROD) activity; <sup>(241)</sup> induction of apoptosis through activation of initiator caspase -9, effector caspase-3 and down regulation of B-cell lymphoma-extra large ( bcl-XL) <sup>(242)</sup>
c) Capsaicin	increases cytosolic cytochrome c; activation of caspase 3 and Poly (ADP-ribose) polymerase (PARP) (p85) levels; increases pro-apoptotic Bcl-2-associated death promoter/ Bcl-2-like protein 4 (Bad/Bax) expression <sup>(243)</sup>
d) silibinin	Inhibition of caspase-3 mediated tubular cell apoptosis and decreased the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, Inducible nitric oxide synthase (iNOS) and Nuclear factor kappa beta (NF-κB) over expression and upregulation of the Nuclear factor (erythroid-derived 2)-like 2 (Nrf2) expression <sup>(244)</sup>
e) Lycopene	Synergistically increases quinacrine activity through inhibition of Wnt-TCF signaling by increasing the levels of adenomatous polyposis coli (APC), Disabled homolog 2 (DAB2), Glycogen synthase kinase 3 (GSK-3β), and Axin, and decreasing β-Catenin, p-GSK3β (ser 9), and Casein kinase 1(CK1) <sup>(245)</sup>
f) Phenethyl, benzyl & allyl isothiocyanates	Induce apoptosis by overcoming inhibitory action of B-cell lymphoma 2 (Bcl-2) <sup>(246)</sup>
g) Delphinidin	Prevents increments in intracellular superoxide or in the protein content of NADPH oxidase (NOX) 2, NOX4, p22phox, orcaspase-3; inhibited the impairment of redox status or cell viability, and prevented the attenuation of mitochondrial enzyme activities and the reductions of Bcl-2, NADH dehydrogenase subunit 1(ND1), or cytochrome b contents; thereby neutralizing the Oxidized Low-Density Lipoprotein (oLDL) harmful effects on mitochondrial dysfunction, oxidative stress, and apoptosis <sup>(247)</sup>
h) [8]-Shogaol	Induction of procaspase-9 and procaspase-3 processing <sup>(248)</sup>
i) Fisetin	promotes caspase-3 activation, downregulation of Bcl-2 and Induced myeloid leukemia cell differentiation protein (Mcl)-1(L), and upregulation of Bax, Bim and Bad <sup>(249)</sup>
<b>Via Extrinsic pathway (Death receptor-mediated apoptosis)</b>	
a) Sanguinarine	decreases Bcl-2 and NF-κB protein expression and a significant increase in Bax protein expression <sup>(250)</sup>
b) Luteolin	enhances the degradation of tyrosine (Tyr)(705)- and serine (Ser) (727)-phosphorylated Signal transducer and activator of transcription (STAT)3 through interacting with heat shock protein (Hsp) 90 <sup>(251)</sup>
c) 3,3-Diindolylmethane	modulates aryl (AhR) hydrocarbon receptors <sup>(252)</sup>
d) Curcumin	enhances loss of membrane potential, blockade of nuclear factor kappa B (NF-κB) activation, induction of cellular apoptosis by activation of caspases, release of cytochrome c, and upregulation of TNF-R for cationic solid lipid nanoparticles (C-SLNs) <sup>(253)</sup>
e) Epigallocatechin-3-gallate	activation of cell death pathways and apoptosis at mRNA level <sup>(254)</sup>
f) Lupeol	induction of active caspase-3 and poly(ADP-ribose)polymerase (PARP) cleavage <sup>(255)</sup>
g) Resveratrol	activation of caspases 9 and 7 and the cleavage of PARP <sup>(256)</sup>

a series of bis-adjacent THF ring acetogenins, those with the stereochemistry of threo-trans-threo-trans-erythro (from C-15 to C-24) were the most potent.<sup>(258)</sup>

The native structure of plant metabolites or natural food extracts also plays an important role in the discovery of their specific mode and site of action using combined metabolomics and nutrigenomics approaches. In fact, desirable food compounds can now be produced in large quantities at low expenditures based on the applications of modern biotechnology and engineering.<sup>(259)</sup> The integration of these fields helps in the understanding of the role of diet in the control of gene expression and to target potential nutritional interventions. Amino acids, fatty acids, vitamins, minerals, glucose, and cholesterol are known to regulate gene expression leading to protein expression.<sup>(260-268)</sup> Nutrient deficiency can affect phenotypic expressions like osteoporosis, central nervous system dysfunction, inflammation, obesity, and neural development.<sup>(269-272)</sup> (Table 8) shows the biological mechanism of some food nutrients and the basic assessment of its efficacy using Hill's criteria.<sup>(273)</sup>

Besides genetics, disease progression involves various factors including lifestyle, environment, and nutrition. This poses an obstacle in the development of diagnostic tools for such diseases. Nowadays, scientists may identify specific genes associated with a certain disorder and the possible reactions to dietary nutrients. For instance, identification

of the Single Nucleotide Polymorphism (SNP) profile of a person that is predictive of its cardiovascular condition in association with a particular fat diet is already possible.<sup>(307)</sup> This advancement can help evaluate the effects of other factors besides genetics.

Freese and Schubert, 2004 emphasized that genetic engineering can possibly result in genetic instability that can alter or reduce the nutritional value of food.<sup>(308)</sup> The problem of nutrient loss in foods is the result from the functional disruption of the chromosomal gene into which the transfected DNA is incorporated. This could lead to an unpredictable and unintended consequence on the nature of genetically modified organism (GMO) which may be hazardous or toxic. Although the transfected DNA is expressed in the same way in both plants and bacteria both organisms translate proteins in a different way. For example, plants undergo glycosylation but this rarely occurs in bacteria. In this case, the immune responses like allergy to the resulting proteins may be influenced by the glycosylation process. In addition to this, there are other possible undesirable effects brought about by engineering natural food.<sup>(309)</sup> Excess lignin production in *Bt* corn,<sup>(310)</sup> reduced levels of certain phytoestrogens in glyphosate-tolerant soybeans<sup>(311,312)</sup> and unpredicted changes in the small molecule metabolism of genetically engineered (GE) potatoes<sup>(313,314)</sup> are among other examples of unintended effects in GE crops.<sup>(315-317)</sup>

Table 8. Some Mechanism of Action of Specific Food Nutrients in Health Phenotypes.				
Food Nutrients	Mechanism	Health Phenotypes	Hill's Criteria <sup>(72)</sup>	References
<b>Omega-3 fatty acids</b>	Decreases transcription of inflammatory cytokines by inhibition of NF- $\kappa$ B signaling pathway; minimizes the loss of connexin 43 (Cx43) induced by IL- $\beta$ signaling through NF $\kappa$ $\beta$ ;	Cardiovascular Health	Biologically plausible, dose dependent, strong association but some studies show equivocal or limited association	(274-282)
	Modulates neuronal excitability; regulates gene expression; acts as endogenous agonists for transcription factors; enhanced endogenous antioxidant systems	Mental & behavioral health	Dose dependent, strong association but some studies show limited effects, Biologically plausible	(283-295)
<b>Sterol/stanol esters</b>	Decrease cholesterol absorption by competing with Transintestinal Cholesterol Excretion (TICE)-derived Cholesterol for incorporation into mixed micelles	Cardiovascular Health	Strong association, dose dependent (Biologic gradient), consistent, coherent, plausible, specific	(296)
<b>Genistein (Soy isoflavone) &amp; Soy Proteins</b>	Enhance insulin action by activating Adenosine Monophosphate-Activated Protein Kinase;	Endocrine & Cardiovascular Health	Strong association, consistent, coherent, plausible, specific, dose dependent (Biologic gradient)	(297,298)
<b>3,6-dihydroxyflavone; Phenoxodiol isoflavone; Quercetin; Garlic oil; Ficus flavonoid</b>	Induce apoptosis by decreasing mitochondrial membrane potential and releasing cytochrome C; MicroRNA (MiR-34a) inhibits tumor proliferation and migration through down-regulation of Bcl-2 and silent mating type information regulation 2 homolog (SIRT)1; MiR- 34a regulates cancer stem cells by inhibition of cell proliferation, cell cycle progression, self-renewal, epithelial to mesenchymal transition (EMT) and invasion; elicits anti-cancer effects through caspase independent apoptotic pathway ; prevents oxidative DNA damage through inhibition of lipid peroxidation	Breast, pancreas, prostate & liver health; Anticancer	Specific, strong association, consistent, coherent, plausible, dose dependent (Biologic gradient)	(299-306)

### Nanonization of Functional Foods

The application of nanotechnology to functional foods is very promising. Perez-Esteve *et al.*, 2012 highlighted the current applications of nanotechnology in the development of novel functional foods.<sup>(318)</sup> In order to impart the desired structural and functional properties to food, principles of nanoscience has to be utilized in order to manipulate and control interactions between food components and their self-assembly behavior on a molecular scale.<sup>(319-321)</sup> The basic application of nanotechnology is the targeted delivery of bioactive components (i.e. carotenes, omega-3 fatty acids, coenzyme Q, vitamins, plant polyphenols etc.). One approach of this delivery system is through microencapsulation. It involves the entrapment of a desired core within a secondary encapsulant in order to mask the taste and color of nutrients and to give protection against transportation, processing, and storage hazards.<sup>(322)</sup> This is beneficial among food industry targeting delivery of healthy food nutrients. Here, encapsulating matrices that are generally regarded as safe are used in the delivery of functional food nutrients.<sup>(323)</sup> For instance, microencapsulation of probiotics for gastrointestinal delivery has been done by Cook *et al.*, 2012.<sup>(324)</sup> In this process, the bacteria are immobilized into a polymer matrix with the bacterial structures unaltered in the stomach reducing cell death during passage in the gastrointestinal tract and providing their efficient release across the intestines. This differs from the diffusion based unloading of most controlled release devices for small molecules. Nanoparticulate food ingredients (i.e. lycopene, carotenoids, and highly unsaturated fatty acids in marine oils) are also incorporated in food matrix development procedures.<sup>(325)</sup>

The demands for functional beverages are rapidly growing these days.<sup>(325)</sup> Vitamin E-enriched beverages are now available in the market. However, application of Vitamin E in beverage fortification poses problems. One problem is the "ringing" of vitamin E emulsion droplets around the bottle neck due to poor physical stability of Vitamin E in water. Stability problems also arise in liquid vitamin E mixed with beverages containing fruit juices. The next problem is the change in beverage appearance due to turbidity. In order to prevent unsightly and regulatory problems, vitamin E products for

beverage fortification should have physical stability in liquids without changing the overall appearance of the beverage.<sup>(325)</sup> In this case, the application of nanotechnology can be an answer. In relation to this, Chen and Wagner 2004 produce vitamin E nanoparticle by ultra-high pressure homogenization stabilized with starch microencapsulation.<sup>(326)</sup> The nanonized vitamin E particle reduces physical stability and turbidity problems.

