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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

You Are What You Inherit, Ingest, Encounter and Manage

In recent years, people are used to saying "you are what you eat" in order to emphasize the importance of food or drugs on a person's health. This statement, indeed, is only partially true.

It is well known that very big people breed tall kids, white people normally produce descendants with fair complexion and type I diabetic patients tend to pass diabetes to their next generation. These are merely a few examples to illustrate that physical characteristics are determined by genetic inheritance which could hardly be altered with contemporary technology. On the other hand, some physical features as well as intellectual ability of a person could be affected by the daily food ingested; e.g. regular consumption of green tea has diverse benefits to health (details can be found in this issue on p31-39),[1,2] while feeding babies with human breast milk is better than formula milk as the former provides sufficient nutrients, and more, for their growth and development (p15-18).[3] On the other hand, poor nutrition could lead to unhealthy growth. On consuming some extremely poor or tainted foods or drugs, physical and intellectual growth of a person may be severely retarded and recurrent health problems may be developed.[4]

Besides the genetic inheritance and consumption of food or drugs, where a person has been raised and how one's life is managed could also affect the development of a person's life. Whether a person could be mature and competent or not depends very much on how a person is raised. People brought up in a conservative environment, such as strict ideology or social behavior, tends to become a disciplined citizen while those who grow up in wicked environment and a bad society tend to become problematic people. In recent years, we have been told that many medical errors have happened and were reported more than ever. This phenomenon may reflect some problems in the current training system arranged for health-care students. Indeed, a study conducted by Lam and Cheung a year ago on course syllabuses taught in both local pharmacy schools concluded that the training is inadequate and narrow in terms of contents and hours (p12-14) by comparison with some similar courses offered by other representative institutes in the Asia Pacific region.[5] Students currently enrolled in these two schools are also aware of their inadequate training. A debate on minimal qualification for the requirement of registration as a pharmacist was held during the 2011 Hong Kong Pharmacy Conference. The content of their debate is presented in this issue from p7-11 for your reference.[6] The problems of inadequate training given to medical care personnel in the last two decades have been emerging. These problems were raised in a report on the Safe Patient Project conducted by the venerable Consumers Union of the United States in year 2009. It was pointed out that no one would knowingly buy any item or service that received a low grade from a well-established protector of everyone's purchases yet they have to give a failing grade to the health care system. It was suggested that it is essential to provide better training in patient safety and it will take more than a handful of graduate-level educational programs to change the training culture completely. They proposed that key curricular materials and evidence-based tools be used in teaching all physicians, nurses, pharmacists, and other professionals.[7] This landmark report, perhaps, is the most out-spoken criticism so far of current education for health care training.

Therefore, in addition to ingested food or drugs, the development of a person is also determined by the genes inherited from parents, and is affected by the environment where one is brought up and is influenced by the ways that one manages their own life every day.

The recent disaster in Japan, perhaps, is a good example to explain this complex issue. On March 11, 2011, a most powerful earthquake (9.0 magnitude) since human records have been kept off the coast of Kesennuma, a city at the Northeastern part of Japan triggered a 10 m high tsunami. The massive wave struck Sendai, deluging roads, farmland and houses, and swept cars off roads, driving sea vessels onto land and carrying away airplanes on the runway at airport for Miyagi and Fukushima prefectures. Thousands of lives in this region were lost and thousands of people are missing.[8] When this kind of natural disaster occurs, it is quite similar to a genetic disease inherited from parents; no one can do much about it. However, people can minimize the undesirable impact by taking proper preventative measures in advance or taking appropriate action right afterward. In this earthquake, the worst scenario evolved due to delayed implementation of some appropriate action after the collapse of four nuclear power plants which were ruined during the tsunami. The impact of the damage was under-estimated at the beginning yet its negative impact will be long lasting. After the eruption and leakage of radioactive materials and, more decisively, the elapse of critical rescue time, all sorts of remediation became ineffective. Fortunately, the majority of Japanese citizens are very self-disciplined; there has been no social turmoil or chaos after the disaster.

The reaction of the Japanese to this big disaster has won great respect from all other countries. Whether it is because of their education or simply an inherited characteristic is an interesting thing to be studied. But what is obvious is that they have shown the whole world that they are really top class citizens.

On the other hand, the response of some Chinese in Southern China and in Hong Kong really made us feel ashamed. When they learned about the radioactive leakage, their immediate response was to purchase and hoard iodinated salt at home from all available sources that could be identified; even though the leakage was so remote and far away. This phenomenon reflects that although material wise, the situation of Chinese people has improved a lot, the tide of kinsmen's love is very poor.

A good curriculum for both professional and kinship training is obviously and absolutely required. But above all, the most difficult thing about learning is to find strict teachers because strict teachers produce outstanding students. Hence, let us restore this best learning mode for our next generation, which has been tried, implemented, and practiced to prove the most successful way of education for more than three thousand years in Chinese history.

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Editor-in-Chief
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INSTRUCTIONS FOR AUTHORS

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

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

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

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

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

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Information on Clopidogrel Bisulfate (marketed as Plavix)

Date: October 27, 2010

The U.S. Food and Drug Administration (FDA) is reminding the public that it continues to warn against the concomitant use of Plavix (clopidogrel) and omeprazole because the co-administration can result in significant reductions in clopidogrel's active metabolite levels and antiplatelet activity. This information was added to the drug label of Plavix in November 2009, and has been the source of continued discussion in the medical literature.

Patients at risk of heart attacks or strokes, who are given Plavix to prevent blood clots, will not get the full anti-clotting effect if they also take omeprazole. FDA wishes to emphasize additional facts that may be a source of confusion among healthcare professionals:

- With regard to the proton pump inhibitor (PPI) drug class, this recommendation applies only to omeprazole and not to all PPIs. Not all PPIs have the same inhibitory effect on the enzyme (CYP 2C19) that is crucial for conversion of Plavix into its active form.
- Pantoprazole may be an alternative PPI for consideration. It is a weak inhibitor of CYP2C19 and has less effect on the pharmacological activity of Plavix than omeprazole.

Source:http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm190836.htm

Canada: Health Canada announced voluntary recall of weight loss product Synerate because of serious adverse reactions

Date: January 10, 2011

The product Synerate is being voluntarily recalled from the Canadian market because of the risk of serious, potentially fatal adverse effects from the combination of the ingredients in the product.

Synerate, a product used for weight loss or body building, contains caffeine and synephrine, which is similar to ephedrine. When used in combination with caffeine and other stimulants, synephrine and/or ephedrine has caused reported adverse events ranging from dizziness, tremors, headaches and irregularities in heart rate to seizures, psychosis, heart attacks and stroke. The product is not authorized by Health Canada.

Source: http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2011/2011_01-eng.php

Amendments to Dangerous Drugs Ordinance and Control of Chemicals Ordinance to be gazetted

Date: January 13, 2011

On January 12, a spokesperson for the Security Bureau said that the Government would publish the Dangerous Drugs Ordinance (Amendment of First Schedule) Order 2011 and the Control of Chemicals Ordinance (Amendment of Schedule 2) Order 2011 in the gazette on January 14. The two Orders will add three types of synthetic substances, namely, "derivatives of piperazine", "synthetic cannabinoids" and "derivatives of cathinone", to the First Schedule to the Dangerous Drugs Ordinance, and the chemical 1-[(2-Chlorophenyl)-N-(methylimino)methyl]cyclopentanol and its salts to Schedule 2 to the Control of Chemicals Ordinance respectively. The amendments aim to deter the trafficking and abuse of the dangerous drugs concerned and help fortify Hong Kong's defence line in the fight against drugs. The synthetic substances 'derivatives of piperazine', 'synthetic cannabinoids' and 'derivatives of cathinone' have gained popularity overseas as psychotropic drugs. Their harm is commensurate with other psychotropic drugs such as ecstasy, cannabis or amphetamines and will bring serious and irreversible harm to abusers.

The Order will subject these substances to the same strict control as other dangerous drugs. Those prosecuted of illicit trafficking and manufacture of these substances are liable to a maximum penalty of a fine of $5 million and life imprisonment. Those prosecuted of possession and consumption of these substances are liable to a maximum penalty of a fine of $1 million and imprisonment for seven years. The chemical 1-[(2-Chlorophenyl)-N-(methylimino)methyl]cyclopentanol and its salts can be used as precursor chemicals for the production of ketamine through simple processes. Whilst there has not been any reported case of manufacturing of ketamine in Hong Kong, taking into consideration of the prevalence of ketamine in Hong Kong, it has been proposed to subject these substances to legislative control as a precautionary measure.

The Order will subject the manufacture, import, export and transhipment of the substances under the control of the Ordinance and its subsidiary legislation. The manufacture, import, export and storage of the substances will require a licence or storage approval from the Commissioner of Customs and Excise. Possession, manufacture, transport or distribution of the substances for the purpose of unlawful production of dangerous drugs is liable to a maximum penalty of a fine of $1 million and imprisonment for 15 years. Both Amendment Orders will be introduced into the Legislative Council on January 19, 2011 and are expected to become effective on April 1.

Source: www.psdh.gov.hk

All Nonsteroidal Anti-Inflammatory Drugs Have Cardiovascular Risks

Date: January 21, 2011

New data showing nonsteroidal anti-inflammatory drugs (NSAIDs) have cardiovascular risks are putting the well-known pain relievers back in the headlines. Investigators evaluating available evidence report they have found little to suggest that any of the investigated options are safe.

During an interview with Medscape Medical News, senior investigator Peter Jüni, MD, from the University of Bern in Switzerland, said his team expected to see an increased risk but was surprised by the magnitude of the signal. "We never thought we'd see 2- and 4-fold increased risks," he said. "The doses were admittedly high," he pointed out, "however, this is clearly clinically relevant."