An alternative to traditional valve homogenization is microfluidization which is producing a tighter particle size distribution.<sup>(325)</sup> It has been successfully applied in syrups, chocolates, malted drinks, yoghurts, salad dressings, fillings, icings, and flavor oil emulsions. This nanoencapsulation procedure draws much attention from food and pharmaceutical industries. For instance, Zhong *et al.*, 2012, found out that aggregation and conformational changes of  $\beta$ -Lactoglobulin ( $\beta$ -LG) under Dynamic High Pressure Microfluidization (DHPM) were related to its antigenicity.<sup>(327)</sup> An increase in  $\beta$ -LG antigenicity resulted upon increase in DHPM pressure from 0.1 to 80 MPa accompanied with disaggregation of  $\beta$ -LG samples and partial unfolding of the molecule. This was reflected in the decrease of particle size, increase of free sulfhydryl (SH) contents and  $\beta$ -strands contents, and slight exposure of aromatic amino acid residues. Contrarily, there is a decrease in antigenicity at pressures above 80 MPa.<sup>(327)</sup> In another scenario, Wang *et al.*, 2012 prepared a novel glucosamine hydrochloride-rectorite (DGH-REC) nanocomposite with antioxidant and anti-ultraviolet activity.<sup>(328)</sup> They found that the nanocomposites can play a potential role in health or functional food because it did not show apparent cytotoxicity. In addition, the application of nanoparticles, nanofluidics, and nanosensors in the miniaturized systems for advanced food analysis and diagnostics has been described by Kuhlmeier *et al.*, 2012.<sup>(329)</sup> In fact, gold nanoparticles-based assay was also used to evaluate antioxidant activity of chrysanthemum extracts and tea beverages.<sup>(330)</sup>

### Nanonization of Traditional Chinese Medicines

In recent years, modern Chinese medicine research has drawn much attention to the nanonization of Traditional Chinese

herbal Medicines (TCM).<sup>(331)</sup> In addition to the advantages of nanotechnology on foods mentioned previously, these advantages extend its application to the herbal medicines. Nanonized drug formulations both enhance therapeutic effectiveness and absorption of poorly water soluble drugs.<sup>(332)</sup> Furthermore, it facilitates reduction of medicinal doses, hastens compound solubility, and efficiency in the absorption of herbal medicines in contrast to their crude preparations.<sup>(333)</sup> As reported by Liu *et al.*, 2008, the active components of *Salvia miltiorrhiza* (Danshen) sample prepared using nanotechnology showed strong antioxidant properties compared to those prepared using traditional grinding method.<sup>(334)</sup> In another study of Tiyaboonchai *et al.*, 2007, a microemulsion technique at moderate temperature was utilized to prepare curcuminoid loaded solid lipid nanoparticles.<sup>(335)</sup> Another traditional Chinese medicine known to have antioxidant property is *Cuscuta chinensis*. Its nanoparticles were found to be more antioxidative and hepatoprotective than its traditional ethanolic extracts.<sup>(336,337)</sup> In another study, ginsenosides extracted from nanoscale Chinese white ginseng enhances anticancer effect.<sup>(338)</sup> Mycosynthesis of silver nanoparticles using *Lingzhi* or *Reishi* medicinal mushroom, *Ganoderma lucidum* (W. Curt.:Fr.) P. Karst., and their roles as antimicrobials and antibiotic activity enhancers were elucidated by Karwa *et al.*, 2011.<sup>(339)</sup>

In summary, there is a shift from the traditional concept that foods should have a clear distinction with drugs. In the new paradigm, foods are taken for disease risk reduction besides being sources of nutrients for growth and development.<sup>(340)</sup> For instance, current studies on different food components may provide dietary choices in the prevention and control of various metabolic disorders. In addition, nanotechnology applications in food research are now advancing. Using this technology, the bioactivity of food and nutraceuticals can be enhanced while reducing the quantity of raw materials being used. However, there are various challenges to be faced including quantitative evaluation of safety of nanotechnology foods and drugs and its concrete metabolism course and pharmacokinetics in the body.<sup>(341)</sup>

## SAFETY REGULATIONS AND FOOD LABELINGS

### Structure/function, nutrient content, and health claims

Structure/function claims refer to the role of the dietary nutrients in the maintenance of normal functions, mechanisms, structures or overall well-being in the human body.<sup>(342)</sup> For example, "Iron is necessary for erythropoiesis and for oxygen transport to different tissues of the body"; Iodine helps in the normal functioning of the thyroid gland; and Calcium is for maintenance and formation of teeth and bones". Structure function claims cannot equivocally or unequivocally refer to a disease condition but they may make reference to a nutrient deficiency provided the prevalence of the deficiency is included in the claim wording. The regulatory procedures for structure function claims on dietary nutraceuticals are presented in the Dietary Supplement Health and Education Act of 1994 (DSHEA) and in CFR 101.93.<sup>(343)</sup> These claims should be accurate, truthful, not misleading and are not pre-approved by the Food and Drug Administration (FDA). It must include a disclaimer that it is not intended to diagnose, treat, cure, or prevent any disease and that it was not evaluated by FDA. In order to substantiate the structure/function claims,

different types of study designs are required to support efficacy. Besides human studies, other types of study designs can be employed to back up the claims. These include animal studies, meta-analyses, *in vitro* studies, review articles, and anecdotal evidences and testimonials. Intervention studies are considered the best to demonstrate causality in human studies while observational studies can be utilized to support cause-and-effect relationship. Randomized, double-blind, parallel group, placebo-controlled trial is considered the gold standard for evaluating the relationship between a nutrient and a specific outcome but has been criticized due to the bias brought about by the limited ability to blind subjects to treatment.<sup>(344)</sup> However, this bias can be overcome in the case of Genetically Modified (GM) crops by using non-GM counterpart as a placebo group.<sup>(345)</sup>

Nutrient content claims refer to the level of a nutrient in food by describing it as: free, high, low, excellent source of, rich in, good source of, provides, contains, etc. It can also be used to relatively compare the level of nutrients in food to a similar food by describing it as: reduced, less, or more, etc. Statements describing the percentage of a nutrient in relation to a reference daily consumption or relative to the amount of the nutrient /dietary substance per serving are also an acceptable way of describing nutrient content claims. The Nutrient Labeling and Education Act of 1990 (NLEA) permits the use of nutrient content claims based on FDA regulations. 21 Code of Federal regulations (CFR) 101 define compositional requirements for nutrient content claims.<sup>(343-344)</sup>

Health claims must be reviewed and approved by the FDA unlike structure/function claims and nutrient claims. It describes the role of dietary ingredient in reducing the risk of a disease or health related condition.<sup>(342)</sup> Examples include the health claims of Calcium and vitamin D on osteoporosis (21 CFR 101.72), folic acid on neural tube defects (21 CFR 101.79) and soy protein on coronary heart disease (21 CFR 101.82). In the US, the health claims are grouped into three: (1) Authorized health claims are used in the labeling of a food as long as the claim is authorized by FDA. Details of scientific and regulatory requirements are found in the 1997 NLEA, The Dietary Supplement Act of 1992, and the DSHEA of 1994;<sup>(342)</sup> (2) Health claims based on authoritative statements from a scientific body of the US government or the National Academy of Sciences are permitted by Food and Drug Administration and Modernization Act (FDAMA) of 1997.<sup>(346)</sup> Similar to authorized health claims, claims based on authoritative statements should meet the Significant Scientific Agreement (SSA) standard and should be based on robust human intervention studies with full scientific support; and (3) Qualified health claims supported by emerging scientific evidence, but do not meet the SSA standard.<sup>(342)</sup> The use of qualified health claims on foods is based on FDA's 2003 Consumer Health Information for Better Nutrition Initiative. Qualifying language must be used in qualified health claims to communicate to the consumer the degree of scientific evidence supporting the health claims which is different from authorized and FDAMA health claims.<sup>(345)</sup> Similarly, scientific evidences are also required for the substantiation of new health claims in Southeast Asia (**Table 9**). Assessment of risk-benefit of functional foods has been proposed and should be performed using common scale measures such as Disability Adjusted Life Years (DALYs) or Quality Adjusted Life Years (QUALYs).<sup>(346)</sup> However, the data available may be limited posing a challenge to this proposal.<sup>(346)</sup>

**Table 9. Types of evidences required to be submitted for the substantiation of new health claims in Southeast Asia<sup>(347)</sup>**

Southeast Asian Countries	Required Evidences	Regulatory Framework or System
<b>Thailand</b>	Human Intervention Study (Clinical trials) of final product must be submitted	<ul style="list-style-type: none"> <li>An approval framework based on risk analysis</li> <li>a) Must submit scientific substantiations of claim</li> <li>b) All substantiations are reviewed by an expert group</li> <li>c) Expert's viewpoints are considered by Thai FDA for approval</li> <li>In the process of drafting of health claim regulation</li> </ul>
<b>Indonesia</b>	<ul style="list-style-type: none"> <li>Scientific evidence data, especially clinical study that published in peer reviewer scientific journal.</li> <li>Nutrient function claim should be supported by at least 1(one) clinical trial (Randomized Controlled Trials, RCT).</li> <li>For reduction of disease risk claim should be supported by at least 3 (three) clinical trial (Randomized Controlled Trials)</li> </ul>	<ul style="list-style-type: none"> <li>Must submit scientific substantiations of claim to be reviewed by an evaluator group and expert group (if needed).</li> <li>Based on the result of the review, evaluators and experts give recommendation to Badan Pengawas Obat dan Makanan or National Agency for Drug and Food Control (BPOM or NA-DFC).</li> <li>a) Based on such recommendation BPOM publishes the approval/reject letter.</li> <li>BPOM is now preparing the guidelines.</li> <li>Draft regulations on Guidelines for Nutrition and Health Claims Control on Food Label and Advertisement</li> </ul>
<b>Malaysia</b>	<ul style="list-style-type: none"> <li>Data from human intervention trials, Randomized Controlled Trials (RCTs) are preferred data from at least 5 human trials are required.</li> <li>In addition, experimental and epidemiological studies may be included to support the application.</li> <li>Reviews and meta-analysis publications may also be included. Studies should preferably be from a variety of organizations.</li> <li>Published in refereed journals</li> </ul>	<ul style="list-style-type: none"> <li>An approval system has been established by Food Safety &amp; Quality Control Division, Ministry of Health (MOH) to review applications for new claims submitted by industry.</li> <li>a) Applications are reviewed by an Expert Group on Nutrition, Health Claims &amp; Advertisement (established in 1996)</li> <li>b) Information required in the forms include physiological role, chemical and physical properties, processing method, safety evaluation, scientific substantiation</li> <li>c) The working group also looks into harmonization of other function claim that already approved by other countries especially the Association of Southeast Asian Nations (ASEAN)</li> <li>No new plans to ammend current regulations on nutrition and health claims</li> </ul>
<b>Philippines</b>	<ul style="list-style-type: none"> <li>The consultants would require substantiation other than scientific data depending on the claim.</li> <li>Evidence from well-designed human intervention studies.</li> <li>These should be peer reviewed, published and can be reproduced</li> </ul>	<ul style="list-style-type: none"> <li>Not an established documented framework but a very simple system.</li> <li>Applications are reviewed by evaluators.</li> <li>For nutrient function claims whose nutrient function is established, the supporting documents came from recognized references, and the level also conform to standard source, they are just discussed among the evaluators.</li> <li>For other function claims and disease risk reduction claims, the evaluations are elevated/referred to the consultants.</li> <li>Planning mandatory nutrition labeling</li> </ul>
<b>Singapore</b>	<ul style="list-style-type: none"> <li>Human studies:                             <ol style="list-style-type: none"> <li>Experimental intervention studies [eg. RCT, Randomized trials (RT)]</li> <li>Observational studies (eg. cohort studies, case-control studies, cross-sectional studies)</li> </ol> </li> <li>Non-human studies eg. animal, ex vivo, in vitro studies</li> <li>Systematic reviews such as pooled analysis, meta-analysis</li> <li>Contradictory information</li> <li>Recommendations by food safety authorities of major developed countries on the use of the proposed claims.</li> </ul>	<ul style="list-style-type: none"> <li>Nutrient specific diet-related health claims should be submitted to Agri-Food and Veterinary Authority of Singapore or Health Promotion Board (AVA or HPB). Details on the requirements and application process can be found at the following URL: <a href="http://www.ava.gov.sg/FoodSector/FoodLabelingAdvertisement/">http://www.ava.gov.sg/FoodSector/FoodLabelingAdvertisement/</a></li> <li>Applications for use of of new nutrient function and other function claims as defined by Codex should be submitted to AVA.</li> <li>No new plans to ammend current regulations on nutrition and health claims</li> </ul>
<b>Vietnam</b>	<ul style="list-style-type: none"> <li>Data on value of nutritive content                             <ol style="list-style-type: none"> <li>Results of clinical intervention studies</li> <li>If necessary, the local clinical trial would be needed</li> <li>Review of meta-analysis results</li> <li>Publications in the journals</li> </ol> </li> </ul>	<ul style="list-style-type: none"> <li>Applications are reviewed by experts                             <ol style="list-style-type: none"> <li>Laboratory analysis of nutrient content if necessary</li> <li>Approved by giving certificate to companies or industry</li> </ol> </li> <li>No new plans to ammend current regulations on nutrition and health claims</li> </ul>
<b>Brunei</b>	Health claims not allowed	<ul style="list-style-type: none"> <li>Director General of Health Services</li> </ul>

## Safety of Novel Food Ingredients

Safety needs to be considered even though there are many studies supporting the health claims of functional foods. Certain substances derived from plants have been indiscriminately added to foods that may be a threat to one's health. This health issue has to be addressed before any untoward incident will occur. There are herbs with known drug interaction when taken. For instance, *Hypericum perforatum* can cause increase in liver enzyme activity causing a decline in plasma concentrations of drugs.<sup>(348)</sup> Safety concerns have been raised because of this matter has triggered the FDA to issue announcements to the food industry regarding the use of novel ingredients in foods.<sup>(349,350)</sup> In fact, the safety of the foods through bioengineering should be evaluated based on existing standards for conventional or traditional foods. The basis for considering a food to be Generally Recommended as Safe (GRAS) is based on the principle of the World Health Organization's Food Safety standard stating that no harm will be brought about by consumption of foods.<sup>(351)</sup> In the United States for instance, foods derived from biotechnology should be considered as safe as traditional foods. Although, many food crops have long been

recognized to contain toxic substances the level of toxicity is considered acceptable because the amount of toxins may be more or less five times lower than the amounts that can cause toxic effects and that its nutritional benefits outweigh risks.<sup>(345)</sup>

Cross breeding practices have long been employed to enhance desirable traits and minimize the undesirable ones. Modern methods like recombinant DNA Technology (rDNA) have recently been employed to enhance these desirable traits without causing significant changes in the existing phenotypes to evade issues on consumer acceptance. In fact, there are some studies involving applications of foodomics to food quality and safety.<sup>(215)</sup> The safety assessment of a bioengineered food includes information about the genetic construct donor (size, marker genes, promoter sequences, and insertion sites) and the donor organism to make sure that there is minimal or no unintentional transfer of genes encoding for toxins, allergenicity or pathogenicity. The focus of the assessment is the resulting novel proteins produced. Although proteins are not considered naturally hazardous to health, they can be possible allergens, toxins, or can be associated with pathogenicity.<sup>(352-354)</sup> A "scientifically based two-tiered, weight-of-evidence strategy

to assess the safety of novel proteins used in the context of agricultural biotechnology” has been proposed.<sup>(355)</sup> Tier 1 is responsible for potential hazard examination. This involves analysis of the mode of action in relation to biological functions of proteins; evaluation of HOSU; bioinformatics studies on amino acid sequence analysis in comparison to known proteins with similar health functions as well as known toxicity or allergenicity; chemico-physical analysis of the protein (stability and digestibility); and expression level and dietary intake. Tier II is proposed when Tier 1 evaluation is insufficient. It involves characterization of hazards identified in Tier 1 on a case by case basis, usually involving evaluation on toxicity levels and hypothesis-based testing strategies. The safety assessment of the genetically modified (GM) foods is initiated with a substantial or equivalence approach where the food characteristics are compared to those of corresponding foods derived from the near iso-genic non-GM counterpart. In fact, the substantial equivalence approach becomes the basis for evaluating safety of a novel food.<sup>(356-357)</sup> Using the traditional foods as controls in assessing the acceptability of these novel foods is based on its history of safe use (HOSU). Foods having common use from different parts of the world become established traditionally and are assumed to have a HOSU. Since the safety of traditional food is not absolute, an appropriate term “history of apparent safe use” has been proposed.<sup>(345)</sup>

### Food and Nutrition Labeling in Different Countries

**Table 2** presented known health benefits of common foods and nutrients but according to FDA the scientific evidence is limited and therefore, not conclusive. In Europe, potential health claims for foods are prohibited unless approved and recommended by the European Food Safety Agency (EFSA) based on the Health Claim Regulation of 2006 (1924/2006). The commission does not allow for health claims on fruits and vegetables and their processed products due to a specific functional ingredient.<sup>(358)</sup> The rationale behind this is based on the belief that potential health benefit is due to food consumption patterns rather than the specific fruit or vegetable. Health claims can only be authorized based on substantiated scientific evidences.

Legislations on food and nutrition labeling vary among different countries. In Europe, there is no specific regulation and uniform label on functional foods.<sup>(359)</sup> However, it is regulated under the general food regulation in Europe (178/2002) for basic quality, safety, and protection against fraud. The *European Novel Food Regulation (258/97)* regulates food that undergoes change in its molecular structure or consists of ingredients that are new to the European market. Southeast Asian countries including Vietnam, Indonesia, Singapore, Malaysia, Brunei

Darussalam, Laos, and Cambodia follow the Codex Guidelines in preparing their regulations.<sup>(359-366)</sup> Philippines and Thailand have adopted the US nutrition labeling guidelines.<sup>(367,368)</sup> Only Malaysia has made nutrition labeling mandatory for fat, energy, protein, carbohydrate, and total sugars for foods that are commonly consumed, such as bread and milk, canned meat, fish, vegetable, fruit and fruit juices, beverages, salad dressing and mayonnaise.<sup>(362,369)</sup> Nutrition labeling is voluntary in other Southeast Asian countries unless nutrition or health claims are made on food packaging or if the food is for a special purpose (ex. fortified foods, foods for diabetics). The amount of protein (g), carbohydrate and fat (g), vitamins and minerals (metric/ % of Nutrient Reference Value, NRV) along with the content of claimed nutrients, the energy value (kcal) and the total energy of all nutrients (per 100g or 100 mL) should be declared by manufacturers based on national dietary guidelines. This is true among countries following the Codex Guidelines.<sup>(370)</sup>

Nutrient declaration in Thailand is similar to US. It involves the lists of total energy (Kcal) and other nutrients in metric amounts in grams or milliliter (Vitamin A, Vitamin B1, Vitamin B2, saturated fat, cholesterol, protein, dietary fibers, calcium, iron, sodium, sugars, and total carbohydrates).<sup>(367)</sup> In order to inform the consumers on how food suits to daily nutrient requirements, the US percent daily values (%DV) and the Recommended Daily Intakes (%RDI) are also presented on the label. Similar to Thailand and the US, the serving sizes requirement in the Philippines is expressed in common household measures or metric units. However, the quantitative declaration of the energy values and amounts of macronutrients is based on Codex Guidelines. The percent Recommended Energy and Nutrient Intakes (%RENI) of vitamins and minerals (mg or µg) are presented in the label along with their specific amounts.<sup>(368, 370, 371)</sup>

The use of different International legislations on food labeling and differences in government policies result in the discrepancies on food regulation that may be brought about by economic, cultural, & political factors (**Table 10**).<sup>(359)</sup> Although it is very challenging, there is a need to harmonize the food labeling legislations both regionally and internationally in order to lessen the time and cost in the export and import processing. In this connection, the Guiding Principles for Food Control Systems (which include the regional requirements for the labeling of pre-packaged foodstuffs) adopted from Codex Alimentarius was drafted and finalized.<sup>(372,373)</sup> The member countries employing Codex standards are presumed to be abiding by the World Trade Organization’s Agreements on the application of Sanitary and Phytosanitary Measures and Technical Barriers to Trade Agreements.<sup>(374,375)</sup>

Countries	International Guidelines	Legislation	Nutrient Declaration	Serving sizes	Nutrient Reference Values (NRV's)	Health Claims	Language
<b>Philippines</b>	Codex Alimentarius & US nutrition & labeling guidelines	Voluntary unless nutritional claims are made on products	Energy, protein, carbohydrate and fat listed quantitatively when nutritional claims are made	Serving sizes are presented in terms of household measures and metric units	Local reference values used in the declaration of micronutrients	Reduction of disease risk claims are allowed	Different local languages used on food packaging in addition to English
<b>Singapore</b>	Codex	Same as the Philippines	Same as the Philippines	Energy and nutrients are expressed per 100 g/ml of the food	Same as the Philippines	Same as the Philippines	Same as the Philippines
<b>Malaysia</b>	Same as Singapore	Mandatory	Energy, protein, carbohydrate, fat and total sugars declared in a quantitative manner	Same as Singapore	Codex %NRVs used in the expression of vitamins and nutrients	Reduction of disease risk claims are prohibited	Same as the Philippines



Countries	International Guidelines	Legislation	Nutrient Declaration	Serving sizes	Nutrient Reference Values (NRV's)	Health Claims	Language
<b>Thailand</b>	US nutrition and labeling guidelines	Same as the Philippines	Quantitative and percentage labeling used to declare 14 nutrients, namely total calories, fat, saturated fat, cholesterol, protein, total carbohydrate, dietary fibre, sugars, sodium, vitamin A, vitamin B1, vitamin B2, calcium and iron	Same as the Philippines	Same as the Philippines	Reduction of disease risk claims are prohibited	Same as the Philippines
<b>Indonesia</b>	Same as Singapore	Same as the Philippines	Same as the Philippines	Same as Singapore	Same as the Philippines	Same as the Philippines	Same as the Philippines
<b>Brunei</b>	Same as Singapore	Same as the Philippines	Same as the Philippines	Same as Singapore	Same as the Philippines	Reduction of disease risk claims are prohibited	Same as the Philippines
<b>Vietnam</b>	Same as Singapore	Same as the Philippines	Same as the Philippines	Same as Singapore	Same as the Philippines	Reduction of disease risk claims are prohibited	Same as the Philippines
<b>Myanmar</b>	Same as Singapore	Same as the Philippines	Same as the Philippines	Same as Singapore	Same as the Philippines	Reduction of disease risk claims are prohibited	Same as the Philippines
<b>Laos</b>	Same as Singapore	Same as the Philippines	Same as the Philippines	Same as Singapore	Same as the Philippines	Same as the Philippines	Same as the Philippines
<b>Cambodia</b>	Same as Singapore	Same as the Philippines	Same as the Philippines	Same as Singapore	Same as the Philippines	Reduction of disease risk claims are prohibited	Same as the Philippines

Regulations for bioengineered foods and crops have been established in developed countries. However, the regulatory protocols for many developing countries are either not well established or do not exist. This may be attributed to religio-political issues, limited knowledge, expertise, and resources. Developing countries have to enhance the institutional capacity of their respective regulatory boards through regional and

international collaboration based on the guidelines of United Nations World Health Organization, Organization for Economic Cooperation and Development, and Food and Agriculture Organization.<sup>(374)</sup> Up to now, there is still no clear consensus on the requirements for GM food labeling even though harmonization efforts and safety guidelines have been finalized by Codex Alimentarius, World Trade Organization (WTO), and Cartagena Protocol on Biosafety (CPB) (**Table 11**).