Investigators saw an increase in myocardial infarctions, stroke, and cardiovascular death in patients taking all of these NSAIDs. Not surprisingly, rofecoxib was associated with the highest risk for myocardial infarction, with a rate ratio of 2.12. The drug's manufacturer, Merck, voluntarily withdrew the product marketed as Vioxx in 2004 because of concerns over cardiotoxicity. Lumiracoxib had the next highest rate of myocardial infarction in the current study. Ibuprofen was associated with the highest risk for stroke with a rate ratio of 3.36 followed by diclofenac at 2.86. Etoricoxib was linked to the highest rate of cardiovascular death at 4.07 followed by diclofenac at 3.98.

Dr. Jüni recommends that physicians take special care in evaluating patients prone to cardiovascular events. Those who require treatment should take the lowest possible dose for the shortest period.

Of all the NSAIDs, naproxen seemed least harmful in this study. "I think we should reserve our final judgment on naproxen until after we've completed the overall safety study," Dr. Jüni said. His team is currently studying the gastrointestinal safety of the drug and weighing the benefits and risks from that perspective. "With naproxen, we tend to need a proton pump inhibitor to protect the stomach," Dr. Jüni added. "This is far from ideal."

The researchers suggest the lack of a clear association between specificity of cyclooxygenase-2 inhibitors and cardiovascular risk implies that other mechanisms should be considered. Multiple effects most probably contribute to the increased risk of cardiovascular events, including differential effects on prostacyclin and thromboxane A2 synthesis, endothelial function, nitric oxide production, blood pressure, volume retention, and other renal effects.

Source: BMJ. 2011;342:c7086

Drug-fake Stores on Shame List Disclosed

Date: February 16, 2011

A name-and-shame list of pharmacies convicted of selling fake drugs has been published to alert the public. In a joint exercise, the Consumer Council, the Custom and Excise Department named 18 stores that were convicted last year of selling counterfeit drugs, including Viagra, Tiger Balm oil and stomach pills. But already some of the stores on the list have closed and reopened under new names. Half the stores were in the New Territories, along the MTR East Line and in Tai Po and Fan Ling. One was situated on Hong Kong Island and eight in Kowloon.

Source: Consumer Council and Customs

Topiramate Linked to Birth Defects

Date: March 4, 2011

Pregnant women taking topiramate (Topamax, Ortho-McNeil Janssen) to treat epileptic seizures or prevent migraine headaches have an increased risk of bearing children with a cleft lip or palate, the US Food and Drug Administration (FDA) announced today. Consequently, clinicians should warn women of childbearing age about the possibility of these birth defects if they become pregnant while taking the medication. "Health care professionals should carefully consider the benefits and risks of topiramate when prescribing it to women of childbearing age," said Russell Katz, MD, director of the Division of Neurology Products in the FDA's Center for Drug Evaluation and Research. Alternative medications that have a lower risk of birth defects should be considered. Pregnant women prescribed the medication should continue to take it unless advised not to by a clinician.

Topiramate, an anticonvulsant, is approved for treating certain seizures in patients with epilepsy and preventing migraine headaches. However, it is not indicated for treating the pain of such headaches when they occur. The drug also is used on an off-label basis to treat weight loss, alcohol dependence, and psychiatric illnesses such as bipolar disorder.

According to new data from the North American Antiepileptic Drug Pregnancy Registry, infants exposed to topiramate as a single therapy in the first trimester of pregnancy had a 1.4% prevalence of oral clefts compared with 0.38% to 0.55% for infants exposed to other antiepileptic drugs. The prevalence rate was even lower — 0.07% — for infants of mothers who did not have epilepsy and were not being treated with other AEDs. These findings have prompted the agency to strengthen the label warning for topiramate by changing its pregnancy classification to category D. This category means that there are human data showing positive evidence of human fetal risk, but that the drug's benefits in pregnant women may outweigh the risks in some situations. The drug's pregnancy category previously had been a lower category C because of the absence of human data.

Source: www.medscape.com

FDA: Avoid Use of Kaletra Oral Solution in Newborns

Date: March 8, 2011

Lopinavir/ritonavir oral solution (Kaletra, Abbott Laboratories) should be avoided in premature or full-term infants for the first 14 days after their due dates because of possible cardiac, renal, or respiratory problems, the US Food and Drug Administration (FDA) announced today in a safety alert announcing a label change.

The solution contains alcohol and propylene glycol; premature infants and newborns are less capable of eliminating propylene glycol than older infants. Because the consequences of using Kaletra oral solution in babies immediately after birth can be severe or possibly fatal, the label is being revised to include a new warning. It is recommended that clinicians avoid the use of Kaletra oral solution in premature babies until 14 days after their due date, or in full-term infants in the first 2 weeks of life, unless it is determined that the benefits outweigh the possible risk. If the solution is administered to at-risk infants, clinicians are strongly advised to monitor for increases in serum osmolality, serum creatinine, and other signs of toxicity.

Source: http://www.fda.gov/MedWatch/report.htm

Queen Mary Hospital awarded full accreditation status on Healthcare Standards

Date: March 15, 2011

On March 15, the Queen Mary Hospital (QMH) announced that the hospital has been awarded full accreditation status for four years by the Australian Council on Healthcare Standards (ACHS). The ACHS conducted the Organisation Wide Survey (OWS) at QMH from October 25 to 29, 2010. The hospital was granted four-year full accreditation with 1 OA (Outstanding Achievement) and 10 EAs (Extensive Achievement) out of the 45 criteria under Clinical, Support and Corporate functions. A total of five public hospitals under the HA have participated in the Pilot Scheme of Hospital Accreditation, which was launched in 2009. Besides QMH, Caritas Medical Centre, Pamela Youde Nethersole Eastern Hospital, Queen Elizabeth Hospital and Tuen Mun Hospital have also been awarded accreditation.

Source: http://www.info.gov.hk

Rush on "Anti-radiation" Tablets after the Leakage of Radioactive Materials to the Environment

Date: March 16, 2011

Japan's nuclear crisis sparked panic buying of iodine pills in southern China and Hong Kong. US-based firms selling potassium iodide, which is claimed to be a radiation sickness preventative, reported to run out of stock following a rush of orders from Japan. Online biding prices had shot up 5,000 percent for a packet of the tablet. But according to an expert from the World Health Organization, he said that iodine tablets are of little use for preventing radiation.

Source: South China Morning Post

Anti-drug efforts bear fruit with improved drug situation in 2010

Date: March 18, 2011

Members of the Action Committee Against Narcotics (ACAN) were pleased to note an improvement in the local drug situation in 2010 over 2009 at its quarterly meeting on March 18. The total number of reported drug abusers and young drug abusers under 21 in 2010 dropped by 11.2% (from 13,988 to 12,420) and 18.7% (from 3,387 to 2,753) respectively compared to last year. There was also a 16.6 % drop in the total number of newly reported drug abusers in 2010 (from 4,458 to 3,719).

ACAN Chairman Professor Daniel Shek Tan-lei said, "We are happy to see the drop in the total number of reported drug abusers, in particular the larger drop in the number of reported young drug abusers. We believe this is a result of our escalated anti-drug efforts in preventive education and publicity, treatment and rehabilitation, legislation and enforcement, external co-operation and research. The support and co-operation of different sectors of the community are also very important.

Members also reviewed other drug-related figures in Hong Kong in 2010 at the meeting. In 2010, the number of reported psychotropic substance abusers (7,561) was higher than the number of abusers taking narcotic analgesics (6,202). Among the reported abusers, heroin remained the most popular type of drug abused but the total number of reported heroin abusers in 2010 was 10.3% lower than that in 2009 (from 6,903 down to 6,191). Ketamine remained the most common type of psychotropic substance abused. There was a 15.3% decline in the number of reported ketamine abusers in 2010 compared to that of 2009 (from 5,278 to 4,473). Among these abusers, 49% were aged under 21.

The number of reported drug abusers for most other groups of psychotropic substances also declined: ecstasy (51.5% lower), cough medicine (23.1% lower), cannabis (16.8% lower), triazolam/ midazolam/ zopiclone (10.8% lower) and nimetazepam (9.9% lower). However, there was an increase of 47% and 12.7% respectively in the number of reported abusers of cocaine and ice in 2010 compared with 2009. Noting the increase in the number of reported cocaine and ice abusers, Commissioner for Narcotics, Ms Sally Wong said, "To address the problem, we will launch new anti-drug publicity initiatives including a new set of Announcements in the Public Interest and posters in June to highlight the harmful effects of the two drugs."

Source: http://www.info.gov.hk

The College of Pharmacy Practice

The Hong Kong College of Pharmacy Practice was chartered in September, 2010, as an independent professional organization dedicated to advancing the standards of pharmaceutical care in Hong Kong. The founders, from various practice settings, have been deliberating on the vision, mission and strategic and tactical objectives of the college for over one year.

After decades of contribution to the Hong Kong healthcare system, pharmacy is gaining momentum of becoming an integral component of the modern healthcare enterprise. The founding of the College of Pharmacy Practice at this critical juncture is therefore timely relative to the advancement of pharmacy practice to a new level. Aspired to be the credentialing and standard setting arm of the pharmacy profession, the College has adopted a multipronged approach to carrying out its mission of establishing a critical mass of expert pharmacists eligible for election to be fellows of the College. This is the highest honor bestowed by the profession on a pharmacist with a record of sustained exemplary contribution to advancing the pharmacy profession in Hong Kong.

Today, the main focus of the multipronged approach is to facilitate the certification of interested pharmacists by the Board of Pharmacy Specialty in pharmacotherapy and to identify the expertise areas relevant to unmet patient needs for advanced pharmacy training. The College will soon carry out a survey and your feedback will be invaluable to the College in prioritizing different specialties.

There is more to the College of Pharmacy Practice than what you just read. We will keep you apprised from time to time. If you have questions, please do not hesitate to contact Mr. Lawrence Lo at 26098019.