	Category 1	Category 2	Category 3	Category 4	Category 5	Category 6	Category 7	Category 8
<b>Countries</b>	EU, East Europe	Switzerland, Norway, Russia, Brazil, China	Thailand, Australia, Japan, Taiwan, Korea, Saudi Arabia	USA, Canada, Philippines, Hong Kong, Argentina, South Africa	Vietnam, Indonesia, Chile, Ecuador	India, Kenya	Bangladesh, Most African Countries	Zambia, Zimbabwe
<b>Labeling Regulations</b>	Stringent mandatory; includes derived products	Stringent mandatory; includes derived products	Product based; mandatory	Voluntary for substantially equivalent	Mandatory	Intention to require labeling	No clear position	None
<b>Specificity</b>	Traceability requirements, 0.9% threshold	No traceability, no threshold	Labeling exceptions; 1-5% threshold	5% threshold for labeling	Pragmatic product based labeling	Slow regulatory process	Wait- and- See Approach	GM Free
<b>Food Safety Approval Regulations</b>	Process-based; mandatory	Process-based; mandatory	Process-based; mandatory	Substantial equivalence; mandatory	Mandatory (in place or pending)	Mandatory (in place or pending)	Considering mandatory	None

In China, the response of the government and industry to food safety problems is focused on the development and strengthening of Food Safety legislation through the development of certification or food label schemes. The agricultural products in China are labeled as Organic products, Pollution-free, and Green foods (**Table 12**). In 2008, a Quality Safety label was introduced for regionally processed products. Each label has to meet different quality standards.<sup>(378)</sup> GM policy in China is viewed as a “positive in research, careful in popularization, strengthening management, and safe promotion”.<sup>(379)</sup> However, it should be noted that different sectors of the Chinese government have conflicting views on the acceptance of this GM policy. At the same time most Chinese consumers have a limited understanding of GM products and government labeling of bioengineered foods.<sup>(380)</sup>

On June 15, 2012, China released a 5-year plan to upgrade its food-safety regulations as part of the country's latest efforts to address critical food-safety concerns. This involves improvement of the national food safety standards by conducting a series of reviews and abolishing overlapping, outdated, or contradicting standards compiled by multiple government agencies in the past years. The government is planning to coordinate with Ministry of Health, Ministry of Science and Technology, Ministry of Agriculture and other ministries to finish revamping the existing standards by 2015. Safety standards for dairy products, infant food, meat, alcohol, vegetable oil, seasoning, health products and food additives will be prioritized in order to specify limits for dangerous ingredients in these foods. In addition, special efforts to set standards for testing various contaminants, food additives, microorganisms, pesticide and animal drug residue in food production will

Food Product Labels	Quality Standard	Remarks	Criteria
<b>Pollution-Free</b>	Pollution-Free agricultural product standards	Compulsory Response to raised public health issues on foods Set since 2001	Field environmental quality standards (air, water, and soil quality) Production technology standards (quality controls of production inputs) Product standards (Primary and processed product standards) Packaging, labeling, storage, and transportation standards
<b>Green Food</b>	Food and Agriculture Organization and World Health Organization	categorized into AA (excludes use of synthetic agricultural chemicals) and A (allows use of synthetic agricultural chemicals) level use of chemical compounds and other poisonous materials are prohibited; Regulation set since 1990	The production area should meet the highest grade of atmospheric standards Residues of heavy metals are restricted in irrigation water and soil Processing water must meet National Drinking Water Standards Application of agro-chemicals are restricted and regulated, and some are banned
<b>Organic Foods</b>	European Union and the International Federation of Organic Agriculture Movement (IFOAM)	prohibits any use of chemical substance during agricultural production or the use of genetic engineering technologies set in 1991	Raw materials should derive from organic agricultural production systems or wild natural products; Products must remain in strict compliance with the organic food processing, packaging, storage, transportation requirements throughout the supply chain Production process and holding must be approved by an independent body of organic food certification.

also be considered. Furthermore, the government vowed to strengthen supervision by setting up an efficient network that covers all links in the food industry. A rigid food recall and a destroy system for defective products to crackdown those endangering food safety are warranted. Violators should be penalized in accordance with laws and regulations.<sup>(381)</sup>

## FUTURE DIRECTIONS AND CHALLENGES

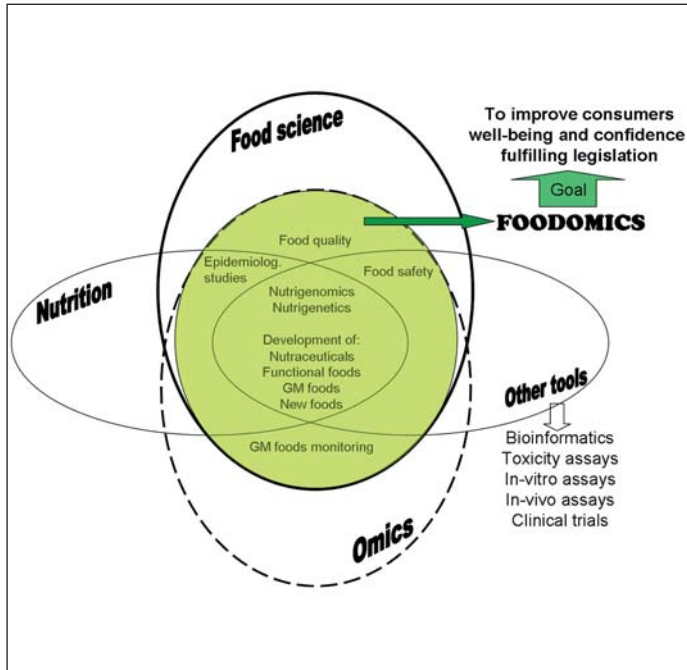
There is an increasing interest on how functional foods really function in the improvement of human health. To be able to predict the long term effects of these nutrients, the underlying mechanism has to be understood carefully.<sup>(296)</sup> The probable impact of high protein diets on risk factors for Cardiovascular Disease (CVD) remains a dynamic field to be investigated.<sup>(298)</sup> There are some studies showing that Polyunsaturated Fatty Acids (PUFA) have limited association to cardiovascular, mental and behavioral health.<sup>(288)</sup> Hence, it is important to address issues on small sample sizes, short follow-up times, variability of selection criteria, variability of the type and dosage of supplementation, and other methodological weaknesses.<sup>(288)</sup> However, the scientific data supporting these claims may be inadequate to affirm overall safety and efficacy.

Consumption of functional foods is not merely to replace good health practice. Rather, it is an effective health education and promotion strategy to communicate with the consumers. There are few specific health claims that have been authorized

for the use of these food products and supplements. According to the US Food and Drug Administration and the Nutrition Labeling Education Act (NLEA), there must be significant scientific evidence for the individual claims.<sup>(382,383)</sup> In addition, according to Dietary Supplement Health and Education Act (DSHEA) of 1994, dietary supplements and functional foods should communicate specific ingredients with health benefits. To facilitate access to scientific information about foods by consumers, the FDA announced its Initiative on Consumer Health Information for Better Nutrition in 2003.<sup>(384)</sup> This initiative allows consumers to make appropriate selections. It also fosters competition within the food industry in developing healthier functional foods and dietary supplements. The initiative involves inclusion of qualified health claims according to the investigation of qualified experts.<sup>(385)</sup> However, the question remains as to whether these initiatives will lessen the current information confusion. Nowadays, the demand for functional food production is fast growing. This offers an opportunity for economic development among countries with abundant sources of these functional foods (**Table 13**).<sup>(386)</sup> However, in-depth studies on market development and functional food production have to be undertaken to assess current trend in most developed countries.<sup>(387)</sup> In this juncture, the field of foodomics is a promising tool tapping a multidisciplinary approach, including Mass Spectrometry (MS)-based strategies, to address public health and regulatory issues raised by regulatory institutions (i.e. European Food Safety Authority, EFSA), thereby, gaining consumers' confidence on such health claims of functional food ingredients (**Figure 1**).<sup>(212,213, 215,216,388)</sup>

Countries	General Attitudes/Awareness/Demands	Legislations	Domestic Market	Agriculture/ Processing/ Manufacturing Activities/	Supports	Challenges	Opportunities
<b>China</b>	Tradition of using food as therapeutic agent; Functional foods based on Traditional Chinese Medicines (TCM); <sup>(400)</sup> Public health problems, such as obesity and related conditions becoming more prevalent	Elaborate legislation in place for "health foods"; includes government testing; Advertising controlled	Traditional products mixed with western type science based functional foods; Growing local demand	Manufacturers need Genetically Modified Products (GMP) certification to gain government approval for products; lack of consistent manufacturing practices and quality standard <sup>(401)</sup>	Research in local institutions and overseas	Markets are urban-based; Underdeveloped infrastructure; large ageing population; <sup>(401)</sup> deficient scientific validation <sup>(401)</sup>	Raw materials and active ingredients from traditional functional foods; need internationally acknowledged research <sup>(400)</sup>

Countries	General Attitudes/ Awareness/Demands	Legislations	Domestic Market	Agriculture/ Processing/ Manufacturing Activities/	Supports	Challenges	Opportunities
Europe	Prefer organic foods rather than functional foods; Organic foods are viewed on its naturalness and are assumed to contain all substances needed for human health while functional foods are viewed as technologically re-designed foods with functional ingredients added or removed or has been changed; or a natural food containing high levels of the functional ingredient or with high functionality; Consumers having distrust on the so called additional benefits in functional foods because they feel unconvinced with the research evidences <sup>(389-395)</sup>	There are number of initiatives about functional foods in Europe largely focusing on scientific issues. The Functional Food Science in Europe (FUFOSE) in coordination with the International Life Science Institute (ILSI) EU was initiated in order to have a clear concept of functional food and to reach a consensus for the requirements on its applications to industry. Another directive is responsible for regulating foods for particular nutritional uses (PARNUTS). These include energy reduced foods and infant foods. Regulations for purified formulations still remain at the level of each state. Therapeutic claims for functional foods are not permitted unless they are submitted to be regulated as drugs. <sup>(393)</sup>	Lack of study material on how functional foods compete with organic and conventional foods but it seems that conventional food with a communicated additional benefit will compete with the conventional counterpart <sup>(389,397)</sup>			More scientific research and evidences for the functionality of food bioactive compounds and to make this information available to consumers <sup>(398,399)</sup>	
India	Tradition of using food as therapeutic agent (ex. based on ayurvedic philosophy); low consumer awareness on functional foods; <sup>(402)</sup> Mainutrition	Bureau of Indian Standards is involved in product certification, quality systems, and consumer affairs; Lack of suitable regulatory category results in misleading advertising and sales of functional foods	Growing functional food market	Until recently, these were severely restricted by government policies; Medicinal plants and ingredients for related industries are an active area, potential for functional foods as well	Active academic research institutions	Retail network unorganized and fragmented; Even general value-added food processing is rare; Little cooperation between academic research and the industry	Biodiversity; Based on traditional knowledge, potential in local foods and ingredients
Brazil	Traditional knowledge of functional foods properties of local plants; Rising incomes; western influences; new products are welcomed; Government promotes healthy diets as public health effort; For consumers, well-being and appearance are important	Regulations are well in line with international standards, but are still evolving; Since 1999, products with health claims must be preapproved by the government; scientific support for product specific health claims is required; Intersections in food legislations <sup>(403)</sup>	Large income disparity, but sizable middle/high income segment interested in functional foods; Better-for-you low-fat, low sugar and fortified products are common; Probiotics gaining popularity	Specialized/ high quality ingredients are imported and expensive; Some local botanical ingredients; exported for dietary supplement and food industries; Great potential in local biodiversity	Functional foods gaining attention through many activities (workshops, lectures)	Most functional ingredients must be imported; Emphasis on low-level processing of bulk commodities; High cost of ingredients and meeting regulations	Biodiversity; Growing local demand and increasing media attention; Alleviating public health problems by dietary means
US		Health claims for foods based on Nutrition Labelling and Education Act (NLEA) are generic rather than product specific. Psyllium, wheat bran and oat containing food products are examples of products wherein food component are mentioned. Nutraceuticals may be classified as dietary supplements if they qualify for the criteria. Their therapeutic claims cannot be mentioned otherwise it is considered a drug. However, medical foods are exempted to NLEA requirements <sup>(396)</sup>					
Canada		In Canada, functional foods and nutraceuticals are used interchangeably, although these two terms are now being defined and existing regulations have to be amended for the approval of these food products under the Food and Drug Act in Canada. There is no approved health claims for functional foods or purified preparations unless it has to be regulated as drugs through the Therapeutic Products Programme of the Health Protection Branch of Health Canada. <sup>(396)</sup>					
Japan		The Japanese Ministry of Health and Welfare is responsible for licensing Foods for Special Health Use (FOSHU). This is only applied to foods that are consumed for the purpose of health maintenance rather than its preventive or therapeutic effects. Nutraceuticals stating the therapeutic effects are regulated as drugs. <sup>(152)</sup>					