辯題：藥劑碩士學位應為香港執業藥劑師的最低學歷要求

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正方主辯（黎文哲, 香港中文大學）

主席，評判，在座各位，大家好！

今天在座有很多位執業中的藥劑師，相信都不會懷疑藥劑師這個行業於社會上有著藥物把關人的角色，例如在醫生作出診斷並處方藥物後，藥劑師可以積極介入，提供用藥的意見。近年來，藥劑行業急速發展，我們的定位及角色逐漸改變，單憑現今的學士課程，我們有沒有足夠的知識和應用技能去迎合這個趨勢，令我們更加有效地發揮藥劑師的角色？

香港現有的藥劑學士課程為期三年，課程的設計是為學生提供基本而全面的知識，當中包括基本醫學訓練、藥物理論等。可是當中應用性較強，與執業方面有關的培訓，尚有不足。以中大為例，如藥理學，總共只有大約200小時去接觸。藥劑執業的實習，更只有100小時接觸。我們只能接觸到很基本的學問。對執業實習未能深化、應用知識方面的教導薄弱。由此可見，我們所學有關藥物知識和執業的時間非常有限，如何能擔當藥物把關人的角色？

醫生是診症及治療的執行者，而藥劑師是藥物把關人提供專業的意見，這是非常理想的互助合作夥伴。可是，香港的學制造成醫生和藥劑師在知識水平上深度有差距，造成醫生和藥劑師在履行專業時有很大分別，令兩者之間的緊密合作不能達至最理想的狀態。事實上，診斷及用藥兩者都同等重要，都同樣需要專業的知識。但是醫生有五年的時間去專注的學習和培訓去判定病症和治療，藥劑師卻只有三年的基本培訓去研習藥物的使用，所以在學士層面，我們欠缺與醫生對等的學識和資歷，從而造成了醫生和藥劑師的差距。正因如此，醫院管理局才會基本上只考慮具碩士學歷或以上的藥劑師擔任臨床藥劑師與醫生直接對話。

除了用藥方面的研習不足，在藥物生產同藥劑生產製造方向，本港藥劑師亦未能有效發揮藥物把關人的角色。三年的學士課程，有關藥物監控、中成藥、保健產品這些社會需求越來越大的知識亦有所不足。

由此可見，專注而穩固的學術基礎是藥劑師發揮藥物把關人角色的最重要關鍵。要解決這個問題，就是將藥劑碩士課程規定為香港執業藥劑師的最低學歷要求。我們可以用英國的學制來說明藥劑碩士課程的範疇和目的。首先，頭三年的課程不變，提供全面而基礎的培訓，而第四個學年，則是學識深化程度超越的過程，例如增強藥理和治療學的知識，亦深化部份應用性較強課程，例如在藥事法規的培訓，藥廠的良好生產規範，中成藥和健康產品的應用課程等，以應付香港執業時的需求。

總括而言，提升學歷要求至藥劑碩士程度，能確保藥劑師得到藥物知識的足夠培訓，令我們更有能力去參與醫生給病人用藥的討論，有助藥劑師更有效地發揮藥物把關人的角色。而這入職要求亦對藥劑行業和病人帶來莫大的益處，我方一副稍後將繼續討論。提升至藥劑碩士要求帶來的益處，所以今日的辯題絕對成立，多謝各位。

反方主辯（劉愷寧, 香港大學）

主席、評判、友方同學、在座各位，大家好！

在2010-2011年度的施政報告當中，香港政府明確表示會鼓勵基層醫療服務的發展。在這發展中藥劑師肩負很重要的使命，正正因為站在社會醫療服務的前線，要為人民提供基層的醫療服務，尤其是透過社區藥房接觸廣大市民。所以在釐訂藥劑業的發展，特別是執業門檻上，必須朝著基層醫療普及化的方向。然而，將門檻由學士學位提升為碩士學位後，帶來的是一連串的資源錯配問題，最終令基層醫療普及化的目標越來越遠。

世界衛生組職在2006年的報告指出，一個地區要達到基層醫療服務普及化，先要有充足的人手服務大眾。然而，現時香港藥劑師的數目與理想尚有一大段距離。在2001年香港藥學會與香港醫院藥劑師學會聯合發表的報告當中反映出香港藥劑師人手短缺的問題。假如把執業門檻由學士提高至碩士，將會直接在兩個方面令問題惡化。

第一，培訓一名碩士比培訓一名學士需要投放更多的資源和時間。如果提高了執業門檻，政府有限的資源就只能增加一小撮人的學歷，而不能夠培訓更多藥劑人才，無法將基層醫療推廣至最多市民受惠。第二，能夠完成兩個學位的人數必定比只需完成一個學位的人數少。原因是在現時香港的大專教育制度下，學院只會收取成績較優秀的學士畢業生修讀碩士學位。因此門檻提高後能夠達到執業最低學歷要求的人數自然大幅下降。

相反，維持執業門檻為學士學位能夠保持資源的彈性運用，以達至最多的病人受惠。在有限的時間和資源下，每位有志投身藥劑界的人仕都可以因應自己的工作環境選擇最為適合個人進修的途徑。我方一副將會就彈性一點作出更詳盡的闡釋。今日的辯題討論範圍是香港執業藥劑師的最低學歷要求應否提升，因此想今日的討論要有意義，就必須考慮兩個因素：一，香港自身社區情況的因素，二，當下時間性的因素。我們今日應該建基於香港現時的實際情況來進行討論。

每個國家每個地區的醫療和教育系統都有顯著的分別，有國家的執業藥劑師最低學歷要求是碩士，不代表香港要盲目跟隨。現時在香港，一般市民未有概念將藥劑師看成是醫療服務的第一線。由此可見，令藥劑師服務普及化是逼在眉睫的事，如果連人手都未夠，試問友方同學如何在社會當基層醫療的把關者呢？

因此，在社會人口老化的香港，將藥劑師的執業門檻提升到碩士學位只會令推廣基層醫療服務更為艱難，相信這是每位藥劑師都不想看見發生的事。為了將基層醫療健康服務帶給最廣泛的社會大眾，今日的辯題是絕對不成立的。謝謝各位！

正方第一副辯 (劉瑋濤, 香港中文大學)

主席、評判、友方同學、在座各位：

正如我方主辯所說，藥劑師的功能在於把關，而事實上提升學歷要求至碩士對藥劑業個人、業界、社會及國際四方面都能帶來益處。

就個人層面方面，碩士學歷的藥劑師可以更有效應付他們的工作。現時學士課程有所不足，根據近年香港中文大學對藥劑學學士舊生的一項調查，高達八成二的受訪者於學士畢業後有繼續進修其他課程，當中六成半受訪者表示是由於學士課程不足以提供工作所需的能力。因此碩士課程能為藥劑師提供實用性強的培訓，彌補學士課程的不足，幫助他們更有效地發揮他們的角色。

在業界層面方面，碩士學歷能提升藥劑業的整體質素。更高學歷的藥劑團隊讓市民對整個行業的服務均信心提升，對藥劑業勢必有更高的期望。這進一步能提升藥劑業在香港的地位及重要性，加強業界發展潛力。眾所周知，藥劑業在香港仍存在很大的發展空間，例如屈臣氏和萬寧等大型連鎖店近年大幅度擴展藥劑業務，醫院亦擴展臨床藥劑服務。在可見的未來，藥劑業的擴張將會更急速，例如最近討論愈漸熾熱的醫藥分家，屆時對藥劑師的知識水平勢必有更高要求，學歷更高的藥劑師有助準備應付業界的迅速發展及改革。

在社會層面方面，碩士學歷能提升藥劑師提供的藥劑服務質素。作為醫療團體的一份子，藥劑師可以擔任更積極的角色，提供專業的藥物知識，令病人得到更優質的醫療服務。

就國際層面方面，更高學歷的藥劑團隊能提升香港藥劑業在世界的聲望。英美等藥劑業發展蓬勃的先驅分別以碩士及博士作為執業藥劑師的最低資格，提升藥劑師學歷要求能拉近與藥劑業先進的國家的距離。

基於藥劑碩士為執業藥劑師最低要求所帶來的四大方面好處，我方認為今日辯體絕對成立。

反方一副（潘誠皓, 香港大學）

主席、評判、友方同學、在座各位，大家好！

友方同學認為將執業門檻提高至碩士學位能夠與國際接軌，這個理由是不合理的。培訓一名藥劑師需要花上一定資源，難道要把納稅人的錢來迎合外國的需要嗎？應把這些投資回饋給香港的納稅人。何況美國、英國都不要求外藉人士持有碩士或博士學位，該申請人只需持有他本國最低學歷資格，就符合成為當地的藥劑師的要求，它們的註冊要求只是一個考試。這證明了外國都認為知識經驗比名函重要。現行香港醫院亦從學士畢業生中挑選人才，這亦證明學歷只是被錄取的入場券，醫院重視的是學歷以外的條件，如溝通技巧、工作經驗、工作熱誠等。

2010年，美國藥劑教育期刊發表了一篇研究報告，指出在美國，一個已實行醫藥分家50多年的國家，那兒的社區藥劑師理應更著重病人護理服務，即評估病人藥物需要及監察病人藥物治療等等。但原來以藥劑學士或藥劑博士為最高學歷的社區藥劑師都用了近70巴仙的工作時間用於配藥，而病人護理的時間都是只佔10巴仙。由此可見，有碩士或博士學歷與否對社區藥劑的工作沒有一個顯著的幫助，因為學士跟碩士都是集中於配藥的工作。

另外這份報告亦指出持有藥劑博士的醫院藥劑師分別用30巴仙的工作時間於配藥40巴仙的時間於病人護理，即評估病人藥物需要及監察病人藥物治療等等；而持有藥劑博士的社區藥劑師則用70巴仙於配藥，只有10巴仙於病人護理。社區藥劑師比醫院藥劑師投放更多的工作時間於配藥。我們亦可看出，社區藥劑師的工作性質與醫院藥劑師大有不同的，兩者有不同的技能要求。在社區藥房能夠還用碩士課程主要學習的臨床藥劑學的機會很少。