**Figure 1.** Foodomics as a Multidisciplinary Approach to Address Public Health and Regulatory Issues on Functional Foods<sup>(2,12,213,215,216,388)</sup>

## CONCLUSIONS

The public health importance of many functional foods is very promising nowadays. However, the known health benefits must be supported by strong scientific evidence so that consumers will be assured that the foods that they purchase are really that functional. Health claims have to be distinguished from structure-function claims to further address the scientific evidences of the health benefits of functional foods. Safety and efficacy studies of such foodstuffs have to be rigidly established before they are widely produced in the markets. Enforcement of existing regulation has to be carried out in response to increasing demands for functional food production. One should remember that diet is only one of the factors in maintaining a healthy well-being.

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### Author's background

**Mr. BAIBADO, Joewel Tarra** holds a Master degree in Biological Sciences from the University of Phillipines. He is currently doing a PhD degree in City University of Hong Kong. **Dr. CHEUNG, Hon-Yeung**, who is an Associate Professor of Pharmaceutical Microbiology & Biotechnology at the City University of Hong Kong, is a manufacturing pharmacist and biotechnologist. He has published more than four hundred papers and articles. His email address is cheung.honyeung@cityu.edu.hk

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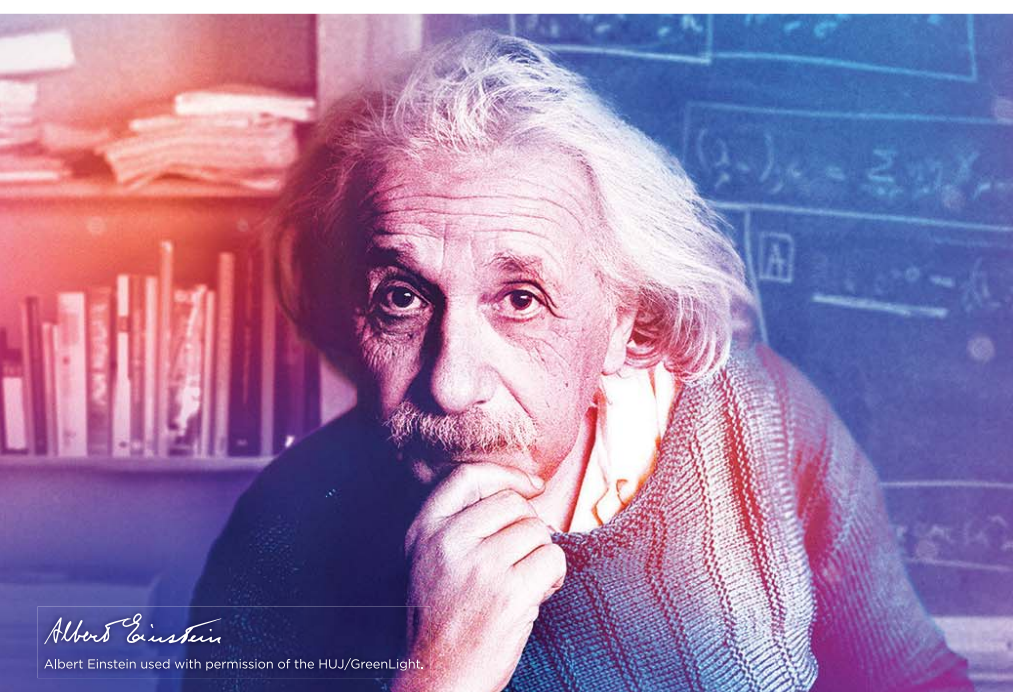
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Albert Einstein

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# BE THE ONE

WHO CAN CHANGE WHAT'S POSSIBLE

For your HCV F0 to F4 compensated cirrhosis GT1 patients<sup>a</sup>:

## CURE

- Overall **97%** cure in HCV GT1 patients<sup>6,b,c</sup>
- Overall cure rates of 94-99% across phase 3 studies<sup>1,3-6</sup>

## LOW DISCONTINUE RATE

- 99%** completed regimens of up to 12 weeks<sup>7</sup>
- ≤1% of patients discontinued treatment with HARVONI due to adverse events<sup>1</sup>

## ONE pill, once a day<sup>1,d</sup>

- Single-Tablet Regimen for the majority of HCV GT1 patients<sup>1,d</sup>

- IFN free
- RBV free<sup>d</sup>
- PI free

<sup>a</sup>As assessed by the Metavir fibrosis stage scoring system.

<sup>b</sup>HARVONI is indicated for the treatment of chronic hepatitis C (CHC) genotype 1 infection in adults. 99% cure rates were observed in the ION-1 study in previously untreated HCV GT1 patients treated with HARVONI for 12 weeks. Across the ION studies, SVR rates between 94-99% were observed in HCV GT1 patients treated with HARVONI for 8-24 weeks. 99% of patients completed regimens of up to 12 weeks.

<sup>c</sup>Sustained virologic response (SVR) was the primary endpoint and was defined as HCV RNA <25 IU/mL at 12 weeks after the cessation of treatment. Achieving SVR is considered a virologic cure.<sup>7</sup>

<sup>d</sup>HARVONI offers a single-tablet, ribavirin-free regimen for the majority of HCV GT1 patients, excluding those with decompensated cirrhosis, or who are pre- or post-liver transplant, etc.<sup>1</sup>

### HARVONI<sup>®</sup> Abbreviated Prescribing Information

**Presentation:** Orange colored, diamond-shaped, film-coated tablet containing 90 mg ledipasvir and 400 mg sofosbuvir.

**Indications:** Treatment of chronic hepatitis C genotype 1 infection in adults.

**Dosage:** **Adults:** One tablet taken orally once daily with or without food. **Pediatric Use:** Safety and efficacy have not been established. **Geriatric Use:** No dosage adjustment is warranted in geriatric patients. **Renal Impairment:** No dosage adjustment is required for patients with mild or moderate renal impairment. Safety and efficacy have not been established in patients with severe renal impairment, or end stage renal disease requiring hemodialysis. No dosage recommendation can be given for these patients. **Hepatic Impairment:** No dosage adjustment is required for patients with mild, moderate, or severe hepatic impairment. Safety and efficacy have not been established in patients with decompensated cirrhosis. **Pregnancy:** HARVONI should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Breastfeeding Mothers:** The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need and any potential adverse effects on the breastfed child from the drug or from the underlying maternal condition.

**Warnings and Precautions:** **Serious symptomatic bradycardia when coadministered with amiodarone:** coadministration of amiodarone is not recommended. Counseling patients about the risk of serious symptomatic bradycardia and cardiac monitoring are recommended for patients taking amiodarone, patients starting amiodarone therapy and patients discontinuing amiodarone just prior to starting HARVONI. **Risk of reduced therapeutic effect due to P-gp inducers:** use with P-gp inducers (e.g., rifampin or St. John's wort) is not recommended. **Related products not recommended:** use with other products containing sofosbuvir is not recommended.

**Adverse reactions:** The most common adverse reactions were fatigue and headache in subjects treated with HARVONI during clinical trials. Serious symptomatic bradycardia has been reported in patients taking amiodarone from postmarketing experience.

**Drug interaction:** Any interactions that have been identified with ledipasvir and sofosbuvir individually may occur with HARVONI. P-gp inducers (e.g., rifampin or St. John's wort), acid reducing agents including antacids (e.g., aluminum and magnesium hydroxide), H<sub>2</sub>-receptor antagonists (e.g., famotidine) and proton-pump inhibitors (e.g., omeprazole); Antiarrhythmics (amiodarone, digoxin); Anticoagulants (carbamazepine, phenytoin, phenobarbital, oxcarbazepine); Antimicrobials (rifabutin, rifampin, rifapentine); HIV antiretrovirals (combination of efavirenz, emtricitabine and tenofovir disoproxil fumarate (TDF), regimens containing TDF and a HIV protease inhibitor/ritonavir (e.g., atazanavir/ritonavir, darunavir/ritonavir, lopinavir/ritonavir), combination of elvitegravir, cobicistat, emtricitabine and TDF, and tipranavir/ritonavir); HCV products (simeprevir); Herbal supplements (St. John's wort); HMG-CoA reductase inhibitors (rosuvastatin).

**Before prescribing, please consult full prescribing information which is available upon request.**

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HK PI version: HK-MAY15-US-MAR15

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Gilead Sciences Hong Kong Limited

Room 2603, 26th Floor, Hysan Place, 500 Hennessy Road, Causeway Bay, Hong Kong  
Tel: (852) 3129 2000 Fax: (852) 2856 2611

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# Closing Remarks of the 2017 Hong Kong Pharmaceutical Conference (HKPC)

**SO, Simon**

*Chairman of the Organizing Committee for the 2018 HKPC*

**Chairman, Distinguished guests and participants of the HKPC 2017,**

On behalf of the Organizing Committee, it is indeed my pleasure to make a few closing remarks and express my gratitude to all those who made this event a reality. It is also a privilege and an honor to be entrusted with such an undertaking, at a gathering of such eminent people from different places of the world, in the fields of government, hospital, industry, academia and professional bodies of the pharmacy profession.

Like previous years, the planning of the HKPC has never been stopped and it is a year-on-year effort for all of us, especially the respective committees under the organizing committee of the conference. This year the planning of the pharmacy conference is paved with challenges by looking back to the success of previous conference programmes. We questioned ourselves that 'Are we grasping the opportunity to envision the preferred future for pharmacy profession?' This year's theme is "*To Innovate and Excel*". As mentioned by our Chairman in the welcome message that, to innovate nowadays is not difficult but to excel is the real challenge as we all facing ahead.

The conference started off yesterday by a series of innovative theme speeches. The core messages delivered are we have already stepped into the pioneering era, with the emergence of advance in technologies and techniques, from research and development in new diagnostic applications, to the drug discovery in human tissue engineering technology. By addressing the increasing health care needs of patients, the excellence of global standards demonstrated the benefits of achieving significant saving while improving hospital patient care in England. We also learnt about the importance of leadership support to empower innovative technologies and facilitate the evolution of practice standards in the increasingly complex health care system in HK.

Today's programme has been another momentous day, it is pleasing to have had three concurrent sessions covering wide ranged topics on: precision medicine, the use of mobile technology & application, innovative medicine, biologics/biosimilars, various clinical specialties of practice, and presentation of local researches.

There have been many interesting and scientific as well as innovative presentations during the conference, especially

in the interactive plenary sessions we just had on the 'Future Community Dispensing Model'. I am confident that everyone applauds the successful efforts of Public Private Partnership (PPP) in certain areas of health care system in HK. I believe many good experiences and ideas have been shared and good lessons learned amongst us profession about the PPP initiatives along with the future development of pharmacy service model in Hong Kong.

Advancing practice through innovation helps to drive the evolution of practice standards to improving patient care and outcomes. To excel along by sustaining innovation among the next generation of pioneering pharmacists is of utmost importance. Once innovations demonstrate value to an organizational process, there will be potential to achieve scalability and sustainability, which are important to extending the impact of innovation to excellence. Various organizations shall take the fullest advantage of opportunity for collaboration that facilitates innovation and excellence to our practice and be able to respond together to issues that we have in common and achieve our common goals.

In closing, I would like to thank the Chairman, Mr. Lot Chan, past chairman, the conference organizer MIMS (HK) Ltd., various committee chairs and members, and the student helpers for the great effort and contributions made towards the success of the pharmacy conference this year. Also, I would like to thank our honorable guests, invited speakers, and various panel members, that their presence has been invaluable and, without any doubt, has helped make the event a great success. We greatly appreciate our sponsors for the continuous and generous support to achieve overwhelming success and response year after year. While they are too numerous to name individually, we are also grateful to all those who have been involved in the organization of the HKPC.

You have given of your time, knowledge, and experience to help craft a picture of the preferred future for the pharmacy profession. The next steps will also depend on you all, as leaders of the pharmacy profession, to make the statement of this year's conference on the future of pharmacy profession a reality, and for the benefit of all the people we serve in Hong Kong.

Finally, I wish you all the best and we look forward to seeing you again in the HKPC in 2018. Thank you.

## NEW INDICATION

**OFEV®**  
(Boehringer Ingelheim)

*Prepared by Fiona Yuen and edited by Ivy Chan*

### Active Ingredient:

Nintedanib

### Presentations:

Ofev 100 mg soft capsules

Ofev 150 mg soft capsules

### Pharmacological Properties:

#### Mechanism of action

Nintedanib is a small molecule tyrosine kinase inhibitor including the receptors platelet-derived growth factor receptor (PDGFR)  $\alpha$  and  $\beta$ , fibroblast growth factor receptor (FGFR) 1-3, and VEGFR 1-3. Nintedanib binds competitively to the adenosine triphosphate (ATP) binding pocket of these receptors and blocks the intracellular signalling. In addition nintedanib inhibits Flt-3 (Fms-like tyrosine-protein kinase), Lck (lymphocyte-specific tyrosine-protein kinase), Lyn (tyrosine-protein kinase lyn) and Src (proto-oncogene tyrosine-protein kinase src) kinases.

#### Pharmacodynamic effects

Nintedanib inhibits the activation of FGFR and PDGFR signalling cascades which are critically involved in proliferation, migration and differentiation of lung fibroblasts/myofibroblasts, the hallmark cells in the pathology of idiopathic pulmonary fibrosis. The potential impact of VEGFR inhibition by nintedanib and the anti-angiogenic activity of nintedanib on IPF pathology are currently not fully elucidated. In preclinical disease models of lung fibrosis nintedanib exerts potent anti-fibrotic and anti-inflammatory activity. Nintedanib inhibits proliferation, migration and fibroblast to myofibroblast transformation of human lung fibroblasts from patients with IPF.

### Indications:

Ofev is indicated in adults for the treatment of Idiopathic Pulmonary Fibrosis (IPF).

### Dosage & Administration:

Treatment with Ofev should be initiated by physicians experienced in the diagnosis and treatment of IPF.

#### Posology

The recommended dose is 150 mg nintedanib twice daily administered approximately 12 hours apart.

The 100 mg twice daily dose is only recommended to be used in patients who do not tolerate the 150 mg twice daily dose.

If a dose is missed, administration should resume at the next scheduled time at the recommended dose. If a dose is missed, the patient should not take an additional dose. The recommended maximum daily dose of 300 mg should not be exceeded.

#### Dose adjustments

In addition to symptomatic treatment if applicable, the management of adverse reactions to Ofev could include dose reduction and temporary interruption until the specific

adverse reaction has resolved to levels that allow continuation of therapy. Ofev treatment may be resumed at the full dose (150 mg twice daily) or a reduced dose (100 mg twice daily). If a patient does not tolerate 100 mg twice daily, treatment with Ofev should be discontinued.

In case of interruptions due to aspartate aminotransferase (AST) or alanine aminotransferase (ALT) elevations  $> 3x$  upper limit of normal (ULN), once transaminases have returned to baseline values, treatment with Ofev may be reintroduced at a reduced dose (100 mg twice daily) which subsequently may be increased to the full dose (150 mg twice daily)

#### Special populations

##### *Elderly patients ( $\geq 65$ years)*

No overall differences in safety and efficacy were observed for elderly patients. No *a-priori* dose adjustment is required on the basis of a patient's age. Patients  $\geq 75$  years may be more likely to require dose reduction to manage adverse effects.

##### *Renal impairment*

Less than 1 % of a single dose of nintedanib is excreted via the kidney. Adjustment of the starting dose in patients with mild to moderate renal impairment is not required. The safety, efficacy, and pharmacokinetics of nintedanib have not been studied in patients with severe renal impairment ( $< 30$  ml/min creatinine clearance).

##### *Hepatic Impairment*

Nintedanib is predominantly eliminated via biliary/faecal excretion ( $> 90$  %). No adjustment of the starting dose is needed for patients with mild hepatic impairment based on clinical data (Child Pugh A). The safety and efficacy of nintedanib have not been investigated in patients with hepatic impairment classified as Child Pugh B and C. Therefore, treatment of patients with moderate (Child Pugh B) and severe (Child Pugh C) hepatic impairment with Ofev is not recommended.

#### Method of administration

Ofev is for oral use. The capsules should be taken with food, swallowed whole with water, and should not be chewed or crushed.

### Contraindications:

Hypersensitivity to nintedanib, peanut or soya, or to any of the excipients listed in the PI.

### Precautions:

#### Gastrointestinal disorders

##### *Diarrhoea*

In the INPULSIS trials, diarrhoea was the most frequent gastrointestinal adverse reaction reported in 62.4 % versus 18.4 % of patients treated with Ofev and placebo, respectively. In most patients the adverse reaction was of mild to moderate intensity and occurred within the first 3 months of treatment. Diarrhoea led to dose reduction in 10.7 % of the patients and to discontinuation of nintedanib in 4.4 % of the patients.

Diarrhoea should be treated at first signs with adequate hydration and anti-diarrhoeal medicinal products, e.g. loperamide, and may require treatment interruption. Ofev treatment may be resumed at a reduced dose (100 mg twice daily) or at the full dose (150 mg twice daily). In case of persisting severe diarrhoea despite symptomatic treatment, therapy with Ofev should be discontinued.

##### *Nausea and vomiting*

Nausea and vomiting were frequently reported gastrointestinal adverse reactions. In most patients with nausea and vomiting,

the event was of mild to moderate intensity. Nausea led to discontinuation of nintedanib in 2.0 % of patients. Vomiting led to discontinuation in 0.8 % of the patients.

If symptoms persist despite appropriate supportive care (including anti-emetic therapy), dose reduction or treatment interruption may be required. The treatment may be resumed at a reduced dose (100 mg twice daily) or at the full dose (150 mg twice daily). In case of persisting severe symptoms therapy with Ofev should be discontinued.

#### Hepatic Function

The safety and efficacy of Ofev has not been studied in patients with moderate (Child Pugh B) or severe (Child Pugh C) hepatic impairment. Therefore treatment with Ofev is not recommended in such patients.

Administration of nintedanib was associated with elevations of liver enzymes (ALT, AST, alkaline phosphatase (ALKP), gamma-glutamyl-transferase (GGT)) with a potentially higher risk for female patients. Transaminase increases were reversible upon dose reduction or interruption. Administration of nintedanib was also associated with elevations of bilirubin. Hepatic transaminase and bilirubin levels should be investigated before the initiation of treatment with Ofev, and periodically thereafter (e.g. at each patient visit) or as clinically indicated. If transaminase (AST or ALT) elevations > 3x ULN are measured, dose reduction or interruption of the therapy with Ofev is recommended and the patient should be monitored closely. Once transaminases have returned to baseline values, treatment with Ofev may be resumed to the full dose (150 mg twice daily) or reintroduced at a reduced dose (100 mg twice daily) which subsequently may be increased to the full dose. If any liver test elevations are associated with clinical signs or symptoms of liver injury, e.g. jaundice, treatment with Ofev should be permanently discontinued. Alternative causes of the liver enzyme elevations should be investigated.

#### Haemorrhage

Vascular endothelial growth factor receptor (VEGFR) inhibition might be associated with an increased risk of bleeding. In the INPULSIS trials with Ofev, the frequency of patients who experienced bleeding adverse events (AEs) was slightly higher in the Ofev arm (10.3 %) than in the placebo arm (7.8 %). Non-serious epistaxis was the most frequent bleeding event. Serious bleeding events occurred with low and similar frequencies in the 2 treatment groups (placebo: 1.4 %; Ofev: 1.3 %).

Patients at known risk for bleeding including patients with inherited predisposition to bleeding or patients receiving a full dose of anticoagulative treatment were not included in the INPULSIS studies. Therefore these patients should only be treated with Ofev if the anticipated benefit outweighs the potential risk.

#### Arterial thromboembolic events

Patients with a recent history of myocardial infarction or stroke were excluded from the INPULSIS trials. Arterial thromboembolic events were infrequently reported: in 0.7 % of patients in the placebo and 2.5 % in the nintedanib treated group. While adverse events reflecting ischaemic heart disease were balanced between the nintedanib and placebo groups, a higher percentage of patients experienced myocardial infarctions in the nintedanib group (1.6 %) compared to the placebo group (0.5 %). Caution should be used when treating patients at higher cardiovascular risk including known coronary artery disease. Treatment interruption should be considered in patients who develop signs or symptoms of acute myocardial ischaemia.

#### Venous thromboembolism

In the INPULSIS trials no increased risk of venous thromboembolism was observed in nintedanib treated patients. Due to the mechanism of action of nintedanib patients might have an increased risk of thromboembolic events.

#### Gastrointestinal perforations

In the INPULSIS trials no increased risk of gastrointestinal perforation was observed in nintedanib treated patients. Due to the mechanism of action of nintedanib patients might have an increased risk of gastrointestinal perforations. Particular caution should be exercised when treating patients with previous abdominal surgery. Ofev should only be initiated at least 4 weeks after abdominal surgery. Therapy with Ofev should be permanently discontinued in patients who develop gastrointestinal perforation.