人各有志，我們應保留空間讓人選擇事業發展的路向，如果有藥劑師一心想透過社區藥房面對面地服務市民，我們不應強制他用多兩年時間讀一個對工作不太有大幫助的學位。而且碩士並非是提升藥劑師工作能力的唯一選擇，他們還可以選擇其他進修途徑，例如學習外語來服務更多種族的病人，或者讀工商管理課程可令社區藥劑師更易經營藥房。

總括來說，現時在香港把執業藥劑師的門檻由學士學位提升至碩士學位不但不能讓最多的市民直接受惠，更會奪去了現時學士學位能讓每位藥劑師可以選擇適合自己的進修途徑的彈性。因此辯題不能成立，謝謝各位！

正方第二副辯 (孫立希, 香港中文大學)

主席，評判，友方同學，在座各位，大家好！

剛剛我浪費了大家五秒鐘的時間，可是友方同學由主辯到第一副辯已經足足浪費了我們六分鐘的時間！友方同學由辯論比賽一開始做的事情只有三件——就是重覆、重覆與重覆——一些不設實際的憂慮。其實我真的非常感動，因為我看到友方同學都是跟我站在同一陣線上，他們都是非常重視藥劑行業對病人能做出的貢獻。可是，他們卻杞人憂天，認為現在藥劑師人數短缺，如果我們投放資源在碩士培訓，會解決不到眼前的問題，而且更是一種資源錯配的做法。

藥劑師人數不足，是不爭的事實，但是從友方同學的觀點，其實他們都認為藥劑服務質素上升是需要的，只是在眼前的情況下，放資源在碩士培訓是一種資源錯配的做法。友方同學說得很動聽，但是這只是一種轉移視線的做法。根據前中大藥劑學院副院長李炯前教授的說法，中大將於5年內逐步增加收生至60人。而貴校香港大學開辦藥劑學士課程，亦有助解決藥劑師人手不足的問題。所以，在可見的將來，人手不足的問題會逐步得到解決。

反之過來，在培訓更多人才之時，我們也需要注目於質素，著力提升人才的質素，進而令整個行業的質素更上一層樓。這是具備長遠的目光，為整個行業的提升而制定的大方向，而這也是辯題達到的目的。由此，顯然可見，友方同學提出資源錯的論點，只是他們嘗試轉移視線的造法。

或者上述的論述過於理論，友方同學難以理解。接著下來不如我們計計數，看看開辦碩士課程是否難於登天的事情。根據大學教育資助委員會公佈的資料，09/10年度每個碩士學位的成本是二十萬三千元。假設我們每年有六十個藥劑學士的學生，那麼二十萬乘以六十，就是一千二百萬元。我們看看，本年度財政預算案有七百一十九億盈餘，為一千二百萬的六千倍。而教育和醫療支出亦比起預期上升6%及9%，試問在有如此多的儲備和資源投入，只要藥劑碩士課程具有其意義，要付之實行時，何來沒有資源？所以本辯題的重點為此措施的需要性，談及資源問題只是友方同學嘗試施展的掩眼法！

友方同學亦談及學士課程的不足之處可由課程改動來解決，言下之意即是，由學士課程轉為碩士課程，只是巧立名目的做法。如果友方同學的課程改革是指課程增減，有增必有減，那就會削弱學士課程的基礎培訓，難以好好裝備藥劑師。如果友方同學指的課程改動是增加課程難度，那麼你們的做法只可以被形容為囫圇吞棗。香港的藥劑學士課程為3年，已經是全世界最短的課程，如果刻意再強化課程深度，學生難以在有限的時間內消化理解，結果只會造成生吞活剝、不求甚解。友方同學，原本大家只是需要在10分鐘內完成1份功課，但是如果突然要你10分鐘內完成10份功課，請問你會怎樣做好這些功課？

總括而言，友方同學的立論盡是不設實際的憂慮和轉移視線的論證，而我方已堅定指出提升至碩士課程的需要性，所以今日的辯題理應絕對成立，多謝各位！

反方二副（李詠兒, 香港大學）

主席、評判、友方同學、在座各位，大家好！

友方同學似乎相信高學歷必然增加市民

對專業人士的信心，然而，不久前有一名從三大院校畢業的碩士生見工200次都失敗，證明200個僱主都有同一觀點，就是高學歷不能必然給予人信心，僱主還會看經驗和溝通技巧。

現在市民不找藥劑師，問題的癥結不是市民嫌藥劑師學識不夠，而是不少市民未清楚了解藥劑師的角色，加上傳統觀念是有病就看醫生，自古如此，所以重點不是學歷。

友方同學又認為，高學歷能夠提高藥劑師的知識水平，因此提高學歷資格是必須實行的。但是友方同學有沒有想過追求知識是無止境的，博士比碩士又更有學識，如果友方同學認為認受性是要靠提升學歷資格來達到的，那根據友方同學的邏輯，你們的支持的辯題應為藥劑博士學位應為香港執業藥劑師的最低學歷要求。友方同學能否告訴我們為何你們又支持將門檻定在碩士學位而不是博士學位呢？

明顯地，友方同學都贊成一個學歷所帶來的知識水平並非唯一考慮的因素。在追求無止境學知識的理想的時候，必須與現實之間取一個平衡。故此，友方同學用提高知識水平來支持提升執業門檻到碩士學位的理據是不成立的。

在討論今日的辯題的時候，必須清楚了解香港藥劑界當下最需要處理的問題。正如我方已經提到，香港藥劑師未能在社會普及化，加上人手不足的原因，當下之務應該增加人手，向港大市民推廣藥劑師的角色。提高執業門檻不但不能直接幫助處理這些問題，更令資源錯配，造成基層醫療普及化的目標又遠了一步。所以今日的辯題是不能成立的。謝謝各位！

正方結辯（林惠婷, 香港中文大學）

主席、評判、友方同學、在座各位：

在座各位未必人人也有自己的孩子，但是也應該知道當一個初生嬰兒不斷長大，需要的食物種類會多了，食量也會大了。藥劑也如是，當藥劑業界不斷發展，其涵蓋的範圍以及所需要的知識也會相應增加。藥劑師，作為掌握和主宰藥劑界前途和命運的主人翁，是否有需要也順應趨勢，增值自己呢？

其實友方同學今日從沒有否認過我們該朝著提升藥劑師學歷和質素這個大方向邁進，他們只是擔心執行上的細節問題，例如人手不足。我住在香港的，也了解香港的情況，亦知道兩間大學已經在增加藥劑課程的學位和投放更多資源以培訓藥劑師。友方同學，撇除這些可以解決的細節問題，今日辯題所提倡提升藥劑師學歷這個長遠的大方向，到底應不應該做？

其實友方同學不斷強調藥劑師需要前線工作，以及他們所講基層醫療服務化的方向，其實友方與我方的發展方向並無衝突，反而正是因為藥劑師要站在前線推廣醫療服務，因此他們的角色更為重要，亦更有提升質素的需要。我方提倡要在藥劑的碩士課程內強化實用性強的知識，例如保健產品、中成藥、臨床用藥等等一些在學士課程學得比較少和不夠深入的課題，而這些亦正是前線藥劑師所必需接觸的層面。

友方主辯有兩句說話說得很好，「要因時制宜，按實際情況而行」，我方絕對認同。就是正正因為我方了解和明白現時的實際情況和問題，看到現行的課程不足以裝備藥劑師應付未來的工作需要，所以才支持提升學歷。其實友方同學也承認了課程的不足，但是他們卻認為改善課程已足以解決問題，但事實又是否如此呢?相信在座各位對藥劑的課程一定不陌生，眾所周知，現時三年的藥劑學士課程內容已經十分緊湊，友方同學聲稱可以以三年的時間學習在我方提倡的方案下一樣的知識，換言之，原來友方同學要多加足足一年的課程內容，要加就必要減，請問友方同學認為在現時的三年制下，有哪一年是可以減的?有哪些部分哪些課堂是沒有用可以不讀的?若然不減，那有多少的空間可以增加課程，可以增加什麼？

事實上，友方同學將碩士課程視作一個「名銜」，是完全忽略了碩士課程的重要性，學士課程是著重基礎的知識，而碩士課程則是配合執業需要，這亦是碩士與友方同學一直提及的博士課程的分別，碩士是應用性的，博士卻是研究性質的。

其實說到底，友方同學反對辯題，是因為碩士課程不是最基本，不是一定必須的，言下之意，是否也認為實習也可以不用呢?實習只是讓你更清楚將來的工作，也沒有任何特別新的知識必須要學的。但是相信在座各位曾經實習過的，也會明白實習的重要性，也會認同有實習的需要。同樣地，友方同學，在座各位，藥劑的課程不是可免則免，沒有迫切需要的就不教，而是當我們看到這個課程這些知識技能大大幫助他們面對將來工作會經常遇到的問題，或是能為他們奠定將來工作的基礎的，這就為之有需要。正因如此，我們才需要在畢業年做專題，才會在暑假到醫管局做義工，才會畢業後要去做實習。面對藥劑業界的發展，現時的學士課程已經漸漸不能應付發展的趨勢了。我們需要藥劑碩士課程，因為我們需要的，市民需要的，不是藥物的奴隸，而是好像在座各位般，是藥物的主人。

嬰兒只是飲奶不會長大，我們需要多給他們一點營養，他們才能健健康康地成長。在此我方也但願香港的藥劑業能快高長大，蓬勃發展！

反方結辯（伍庭發, 香港大學）

主席、評判、友方同學、在座各位，大家好！

所謂誰知盤中飧，粒粒皆辛苦。香港政府投放在藥劑界教育和醫療上的一分一毫皆是香港市民的血汗錢，不應該有任何浪費，而這些服務的對象亦應為香港普羅大眾。

今日的辯題正正違背了這個原則——它除了窒礙藥劑界人手的增長，限制了基層醫療的發展外，亦降低了藥劑師進修的彈性，導致資源錯配。

藥劑師作為其中一位重要的基層醫療提供者，其發展進程應該與基層醫療互相配合。根據政府近年的施政及財政報告，政府將推廣基層醫療定為醫療改革的大方向。根據我方已提到，培訓一名藥劑碩士卻要用到培訓幾名藥劑學士的資源。