#### Hypertension

Administration of Ofev may increase blood pressure. Systemic blood pressure should be measured periodically and as clinically indicated.

#### Wound healing complication

No increased frequency of impaired wound healing was observed in the INPULSIS trials. Based on the mechanism of action nintedanib may impair wound healing. No dedicated studies investigating the effect of nintedanib on wound healing were performed. Treatment with Ofev should therefore only be initiated or - in case of perioperative interruption - resumed based on clinical judgement of adequate wound healing.

#### Co-administration with pirfenidone

Concomitant treatment of nintedanib with pirfenidone was investigated in a parallel group design study in Japanese patients with IPF. Twenty four patients were treated for 28 days with 150 mg nintedanib twice daily (13 patients received nintedanib on top of chronic treatment with standard doses of pirfenidone; 11 patients received nintedanib alone). Due to the short duration of concomitant exposure and low number of patients the benefit/risk of the co-administration with pirfenidone has not been established.

#### Effect on QT interval

No evidence of QT prolongation was observed for nintedanib in the clinical trial programme. As some other tyrosine kinase inhibitors are known to exert an effect on QT, caution should be exercised when administered nintedanib in patients who may develop QTc prolongation.

#### Allergic reaction

Dietary soya products are known to cause allergic reactions including severe anaphylaxis in persons with soya allergy. Patients with known allergy to peanut protein carry an enhanced risk for severe reactions to soya preparations.

#### **Drug Interactions:**

##### P-glycoprotein (P-gp)

Nintedanib is a substrate of P-gp. Co-administration with the potent P-gp inhibitor ketoconazole increased exposure to nintedanib 1.61-fold based on AUC and 1.83-fold based on C<sub>max</sub> in a dedicated drug-drug interaction study. In a drug-drug interaction study with the potent P-gp inducer rifampicin, exposure to nintedanib decreased to 50.3 % based on AUC and to 60.3 % based on C<sub>max</sub> upon co-administration with rifampicin compared to administration of nintedanib alone. If co-administered with Ofev, potent Pgp inhibitors (e.g. ketoconazole or erythromycin or cyclosporine) may increase exposure to nintedanib. In such cases, patients should be monitored closely for tolerability of nintedanib. Management

of side effects may require interruption, dose reduction, or discontinuation of therapy with Ofev.

Potent P-gp inducers (e.g. rifampicin, carbamazepine, phenytoin, and St. John's Wort) may decrease exposure to nintedanib. Selection of an alternate concomitant medicinal product with no or minimal P-gp induction potential should be considered.

#### Cytochrome (CYP)-enzymes

Only a minor extent of the biotransformation of nintedanib consisted of CYP pathways. Nintedanib and its metabolites, the free acid moiety BIBF 1202 and its glucuronide BIBF 1202 glucuronide, did not inhibit or induce CYP enzymes in preclinical studies. The likelihood of drug-drug interactions with nintedanib based on CYP metabolism is therefore considered to be low.

#### Co-administration with other medicinal products

The potential for interactions of nintedanib with hormonal contraceptives was not explored.

#### Side Effects:

##### Summary of the safety profile

Nintedanib has been studied in clinical trials of 1,529 patients suffering from IPF. The safety data provided in the following are based on the two Phase III, randomised, double-blind, placebo-controlled studies in 1,061 patients comparing treatment with nintedanib 150 mg twice daily to placebo for 52 weeks (INPULSIS-1 and INPULSIS-2).

The most frequently reported adverse events associated with the use of nintedanib included diarrhoea, nausea and vomiting, abdominal pain, decreased appetite, weight decreased and hepatic enzyme increased.

Summary of ADRs per frequency category

Frequency System Organ Class	Very common (≥ 1/10)	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1,000 to < 1/100)
Metabolism and nutrition disorders		Weight decreased, Decreased appetite	
Vascular disorders			Hypertension
Gastrointestinal disorders	Diarrhoea, Nausea, Abdominal pain	Vomiting	
Hepatobiliary disorders	Hepatic enzyme increased	Alanine aminotransferase (ALT) increased, Aspartate aminotransferase (AST) increased, Gamma glutamyl transferase (GGT) increased	Hyperbilirubinaemia, Blood alkaline phosphatase (ALKP) increased

#### Description of selected adverse reactions

##### Diarrhoea

Diarrhoea was reported in 62.4 % of patients treated with nintedanib. The event was reported to be of severe intensity in 3.3 % of nintedanib treated patients. More than two thirds of patients experiencing diarrhoea reported its first onset already during the first three months of treatment. Diarrhoea led to permanent treatment discontinuation in 4.4 % of patients; otherwise the events were managed by anti-diarrhoeal therapy, dose reduction or treatment interruption.

##### Hepatic enzyme increased

Liver enzyme elevations were reported in 13.6 % of nintedanib treated patients. Elevations of liver enzymes were reversible and not associated with clinically manifest liver disease.

#### Forensic Classification:

P1S1S3



College of Life Sciences & Technology

<http://hkuspace.hku.hk/>

### MSc in Clinical Pharmacy\* Application Code: 1550-HS073A

This is a 2-year part-time programme in HK delivered through face-to-face and distance learning. Tutorials / workshops are run by visiting academics from the University of Sunderland, U.K. The degree is awarded by the University of Sunderland.

#### Programme Features:

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

#### Teaching and Assessment:

Teaching is conducted through e-learning and conference days, which consists of seminars, workshops and structured practical experience. Project work is required on a topic relevant to patients' needs from the students' area of study.

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

#### Entry Requirements:

A minimum of lower second class honours degree in pharmacy (or equivalent) and registration as a pharmacist in Hong Kong. BPharm graduates from countries that do not normally award honours may also apply, provided they are registered as a pharmacist in Hong Kong. The programme is open to both hospital and community pharmacists.



### BSc (Hons) Pharmaceutical Science\* Application Code: 1550-HS072A

This programme is a 2-year top-up degree offered in part-time mode of study in Hong Kong. The BSc (Hons) Pharmaceutical Science is to be awarded by the University of Wolverhampton, UK. The programme aims to produce high quality pharmaceutical science graduates with the generic, subject-specific and transferable knowledge and skills suited to a career in the pharmaceutical industry or other related laboratory based scientific discipline.

#### Programme Features:

- a 24-month part-time undergraduate programme
- it covers the area of pharmaceutical science including pharmacology, pharmaceutical design and manufacture, biopharmaceutical, methods of analysis, quality assurance and delivery of pharmaceutical substances

#### Teaching and Assessment:

Teaching is delivered via face-to-face lectures, laboratory sessions and tutorials.

Assessment includes a combination of examinations and coursework including laboratory reports, in-class assignments, quizzes, projects, dissertations etc.

#### Entry Requirements:

- Applicants should hold either:
- Associate of Health Science (Biomedical Sciences) / Advanced Diploma in Pharmaceutical Science (HKU SPACE); or
  - Higher Diploma in Medical and Health Products Management (HPSHCC); or
  - Higher Diploma in Pharmaceutical Technology (Western Medicine) / Dispensing Studies / Pharmaceutical Science / Hospital Dispensing Studies (HKIVE); or
  - Higher Diploma in Pharmaceutical Dispensing (CBCC)



Application Deadline: 30 June 2017 (Friday)

Enquiries: 3762 0096 2571 8480 sherip@hkuspace.hku.hk

\* These are exempted courses under the Non-Local Higher and Professional Education (Regulation) Ordinance. It is a matter of discretion for individual employers to recognize any qualification to which these courses may lead.

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# Hong Kong Pharmaceutical Journal: For Detailed Instructions for Authors

### INTRODUCTION

Hong Kong Pharmaceutical Journal (HKPJ) is the official publication of the Pharmaceutical Society of Hong Kong, the Practising Pharmacists Association of Hong Kong and the Society of Hospital Pharmacists of Hong Kong. It is a journal of the pharmacists, for the pharmacists and by the pharmacists. The Journal is currently divided into several sections: **Editorial Comment; News & Short Communications; Pharmacy Practice; Over-the-Counter & Health; Drugs & Therapeutics; Herbal Medicines & Nutraceuticals; Pharmaceutical Technology** and **New Products**. It publishes review articles or original papers relevant to these different fields of pharmacy. In addition to the regular four issues of the Journal per year, there are issues dedicated solely to reports on special function of the society. The Aims and Scope of the Journal are published on the inside back cover of each issue.

### Submission of Manuscript

Submission of a paper implies that it has not been published previously, that it is not under consideration for publication elsewhere, and that if accepted it will not be published elsewhere in the same form, in English or in any other language, without the written consent of the publisher. Authors are specifically discouraged from submitting papers as fragmented studies of a particular topic. A manuscript must be indicated which section it is belonged. Upon received, it will be screened by a **Sectional Editor** of HKPJ for initial consideration before it is sent out for further review or comment.

#### For online submission:

Authors are encouraged to submit manuscripts using the online submission system. Access to the system, and full instructions on its use, can be found on the HKPS website at: <http://www.HKPS.org/HKPJ/Guidelines>. In creating the electronic version of their manuscript, authors are requested to follow the guidelines for submitting files. The paper should be submitted as a single file, prepared with a standard word-processor such as Microsoft Word, with embedded tables and graphics. Please note that any embedded graphics must also be submitted as separate, original files. The preferred formats for graphics files are tiff or postscript. All correspondence between Editor and author is performed by email. Authors are reminded that the copyright of their article or paper is automatically transferred to HKPJ once it is accepted for publication in the journal.

#### For hardcopy submission:

Three copies of the manuscript are required on either 8.5"x11" or A4 paper (two copies are used for review purposes and the original is kept on file at the Section Editor). Copies must be produced on a high-quality printer, and originals and copies of all Figures and Schemes must be fully legible. Initially only send hard copies of the paper; when it has been refereed, revised if necessary, and accepted, you will be requested to send a disk containing the final version with the final hard copy to the appropriate Editor. Make sure that the disk and the hard copy match exactly. The revised manuscript must be returned to the Editors within one month, otherwise it may be deemed to be new and subject to further review. When submitting the final version with a disk please label all disks with "HKPJ", your name, software (e.g. word 2000), hardware used (e.g. PC or Macintosh) and file names with the correct extension (e.g. Fig 1.cdx, Table 1-6.xls). Save text on a separate disk from the graphics, include the text and tables in one file, and provide graphics and structures in separate numbered files. Please remember to keep a backup copy of both the electronic files and original manuscript for reference and safety since we cannot accept responsibility for damage or loss of papers. Original manuscripts are discarded three months after publication unless the Publisher is asked to return original material after use.

### Suggested Referees

Please submit, with your manuscript, the names and addresses of 2 potential referees. You may also mention persons who you would prefer not to review your paper.

### Editorial Authority

The Editors of HKPJ reserve the right to make alterations to manuscripts submitted for publication. Such alterations will be made if manuscripts do not conform with accepted scientific standards or if they contain matter which in the opinion of the Editors is unnecessarily verbose or unclear. Alterations may be queried, but this will inevitably delay publication.

### Preparation of manuscript

The manuscript is required to be written in English, with numbered pages, single-spaced, using Arial 9 point font, and in a suitable word-processing format. Each page should have adequate margins (4 cm) and liberal spaces at top and bottom of the manuscript. All textual elements should begin flush left, with the second paragraphs onwards indent, and should use the wrap-around end-of-line feature, i.e. no returns at the end of each line. Place two returns after every element such as title, headings, paragraphs, figure and table call-outs. Most formatting codes will be removed or replaced on processing your article. Please do not use options such as automatic word breaking, justified layout, double columns or automatic paragraph numbering (especially for numbered references). However do use bold face, italic, subscripts, superscripts etc. The Editors reserve the right to adjust style to certain standards of uniformity. If authors are unfamiliar with HKPJ, they should consult a recent copy (or the free online sample copy available from [www.HKPS.com/HKPJ](http://www.HKPS.com/HKPJ)) to see the conventions currently followed for guidance in preparing submissions.