把執業的基本資格提高到碩士其實正剝削藥劑師數目的增長，限制了基層醫療的普及化，這與政府和業界擴充基層醫療的方向是南轅北轍。

另外，就衞生署2009年醫療衞生服務人力統計調查，於1251名執業藥劑師中，有近6成半人士從事私營機構工作。從第一副辯所提供的資料，在這些機構工作的藥劑師無論是學士還是持有更高的學歷，他們的工作其實都大致相同。有見及此，於藥劑碩士課程中涉取的知識在這些環境中並無用武之地。

再加上，現時全部醫院藥劑師都已經為藥劑碩士，將執業門檻提高亦無助改善醫院藥劑服務的質素。如果今天的辯題成立的話，那麼政府每年就要花費大量資源於對執業無實則用途的教育上，浪費了社會的寶貴資源。

相反，將執業的最低要求定為學士的話，藥劑師的發展就能更加有彈性。藥劑師可以在有志成為醫院藥劑師的時候才修讀碩士課程，而其他種類的藥劑師就能更早投入服務大眾的工作，並且，有更大的空間去根據興趣和需要選擇自己事業發展的路向。例如，工商管理或者外國語言等。這樣可以讓藥劑師的發展更加多元化，觸及到更多社會不同的層面，從而充分達到資源的彈性運用。

名銜的追求是無止境的，當達到某一個名銜就希望追求更高、更多既名銜。要釐訂一個執業的最低資格應該從大眾利益、經濟和實質用途出發。因此，今日的辯題是絕對不成立的！謝謝各位！

Pharmacy Education and Trainings in Asian-Pacific Region: How Good are the Hong Kong Programmes in Comparison to Nearby Countries?

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ABSTRACT

This paper compares the pharmacy education and trainings of Hong Kong to those of selected countries in the Asian-Pacific region. Although the entry level to the bachelor of pharmacy course meets the international standard and requirement, trainings offered to students in the existing programme are inadequate. Pharmacy curricula in the Hong Kong programmes are too focuses on the practices in hospitals. It hasn't equipped students with sufficient knowledge on basic life sciences for a specialized field at the advance level. It is suggested that the number of credits taken by students should be increased by 30-40% and the length of study should be extended. Expertise in the teaching staffs should also be diversified in order to cope with the trends of specialization in pharmacy practices in the 21st Century.

Keywords: *Pharmacy education; Training programme; Expertise; Hong Kong; Asian-Pacific region; Specialization*

INTRODUCTION

A pharmacist is a person whose job is to prepare medicines and sell or give them to the public in a drugstore or in a healthcare facility, like a hospital, nursing home, mental health institution and clinic.[1] A pharmacist has many duties. Dispensing drugs that physicians prescribe to patients is probably the most obvious job of most pharmacists. Educating consumers about medications is also part of their routine duty.[2] Hence, whoever works as a pharmacist has to provide expert advice on the use, preparation and effects of drugs and medicines.

Increasingly though, those who train pharmacists are also engaged in non-traditional types of pharmacy work. Some pursue in research for pharmaceutical manufacturers, for example in the formulation of new drugs and assessment of their effects. Others work in sales or marketing, providing clients with expertise on the use, effectiveness, and possible side effects of drugs. In recent years, because so many biopharmaceuticals have been discovered and are being introduced everyday, a pharmacist will also have to advise physicians on possible drug interaction and effects.[3] On top of these duties, pharmacists have to maintain good medical records and medications in their practices in order to be certain that a patient is not using drugs that should not be mixed.

Because a pharmacist's duties could vary greatly and encompass aspects of practices and medicines that one would not traditionally think about some years ago, the contents of pharmacy education and trainings have been reshuffled and modified.[4,5] Like any other educational trainings, some pharmacy programmes are even tailor made to fit the need of their own society. During the early 1990s, when Hong Kong people were preparing for the return of Hong Kong sovereignty to China, all three professional bodies of pharmacists, i.e. the Pharmaceutical Society of Hong Kong, the Practising Pharmacist Association of Hong Kong and the society of Hospital Pharmacists of Hong Kong as well as the manufacturing and wholesaling sectors projected that a serve shortage of manpower of qualified pharmacists would occur. Therefore, a new pharmacy school was established in 1992 with a mission envisaged to produce competent pharmacists for upgrading the competitiveness of manufacture of Western drugs and Chinese medicines and other services.[6] More recently, another pharmacy school in Hong Kong University has also launched. With these two pharmacy programmes both claiming to produce qualified pharmacists for local needs, do they really fulfill the expectations? Have their course designs really produced the right manpower to meet the demands in comparison to the graduates produced by nearby countries? In this article, the authors try to answer these questions through a systematic comparison and anslysis of the courses offered by these different institutes. It was found that the courses offered leave room to be improved.

METHODOLOGY

Selection of Institutes for comparison

Institutes were selected from countries in the Asian-Pacific region. These countries cover Australia, Bangladesh,[7] China,[8] Hong Kong, Japan, Taiwan,[9] Thailand,[10] UAE[11] and USA. From each country, one pharmacy programme except Hong Kong, was chosen for compartive study. The later covers the programmes offered by two Universities. The programmes chosen were normally from one of the best departments or schools for training pharmacists in their home country.

Parameters of comparison

The comparison covers length of schooling; numbers of credits required prior to taking part in registration examination; the diversity and the nature of courses offered; core courses and pre-registered trainings leading to specialized themes were also considered.

RESULTS AND DISCUSSION

Length of schooling

Table 1 shows the schooling years for training a student to become a pharmacist in each country within the Asian-Pacific region. The schooling time of USA is listed as a reference in order to contrast the differences. In general, the schooling years are not significantly different between the countries. Some countries,

such as Japan, Taiwan and Thailand are diverting to a PharmD programme and the length of study is no different from USA while pharmacy training in the rest of Asian-Pacific countries still retains a four year programme. Nevertheless, no institute offers the bachelor degree of pharmacy to student in less than 16 years of schooling.

Requirement of courses taken prior to registration

By analyzing the BPharm programme of different countries in the Asian-Pacific countries, it reveals that the Hong Kong programmes share some common characteristics (Table 2). First of all, total credit units of professional courses required for graduation are comparatively low; only 73 credits are required. In comparison to the requirements of other similar professional trainings in nearby countries, such as Japan, which has a requirement of108 credits (Kyoto University) and Taiwan whose requirement is for 95 credits (NDMC). Hence, the training being given to students in Hong Kong may be inadequate.

The inadequate training becomes more obvious when the total number of training hours and the variety of courses offered in the curricula are simultaneously taken into account. Table 3 shows that there are 26 and 28 pharmacy related courses offered by CUHK and by HKU, respectively. The relatively limited number of courses offered reflects not only that areas of expertise in the school are narrow but also indicates that some kinds of imbalance in training or perhaps, a fragmentary course structure, may be embedded in the programmes.

Nature of courses offered

During the programme analysis, it was found that courses relevant to life and applied science share quite a big proportion except for the courses offered by institutes in Hong Kong; nearly one third of all courses provided are regarded as belonging to basic life sciences (Table 3). Hence, life sciences rather than chemistry subjects have emerged to become the dominant components in pharmacy education today. However, only 20% of the courses offered by CUHK and by HKU are related to basic life sciences (Fig.1 & 2). Students would find it difficult to do advanced study in the area of drug discovery and pharmaceutical sciences because of inadequate trainings in these areas. Therefore, solid education and trainings in basic life sciences should not be overlooked.

Table 1. Comparison of schooling years in different pharmacy education systems.

Schooling	Australia	Bangladesh	China	Hong Kong	Japan	Taiwan	Thailand	UAE	USA
High School & Elementary School	12	10	12	13	12	12	12	12	12
Intermediate College	0	2	0	0	0	0	0	0	0
Pre-Pharmacy College	0	0	0	0	0	0	0	0	2-4
BPharm	4	4	4	4	4 to 6[c]	4	5	4.5	3
PharmD	N/A	N/A	N/A	N/A	N/A	2[b]	1	N/A	3
Total (year)	16	16	16[a]	17	16-18	16-18	18	16.5	17-20

a: In China 3 year related experience is required for registration after graduation.

b: The name of the course is called "Master of Clinical Pharmacy" but upon graduation, a titile of PharmD is granted.

c: The 6-year programme allows graduate to be registered as a clinical pharmacist.

Table 2. Number of credits required prior to take part in registration examination

Name of Institution	Level	Credit Required prior to Graduation				Total
		GE and Language	Pre-Pharmacy	Professional Courses	Professional Practices	
NDMC	BPharm	37	81		14	132
KU	BPharm	32	26	60	22	140
CUHK*	BPharm	3	12	43	18	76
HKU*	BPharm	N/A	N/A	N/A	N/A	N/A
FDU#	BPharm	804 hr (53)	1209 hr (67)	932 hr (52)	N/A	2945 hr (172)
RAK	BPharm	18	9	106	15	148
MU	PharmD	36	17	160	12	225

* A 3-year programme plus 1 year training

The courses in this programme are indicated as hours instead of exact credit units; figure in the bracket is a rough calculation of total credit based on an assumption that one third of the courses are practicals and each two hours of practical exercises for one semester is equivalent to one credit.