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

**Title Page and Author Names:** Titles must be as brief as possible, consistent with clarity, and should not exceed 10 words in length. Uninformative phrases such as "Chemical examination of", "Studies on", "Survey of", "New", "Novel" etc. will be deleted. If a paper is part of a series, this must not be given in the heading, but referred to in a footnote in the form: "Part 9 in the series "The Role of Pharmacists in Medical Care of Patients" followed by a numbered reference to the previous part. Author names should be typed right underneath the article title. Each author should identify himself or herself with Surname in capital letters, followed by the first name. All names are separated by a semicolon (;). An asterisk should be placed following the name of the author to whom correspondence inquiries should be made. Full postal addresses must be given for all co-authors. Superscript letters; a, b, c should be used to identify authors located at different addresses.

An **Author's background box** at the end of each article is mandatory to include the author's job title and the affiliated institute or organization. Full details of telephone, fax numbers and e-mail address should also be indicated for the corresponding authors. No academic or professional membership title is allowed.

**ABSTRACT:** The abstract should be on a separate page and briefly describe the results obtained and conclusions reached, not the methods used, or speculations on any other matter. They are not expected to be a complete summary but only an outline of the main findings. The abstract should be contained within 250 words and should be readable without reference to the rest of the paper.

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

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

**RESULTS AND DISCUSSION:** These sections should be carefully prepared with discussions of the results being compared with existing and/or previous knowledge within the field. Authors are, however, encouraged to combine the Results and Discussion sections wherever possible.

**EXPERIMENTAL:** Subsections on the Experimental Procedures should be italicized and inserted as part of the first line of the text to which they apply. HKPJ encourages an extensive use of abbreviations (these are listed at the back of the Instructions to Authors, or the reader is referred to other sources). The Experimental should begin with a subsection entitled General Experimental Procedures. This subsection will typically contain brief details of instruments used, and identification of sources of specialized chemicals, biochemicals and molecular biology kits. The next subsection describes the source(s) and documentation of biological materials used, whether in reference to whole plants or parts there from, crude drugs, or any other plant material from which identifiable chemical substances are obtained for the first time. Documentation must also include a reference to voucher specimen(s) and voucher number(s) of the compounds, plants or other material examined. If available, authors should quote the name and address of the authority who identified each sample investigated. Specimens should preferentially be deposited in a major regional herbarium where the collection is maintained by state or private institution and which permits loan of such materials. With other microorganisms, the culture collection from which they were either accessed and/or deposited should be included, together with identification of the strain designation code. The Experimental Procedures employed should be concise but sufficiently detailed that a qualified researcher will be able to repeat the studies undertaken, and these should emphasize either truly new procedures or essential modifications of existing procedures. Experimental details normally omitted include: (1) method of preparation of common chemical and biochemical derivatives, (2) excessive details of separation of compounds, proteins and enzymes, e.g. preparation of columns, TLC plates, column and fraction size. Compound Characterization: Physical and spectroscopic data for new compounds must be comprehensive, and follow the order shown below: compound name (and assigned number in text); physical state of compound (e.g. oil, crystal, liquid, etc.), melting and/or boiling point; optical rotation and/or circular dichroism measurements, if optically active; UV; IR; <sup>1</sup>H NMR; <sup>13</sup>C NMR; MS. For all new compounds, either high-resolution mass spectral or elemental analysis data is required. See later section for method of data presentation.

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

**ACKNOWLEDGMENTS:** This section is used to provide brief credit for scientific and technical assistance, and in recognition of sponsorship through financial support and any other appropriate form of recognition.

**References:** All publications cited in the text should be presented in a list of references following the text of the manuscript. In the text refer to the author’s name (without initials) and year of publication (e.g. “Since Peterson (1993) has shown that ...” or “This is in agreement with results obtained later by Kramer.”<sup>(4)</sup>) For two authors both authors are to be listed, with “and” separating the two authors. For more than two authors, use the first author’s surname followed by et al. The list of references should be arranged according to the order of their appearance in the text with no more than three authors listed. If number of authors of a reference exceeds three, “et al” is used followed by year of publication in bracket after the first author. Journal titles should be completely shown followed by the volume, issue number in bracket if included, colon and start – final page number. The manuscript should be carefully checked to ensure that the spelling of authors’ names and dates are exactly the same in the text as in the reference list. Some examples of references are shown below:

- (1) Cabello-Hurtado F, Durst F, Jorrián JV, Werck-Reichhart D. et al. (1998). Coumarins in *Helianthus tuberosus*: characterization, induced accumulation and biosynthesis. *Biochemistry*, 49(1):1029-1036.
- (2) Mabry T, Markham KR, Thomas MB. (1970). *The Systematic Identification of Flavonoids*. 2<sup>nd</sup> Ed, pp. 79-105. Springer Verlag, New York.
- (3) Harborne JB. (1999). Plant chemical ecology. In: Barton D, Nakanishi K, Meth-Cohn O, (Eds.), *Comprehensive Natural Products Chemistry*, Vol. 8. pp. 137-196. Pergamon, Oxford.

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#### Abbreviations

About, approximately: ca.  
Anhydrous: dry (not anhyd.)  
Aqueous: aq.  
Circular dichroism: CD  
Concentrated (or mineral acids): conc.  
Concentrations: ppm (or ppb),  $\mu\text{M}$ , mM, M, %, mol  
Dry weight: dry wt; fresh weight: fr. wt  
Electricity: V, mA, eV  
Force due to gravity (centrifugation): g; rpm (revolutions  $\text{min}^{-1}$ )  
Gas chromatography: GC  
Gas chromatography-mass spectrometry: GC-MS Trimethylsilyl derivative: TMSi (TMS cannot be used as this refers to the internal standard tetramethylsilane used in  $^1\text{H}$  NMR)  
High performance liquid chromatography: HPLC  
Infrared spectrophotometry: IR  
Length: nm,  $\mu\text{m}$ , mm, cm, m  
Literature: lit.  
Mass spectrometry: m/z [ $\text{M}$ ]<sup>+</sup> (molecular ion, parent ion)  
Melting points: uncorr. (uncorrected)  
Molecular mass: Da (daltons), kDa  
Molecular weight: M<sub>r</sub>  
Nuclear magnetic resonance:  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR, Hz,  $\delta$   
Numbers: e.g. 1, 10, 100, 1000, 10000; per or  $^{-1}$   
Optical rotatory dispersion: ORD  
Paper chromatography: PC  
Precipitate: ppt.  
Preparative thin-layer chromatography: prep. TLC  
Radioactivity: dpm (disintegrations per min), Ci (Curie), sp. act (specific activity), Bq (1 becquerel = 1 nuclear transformation  $\text{sec}^{-1}$ )

Repetitive manipulations: once, twice, x3, x4, etc.  
RR<sub>t</sub> (relative retention time), R<sub>i</sub> (Kovats' retention index), ECL (equivalent chain length- term frequently used in fatty acid work)  
Saturated: satd.  
Solution: soln.  
Solvent mixtures including chromatographic solvents: abbreviate as follows n-BuOH-HOAc-H<sub>2</sub>O (4:1:5)  
Statistics: LSD (least significant difference), s.d. (standard deviation), s.e. (standard error)  
Temperature: (with centigrade), mp, mps, mmp, bp  
Temperature: temp.  
Thin-layer chromatography: TLC, R<sub>f</sub>  
Time: s, min, h, day, week, month, year  
Ultraviolet spectrophotometry: UV, A (absorbance, not aD-optical density)  
Volume: l, (litre),  $\mu\text{l}$ , ml  
Weight: wt, pg, ng,  $\mu\text{g}$ , mg, g, kg

Inorganics, e.g. AlCl<sub>3</sub> (aluminum chloride), BF<sub>3</sub> (boron trifluoride), Cl<sub>2</sub>, CO<sub>3</sub>, H<sub>2</sub>, HCl, HClO<sub>4</sub> (perchloric acid), HNO<sub>3</sub>, H<sub>2</sub>O, H<sub>2</sub>O<sub>2</sub>, H<sub>2</sub>SO<sub>4</sub>, H<sub>3</sub>BO<sub>3</sub> (boric acid), He, KHCO<sub>3</sub> (potassium bicarbonate), KMnO<sub>4</sub> (potassium permanganate), KOH, K-Pi buffer (potassium phosphate buffer), LiAlH<sub>4</sub> (lithium aluminium hydride), Mg<sup>2+</sup>, MgCl<sub>2</sub>, N<sub>2</sub>, NH<sub>3</sub>, (NH<sub>4</sub>)<sub>2</sub>SO<sub>4</sub>, Na<sup>+</sup>, NaBH<sub>4</sub> (sodium borohydride), NaCl, NaIO<sub>4</sub> (sodium periodate), NaOH, Na<sub>2</sub>SO<sub>3</sub> (sodium sulphite), Na<sub>2</sub>SO<sub>4</sub> (sodium sulphate), Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (sodium thiosulphate), O<sub>3</sub>, PPI (inorganic phosphate), SO<sub>4</sub><sup>2-</sup>, Tris (buffer).

Organics, e.g. Ac<sub>2</sub>O (acetic anhydride), n-BuOH (butanol), C<sub>6</sub>H<sub>6</sub> (benzene), CCl<sub>4</sub> (carbon tetrachloride), CH<sub>2</sub>Cl<sub>2</sub> (methylene chloride), CHCl<sub>3</sub> (chloroform), CH<sub>2</sub>N<sub>2</sub> (diazomethane), CM (carboxymethyl), DEAE (diethylaminoethyl), DMF (dimethylformamide), DMSO (dimethyl sulphoxide), EDTA (ethylene-diaminetetra-acetic acid), Et<sub>2</sub>O (diethyl ether), EtOAc (ethyl acetate), EtOH (ethanol), HCO<sub>2</sub>H (formic acid), HOAc (acetic acid), iso-PrOH (iso-propanol), Me<sub>2</sub>CO (acetone), MeCOEt (methyl ethyl ketone), MeOH (methanol), NaOAc (sodium acetate), NaOMe (sodium methoxide), petrol (not light-petroleum or petroleum ether), PhOH (phenol), PrOH (propanol), PVP (polyvinylpyrrolidone), TCA (trichloroacetic acid), TFA (trifluoroacetic acid), THF (tetrahydrofuran).  
 $^1\text{H}$  NMR solvents and standards: CDCl<sub>3</sub> (deutero-chloroform), D<sub>2</sub>O, DMSO-d<sub>6</sub> [deuterodimethylsulphoxide not (CD<sub>3</sub>)<sub>2</sub>S], pyridine-d<sub>5</sub> (deuteropyridine), TMS (tetramethylsilane).

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

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<sup>[1]</sup> Danesch et al., J Arthritis 2014, 3(3):1000136

<sup>[2]</sup> Ruff KJ, et al., Clinical Interventions In Aging, 2009, (4):235-240

<sup>[3]</sup> Ruff KJ, et al. Clinical Rheumatology 2009, (28):907-914.

<sup>[4]</sup> NNT for glucosamine and chondroitin calculated from the GAIT study. (N Engl J Med 2006, 354(8):795-808).



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