NDMC = National Defense Medical Center (Taiwan); KU = Kyoto University (Japan); CUHK = The Chinese University of Hong Kong (Hong Kong); HKU = The University of Hong Kong (Hong Kong); FDU = Fudan University (Shanghai); RAK = RAK Medical and Health Sciences University (UAE); MU = Mahidol University (Thailand)

N/A = Information not available yet

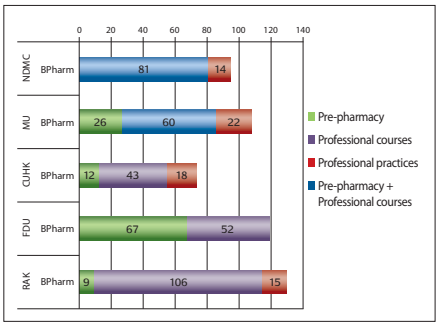

Figure 1. *Distribution of credit units categorized according to the nature the courses of pharmacy education offered by different institutes (General education is not counted)*

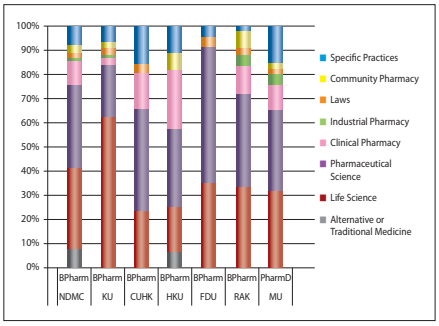

Figure 2. *The percent distribution of courses in each pharmacy programmes offered by different institutes*

Table 3. Distribution of training in term of course nature relevant to specialized fields of pharmacy practice

Name of Institution	Level	Alternative or Traditional Medicine	Life Science	Pharmaceutical Science	Clinical Pharmacy	Industrial Pharmacy	Laws	Community Pharmacy	Specific Practices	Total Number of Courses
1. NDMC	BPharm	5	20	21	6	1	1	2	5	61
2. KU	BPharm	0	46	16	2	1	2	2	5	74
3. CUHK*	BPharm	0	6	11	4	0	1	0	4	26
4. HKU*	BPharm	2	5	9	7	0	0	2	3	28
5. FDU	BPharm	0	8	13	0	0	1	0	1	23
6. RAK	BPharm	0	14	16	5	2	1	3	1	42
7. MU	PharmD	0	28	30	9	4	2	2	14	89

Note: General education courses and language courses are not counted.

NDMC = National Defense Medical Center (Taiwan); KU = Kyoto University (Japan); CUHK = The Chinese University of Hong Kong (Hong Kong); HKU = The University of Hong Kong (Hong Kong); FDU = Fudan University (Shanghai); RAK = RAK Medical and Health Sciences University (UAE); MU = Mahidol University (Thailand)

HKU and CUHK provide 1 year training before graduation, the quantities of practical training hours may be underestimated base on this figure.

Recently, there have been a couple reports indicating one of the major problems of current pharmacy education is that biopharmaceutical biotechnology and genetic engineering are overlooked.[4,7] Biotechnology is essential knowledge for today's healthcare professionals because most novel drugs discovered or produced in recent years have been derived from biotechnological studies. For example, the production of recombinant subunit vaccines, peptide drugs, antibiotics, hormone etc, is all belong to this category. Besides, the knowledge of biotechnology, other newly established knowledge and technologies due to a multidisciplinary approach, such as bioinformatics, high content drug screening, computer-aided drug design, applied genetics and molecular pharmacology, are emerging and are becoming essential innovative tools for drug discovery. Pharmacists, who claim themselves experts of drug, could not be competent professionals without this kind of knowledge. It is, therefore, the responsibility of an institute engaged in pharmacy education and training to provide such vital knowledge for today's youth who prepare to be a pharmacist. The current curricula of CUHK and HKU appear to be inadequate in this aspect; both programmes consist of only one biomedicine course and no professional bioinformatics course offered. In the curriculum of pharmacy programme of Kyoto University, bioinformatics and applied genetics are actually important elective courses; ten biology courses (three cores and seven electives) are offered as one major theme of the pharmacy programme in order to meet the rocket like development of biopharmaceuticals.

CONCLUSION

Courses offered at school of pharmacy are normally designed to teach a student to become a pharmacist or a professional mastering pharmaceuticals, such as drug therapy and manufacturing. When the two local BPharm programmes are analysed separately, some unique features are observed. The programme promoted by HKU is claimed to be more clinically orientated while CUHK's programme puts equal emphasis on trainings in both community and clinical practice. None of these two institutes has complete courses on the discovery and manufacturing of drugs. Since the outbreaks of SARS, avian flu and more recently, swine flu, it is reasonable to give more weighting to clinical and community pharmacy. These two specialized practices are, indeed, the hot areas in pharmacy education worldwide. However, whether this development trend is the right track for both local institutes remain arguable. According to some figures disclosed by Fudan University, about 13.7 and 7.6% of pharmacy graduates in year 2003 and 2004, respectively, were employed by hospitals during the period when SARS was a threat. Since then only 3.2% of pharmacy (MS) graduates from Fudan University could find jobs in hospital in subsequent years while nearly 40% and 25% of graduates, respectively, found jobs in the manufacturing sector and research institutes. This data suggests that there is a limited number of jobs available in hospitals to work as a clinical pharmacist in China. In the coming decade, the situation of employment in Hong Kong won't be better than that in mainland China unless the roles of prescribing and dispensing are separated and implemented here. Otherwise, the current mode of pharmacy training in Hong Kong may create more not-required professionals resulting in more unemployed people. On the bases of this analysis, there is an urgent need to diversify pharmacy education so that the supply of manpower for the pharmaceutical sector in Hong Kong can be sustainable and maximized.

In other Asian nations, such as Japan and Taiwan, the registration requirement for a clinical pharmacist is very punctilious. In these two countries, a six-year period of professional education and a sufficient amount of training are required. While in China, the requirement is even harsher; it requires three-years related job experiences before one can be registered as a pharmacist. Contrary to these nearby countries, the requirement of pre-registry working experiences is rather short for a local pharmacy graduate; only three-years of education and a year of on-the-job training are required. Due to the less sufficient training in both education backgrounds and practical experiences, local pharmacists may not be able to handle any crisis that may arise during execution of their duties in a clinical ward as efficiently as a clinical pharmacist from other counties.

Although the job nature of a pharmacist has been known for centuries as chemists, the things handled by a pharmacist in these days are not necessary a synthetic chemical substance. They could be biological materials or products. However in the local pharmacy programme, the weighting of courses relevant to biological aspect is quite small. The programmes consist of little contents related to Chinese medicines or recombinant pharmaceutical products. Nowadays, the Hong Kong government is promoting the idea of development of a centre of Chinese medicine in Hong Kong. A lot of modernized Chinese medicines have to be standardized, manufacturing facilities have to be brought and installed, pharmacological activity at molecular levels has to be explored alone or in combination with drugs and foods. Job opportunities for people who are expert on the quality assurance of Chinese medicines are, therefore, increasing. These posts require people possessing professional trainings and knowledge in Chinese medicines and biopharmaceuticals. On top of these, demands for experienced peoples to operate modern facilities and equipment are also growing. If the programme has no Chinese medicine and biopharmaceutically related courses, the graduates will have less chance to get jobs in these emerging areas.

Author's background

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Paediatric Nutrition: Breastfeeding and Infant Formula

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ABSTRACT

In recent years, both local and mainland mothers have been found scrambling in community pharmacies in the New Territories to buy infant formula. In fact, the superiority of breastfeeding over formula feeding is well recognised internationally. Breastfeeding not only supports the growth and development of infants but enhances maternal health as well. However, on occasion, if certain infant or maternal medical conditions hinder breastfeeding, infant formula, including cow milk-based formula, soy formula and hypo-allergic formula, might be indicated as an alternative feeding method. Components in infant formula generally approximate those in human milk but qualitative and quantitative differences are inevitable. In addition, scientific evidence proofing functions of individual components or superiority of one brand over another is not always available. Pregnant women and mothers might not be able to access or evaluate relevant information before making informed decisions. In this regard, pharmacists are professionals evaluating the claims of the manufacturers and guaranteeing compliance with the International Code of Marketing of Breast-Milk Substitutes.

Keywords: *paediatric nutrition, breastfeeding, infant formula, formula feeding, milk powder, galactosaemia*

INTRODUCTION

The melamine milk scandal was unfolded in mainland China two years ago but the fear of adulteration has never faded. Despite a series of government crackdowns on food safety, some batches of tainted supplies have been found on sale in China since 2008.[1] Terrified mainland mothers are found to have flocked across the border to procure milk products, in particular, in community pharmacies in the New Territories.[2]

While continuing education of the pharmacy profession usually encompasses pharmacotherapy, traditional Chinese medicine, dietary supplements, cosmetics and even toiletries, milk powder for paediatric nutrition ("formula") constitutes one of the many shelves that deserve more attention in future.

Attempts to produce breast milk substitutes date back to the mid-19th century.[3] Production of formula was still in embryo and home mixing of raw materials might be required. In the last century, nutrition technology has evolved to allow the supply of formula in powder form as a widely accepted feeding method around the world.

BREASTFEEDING

In fact, the World Health Organization (WHO) recognises the supremacy of breastfeeding in paediatric nutrition and recommends exclusive breastfeeding, i.e. feeding of breast milk exclusive of other food and drink, for the first six months after birth.[4] Complementary foods are introduced thereafter with breastfeeding uninterrupted up to the age of two or beyond.

In brief, breast milk represents the gold standard for infant nutrition and supports the optimal growth and development of infants.[5]

In terms of energy and nutrients, breast milk provides what an infant needs for his or her first months of life.[4] Compared to cow milk and formula, human milk may contain nutrients in lower concentrations yet in more bioavailable forms.[6] For example, calcium and phosphorus in human milk are bound to digestible proteins and in complexes and ionised states. Likewise, although there is less iron in human milk than in cow milk, lactose and ascorbic acid in human milk facilitate iron absorption and increase iron bioavailability.

In addition to merely nutritional aspects, breast milk is also known to improve the gastrointestinal function in infants.[6] Certain components in human milk, including bioactive factors, glutamine, nucleotides and interleukin-10, may exert specific roles in the maturation of the gastrointestinal tract. In particular, unabsorbed lactose may contribute to softer stools and epidermal growth factors form part of a surveillance system that is responsible for repairing mucosal injury.

Other constituents in human milk, including sIgA antibodies, lactoferrin, lysozyme, oligosaccharides, growth factors, macrophages, neutrophils and lymphocytes, are thought to strengthen host defence.[6] Through lactation, maternal sIgA antibodies and therefore passive immunity are transferred to breastfed infants. In addition, the structure of oligosaccharides in breast milk resembles that of certain bacterial antigen receptors and therefore decreases bacterial attachment to the mucosa. Consequently, breastfeeding may protect breastfed infants against a wide range of paediatric diseases, including diarrhoea, otitis media, urinary tract infection and necrotising enterocolitis.[6, 7]

Notwithstanding the advancement of knowledge in human milk, the complexity of human milk makes it difficult, if not impossible, for scientists to duplicate the composition of human milk.[8] For example, the whey-to-casein ratio in human milk is 70:30 while that in cow milk is 18:82.[6] Whey proteins are generally more easily digested than casein proteins, thus making human milk

proteins more bioavailable to infants. Although it is possible to adjust the whey-to-casein ratio in formula to approximate that in human milk, the types of whey and casein proteins in the two remain significantly different.[8]

Meanwhile, the act of breastfeeding contributes to the health and wellbeing of mothers per se. It saves mothers time and effort in sourcing and preparing milk powder products.[9] Breastfeeding mothers lose weight more rapidly.[4, 6, 7] Epidemiological studies have shown that breastfeeding decreases the incidence of premenopausal breast cancer and ovarian cancer and possibly the risk of late onset osteoporosis. Lactation also delays the return of fertility in most mothers and help to space children. Finally yet importantly, breastfeeding provides warmth and closeness to both mothers and infants and enhances the maternal-infant bonding.[9]

Despite the convincing evidence supporting breastfeeding, the rates of breastfeeding around the world are far from satisfactory. According to the results of the Centres for Disease Control and Prevention National Immunization Survey in the United States, about 43.5% of children born in 2006 were breastfed at six months of age while only around 13.3% were exclusively breastfed for the first six months after birth.[10]

In Hong Kong, the Department of Health has endorsed the WHO recommendations in exclusive breastfeeding and complementary feeding.[7] The regular breastfeeding survey conducted by the Family Health Service in Maternal and Child Health Centres reveals that 74% of children born in 2008 had a history of being breastfed and 13% of infants four to six months old were exclusively breastfed.

CONTRAINDICATIONS TO BREASTFEEDING

Breastfeeding is not always recommended in all infants and mothers. There are a few possible contraindications.

Some of them are related to infant health, for example, galactosaemia. Infants with galactosaemia are deficient in galactokinase or galatose-1-phosphate uridyl transferase and cannot metabolise galactose.[6, 11] If they are breastfed, lactose, the major carbohydrate in human milk, may elevate the galactose blood level and eventually cause cataract, hepatic cirrhosis and mental retardation. They are therefore advised to avoid breast milk as well as lactose-containing formula. Infants with other inborn errors of metabolism, like phenylketonuria and maple syrup urine disease, may opt to receive breast milk supplemented with formula low in the nutrients concerned.

Others are related to maternal health. Indeed, breastfeeding is only contraindicated in cases of severe maternal illness, such as heart failure or serious kidney, liver or lung disease.[11] It is also recommended that women receiving certain anti-metabolite chemotherapy or ingesting drugs of abuse should not breastfeed.[6] Nevertheless, mothers with non-aggressive depression, urinary tract infection, tuberculosis or common viral diseases like rubella, chicken pox, measles and mumps, are generally allowed to breastfeed as long as they are receiving treatments accordingly.

Pharmacists and other healthcare professionals must understand that few true contraindications to breastfeeding exist, for example, breast abscess is not an absolute contraindication because the mother may continue breastfeeding at the non-infected breast.[11] It is also necessary to distinguish between infants who are contraindicated to human milk and those who are contraindicated to feeding at the breast. A typical example is that breast milk is still the food of choice in infants born with a cleft lip or cleft palate, even though they may not be able to create the negative pressure necessary for breastfeeding.

INDICATIONS FOR THE USE OF INFANT FORMULA

The American Academy of Pediatrics has proposed three indications for the use of infant formula: as a substitute (or supplement) for human milk in infants whose mothers choose not to breastfeed (or not to do so exclusively); as a substitute for human milk in infants for whom breastfeeding is medically contraindicated and as a supplement for breastfed infants whose intake of human milk is inadequate to support adequate weight gain.[8]

Nowadays preference of mothers is probably the single most important factor in the initiation of formula feeding. Employment has been associated with lower rates of initiation and duration of breastfeeding in some studies.[8] It is also possible that the superiority of breastfeeding over formula feeding is under-recognised by the public. On occasion, mothers may confuse lactation failure with "perceived milk insufficiency".[11] Indeed, even in the case of true lactation failure, mothers are advised to continue breastfeeding in view of the overwhelming benefits of breastfeeding.

To safeguard the appropriate use of breast milk substitutes, the WHO published the International Code of Marketing of Breast-Milk Substitutes in 1981.[12] The Code guides the labelling, marketing and distribution of breast milk substitutes with the aim of providing adequate information to mothers, in particular, the benefits of breastfeeding and the hazards associated with formula feeding.[13]

CLASSIFICATION OF INFANT FORMULA

There is a wide range of infant formula on the shelves and they differ qualitatively and quantitatively. A standard of infant formula is available in the Codex Alimentarius, a collection of Food and Agricultural Organization/World Health Organization food standards, guidelines and codes of practice.[14] The United Nations advises governments to support and, as far as possible, adopt standards from the Codex Alimentarius but individual countries may opt for additional regulation.[15] For example, in the United States, the Food and Drug Administration inspect all production plants at least once a year and the legislation has specified the minimum levels of 29 nutrients and the maximum levels of nine.[8] The standard of infant formula in the Codex Alimentarius is summarised in Table 1.

In the Codex Alimentarius, infant formula is defined as a breast milk substitute specially manufactured to satisfy, by itself, the nutritional requirements of infants during the first months of life up to the introduction of appropriate complementary feeding.[14] The American Academy of Pediatrics has further classified infant formula into three major types.[8]

A large majority of infant formula

Table 1. Standard of Infant Formula in the Codex Alimentarius[14]

Nutrient	Unit per 100 kcal	Minimum	Maximum
Protein	g	1.8	3
Fat	g	4.4	6
Linoleic acid	mg	300	-
α-Linolenic acid	mg	50	-
Carbohydrates	g	9	14
Vitamin A	IU	200	600
Vitamin D	IU	40	100
Vitamin K	mcg	4	-
Vitamin C	mg	10	-
Thiamin (Vitamin B1)	mcg	60	-
Riboflavin (Vitamin B2)	mcg	80	-
Vitamin B6	mcg	35	-
Vitamin B12	mcg	0.1	-
Niacin	mcg	300	-
Folic acid	mcg	10	-
Pantothenic acid	mcg	400	-
Biotin	mcg	1.5	-
Choline	mg	7	-
Inositol	mg	4	-
L-carnitine	mg	1.2	-
Calcium	mg	50	-
Phosphorus	mg	25	-
Magnesium	mg	5	-
Iron	mg	0.45	-
Iodine	mcg	10	-
Zinc	mg	0.5	-
Copper	mcg	35	-
Manganese	mcg	1	-
Sodium	mg	20	60
Potassium	mg	60	180
Chloride	mg	50	160
Selenium	mcg	1	-

on the market are intact cow milk-based formula. In compliance with the previous indications, it is an appropriate substitute for feeding healthy, full-term infants during the first year of life.[8, 16] Although the composition of human milk provides a basis for the composition of infant formula, the manufacturers seldom attempt to duplicate the composition of human milk. Not only is it an impossible mission, careful consideration must also be given to allow heat treatment and reasonable shelf lives.

It is also common to find soy formula on the shelves. It is lactose free but otherwise similar in composition to cow milk-based infant formula.[8, 16] Certain components, for example methionine, are added to compensate for their low concentrations and poorer bioavailabilities in soy proteins. Soy formula is indicated for infants with intolerance to lactose or to milk protein, infants with galactosaemia and infants whose parents prefer a vegetarian diet. Acute gastroenteritis may induce lactose intolerance in some infants but it is generally safe to re-challenge them with a lactose-containing formula after one month. The presence of phyto-oestrogens in soy formula and their physiological activity may worry some parents. Nonetheless, in a comprehensive follow-up study conducted in the United States in 2001, no significant differences in pubertal development and reproductive outcomes have been identified between groups of 20- to 34-year-olds fed with cow milk-based and soy formula in infancy.

Hypo-allergic formula contains extensively hydrolysed proteins. It is more or less a mixture of free amino acids and short-chain peptides incapable of eliciting an immunological response in most infants.[8, 16] This formula is therefore preferred for infants intolerant of cow milk proteins and soy proteins. The major drawback to it is probably its poor taste in the presence of certain amino acids and peptides. Introduction in the early months of life before the sense of taste is well developed normally aid acceptance.

Follow-up formula is a type of milk powder distinct from infant formula.[8] It usually contains more proteins and minerals but is not necessarily superior to standard infant formula. Meanwhile, they may be beneficial to toddlers not receiving adequate amounts of nutrients in their diets.

Parents and healthcare professionals must be cautioned that full fat cow milk, low fat cow milk, skimmed cow milk and goat milk are not appropriate substitutes to meet infants' nutritional requirements.[8] In particular, they have less iron in a less bioavailable form and are associated with iron deficiency anaemia. On the other hand, the excess amounts of protein, sodium, potassium and chloride therein tend to increase the renal solute load. Consequently, they are not recommended for use in the first year of life.

Proteins

The Codex Alimentarius allows a range of 1.8 to 3.0 g of proteins per 100 kcal in infant formula but specifies that formula must contain a higher or equal amount of each essential and semi-essential amino acid than breast milk does.[14] The whey-to-casein ratio is not standardised and varies from formula to formula. As explained previously, compositional and functional differences between whey proteins in cow milk and in human milk exist even if the whey-to-casein ratio of one approximates that of another.[8] Each type of formula therefore results in a characteristic pattern of serum amino acid concentrations. However, the clinical significance of these patterns has not been demonstrated.

Lipids

About 40% to 50% of the energy in cow milk-based formula comes from fats therein.[8] The amount of fats in infant formula may range from 4.4 to 6 g per 100 kcal according to the Codex Alimentarius but commercially hydrogenated oils and fats must not be used.[14] Various types of vegetable oils are common raw materials in the production of a balance of saturated, monounsaturated and polyunsaturated fatty acids.

The Codex Alimentarius has also stated that formula must contain not less than 300 mg of linoleic acid and not less than 50 mg α-linoleic acid per 100 kcal.[14] Parents may be surprised to learn that docosahexaenoic acid (DHA) and arachidonic acid (AA), two of the most heavily promoted fatty acids, are not strictly required in infant formula. In fact, both preterm and full-term infants are capable of synthesising these long-chain polyunsaturated fatty acids from linoleic acid and α-linoleic acid.[8] They are constituents of retinal and brain phospholipid membranes

and are functionally associated with improved short-term visual function and neurodevelopmental outcomes in some studies.

Carbohydrates

Like human milk, cow milk and cow milk-based formula contain lactose as the major carbohydrate.[8] The Codex Alimentarius requires all infant formula to contain not less than 9 g and not more than 14 g of carbohydrate per 100 kcal.[14] The addition of sucrose and fructose in infant formula is principally avoided to minimise the risks of triggering potential life-threatening symptoms in infants with unrecognised fructose intolerance. In addition to providing energy for infants, some carbohydrates, for example oligosaccharides, are known to play a role in strengthening host defence.

Probiotics

Infant formula is sometimes fortified with probiotics. They are living "good" bacteria that are introduced in infants' intestines to limit the growth of "bad" organisms there and thought to diminish infections and inflammation.[17]

The most common types of probiotics are *Bifidobacterium* and *Lactobacillus*.[17] Studies have revealed that they may prevent or treat infectious diarrhoea and atopic dermatitis in children. However, whether probiotics can lower the risk of food-related allergies and asthma remains in question.

SELECTION OF INFANT FORMULA

Indeed, every manufacturer provides a rationale for formula composition but physiologically significant differences among the various products have rarely been demonstrated.[8] The American Academy of Pediatrics recommends healthcare professionals to rely on the results of clinical studies instead of on composition alone. However, clinical studies comparing individual brands are lacking, not to mention those conducted in Hong Kong or targeting at the Chinese population.

As in the case of many other over-the-counter products, there is no definite "algorithm" in recommending a particular brand over another. Sometimes reputation, price and promotions may take over as the prime concern. In this regard, accurate information from pharmacists is crucial to allowing an informed decision.

Exchange of information starts the moment a customer enters a pharmacy looking for formula. Prior to the sale of an over-the-counter antihistamine, asking about his or her past medical history is often the first move. It facilitates further counselling and helps build relationship. Likewise, pharmacists may enquire about the health of the infant as well as that of the mother. If no contraindications to breastfeeding apply, the pharmacist may introduce or reinforce the WHO recommendation that exclusive breastfeeding is the feeding method of choice for the first six months of life and discuss the feasibility of breastfeeding with the mother.[4] If breastfeeding is considered inappropriate or unfeasible, the pharmacist can then advise the mother on the various types of formula as appropriate.

Even though clear-cut superiority of one brand over another is rare, it lies with pharmacists to evaluate the composition and claims of each brand. On top of nutrients mentioned, new ingredients would only keep emerging. Whilst parents may lose their heads and go after them, pharmacists must uphold professionalism and critically assess the evidence available before recommendations are made.

At the same time, since pharmacies are distributors of breast milk substitutes, compliance with the International Code of Marketing of Breast-Milk Substitutes is obligatory.[13] No advertisement for breast milk substitutes, feeding bottle or teats shall be allowed in pharmacies. The Code also forbids the distribution of samples, gifts or utensils promoting the use of these products to pregnant women and mothers of infants.

CONCLUSIONS

Birth rate in Hong Kong has been falling in recent years, yet love and care from parents never dissolve. Whilst breastfeeding is internationally recommended as the feeding method of choice in infants, it might be difficult for parents to resist the possible edge of infant formula over human milk. However, it must be taken into consideration the possible harm of artificial infant formula. Community pharmacies constitute an extensive group of formula retailers and pharmacists working therein definitely play a pivotal role in the provision of safe and adequate nutrition for infants.

Author's background

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Diagnosis and Treatment of Herpes Simplex Virus Epithelial Keratitis

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ABSTRACT

Herpes Simplex Virus (HSV) can affect the eye as a primary, latent or secondary infection. Ocular manifestations can involve the adnexa, conjunctiva, cornea, anterior chamber or the retina. HSV keratitis is a leading cause of infectious corneal blindness with vision loss largely due to its recurrent nature. This case discusses the presentation and therapeutic management of a patient JK, who presented with a red right eye associated with photophobia. Visual acuity in the right eye was reduced to 6/24. Slit lamp examination showed a characteristic dendritic ulcer with positive staining of rose Bengal and fluorescein. JK was diagnosed with herpes simplex virus epithelial keratitis and was treated with 3% acyclovir ointment. JK was managed successfully. The following case study discusses the disease classification, differential diagnoses, epidemiology and therapeutic treatment.

Keywords: *epithelial keratitis, viral infection, herpes simplex virus, acyclovir treatment*

INTRODUCTION

Keratitis is inflammation of the cornea, which can arise as a result of infectious or non-infectious agents. The hallmark of infectious keratitis is a defect in the corneal epithelium with underlying inflammation of the corneal stroma arising from infection by a foreign organism. These organisms could be bacteria, viruses, fungi or protozoa.[1] Occurrence is acute with significant pain and distress. Infectious keratitis is a potentially blinding medical emergency requiring prompt diagnosis and treatment.

In all infectious eye diseases, epithelial keratitis is the most common form of ocular disease, which is due to the infection of herpes simplex virus (HSV). Epideriologic data indicate a prevalence of ocular HSV disease in 149 people per 100,000 population in the United States. HSV can be found in almost every human society throughout the world. Liedtke et al. (1993) found traces HSV in almost all the trigeminal ganglia of cadavers over the age of 60 years.[2] A unique feature of HSV is its ability to present as a primary or latent infection. The virus can remain dormant in the trigeminal ganglia for some time after a primary infection, allowing for periodical reactivation. During active infection, HSV ocular complications can include blepharitis, conjunctivitis, corneal and intraocular infection and retinitis.

Herpes simplex keratitis (HSK), as shown in Fig. 1, is a significant ocular disease and is known to be the leading cause of infectious corneal blindness in the developed world.[3] Whilst there is some confusion in the terminology used to describe HSK, disease entities can be classified as epithelial keratitis, neurotrophic keratopathy, stromal keratitis, necrotising stromal keratitis, disciform keratitis or endotheliitis and keratouveitis.[4] Epithelial disease is further subdivided into dendritic ulcers, geographic ulcers and metaherpetic disease. The characteristic signs of HSV epithelial keratitis are the presence of a dendritic corneal ulcer and reduced corneal sensation. Diagnosis can be confirmed using laboratory testing.

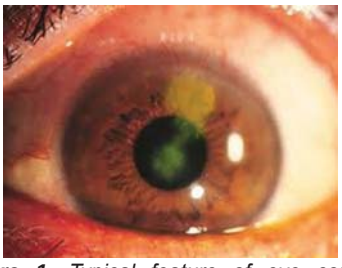

Figure 1. *Typical feature of eye corneal infection due to herpes simplex virus.*

DEVELOPMENT OF TREATMENT FOR EPITHELIAL KERATITIS

Treatment of ocular keratitis was initially based on recounting experience. Bloodsheding, purgatives, and poultices were used for hundreds of years. Various cauterizing and curettage methods have been applied (Table 1). Analgesics and patching were commonly recommended at the beginning of last century. Topical corticosteroids, introduced in 1950, were found to worsen corneal destruction when applied during active epithelial keratitis. In the early 60's, Kaufamn reported the successful use of idoxuridine in HSV epithelial keratitis. The effectiveness of idoxuridine subsequently led to the development of other pyrimidine and purine analogues, such as vidarabine and trifulridine. All these antiherpetic nucleotides were found to undergo phosphorylation by cellular kinases to form nucleoside triphosphates that bind to virally encoded DNA polymerase and other enzymes. More recently, acyclovir was developed to be selectively activated in virus-infected cells by virally induced thymidine kinase and to selectively inhibit viral DNA polymerase.

Today, treatment of HSV epithelial keratitis is generally with topical or oral antivirals and the drug of choice is acyclovir, which selectively targets virus DNA and has shown a low toxicity. Other antiviral drugs such as vidarabine and trifluridine are also used but not as common as acyclovir.

CASE REPORT

A 53 year-old Caucasian female, JK, presented to an optometry clinic with Herpes Simplex keratitis. Her keratitis responded very well to Zovirax ointment

JK first presented with a moderately painful, photosensitive right eye with decreased vision with an onset of one week. She mentioned a history of cold sores around the eyelids and lips. On examination, visual acuities measured R: 6/24 and L: 6/7.5^{-}. On slit lamp examination herpetic ulcers were seen on the right cornea staining with both rose Bengal and fluorescein (Fig. 2 and 3).

Table 1. Different types of recorded treatments for HSV epithelial keratitis

Physical Methods of Currettage: Cryoapplication, with or without mechanical debridement; Mechanical debridement with swab, metallic instrument, or corneal impression; Thermocauterization with electrocautery, steam cautery, or diathermy	**Antiseptics and Other Chemical Agents:** Acetyl cysteine; Bismuth tribromophenate; Boric acid and boroglycerin solutions; Calomel dust; Catgut; Citral; Cupric sulphate solution; Epinephrine; Ergotamine and dihydroergotamine; Ethoxyphenylphenacylaminobenzoic acid; Formyltriiodide; Gamma globulin, IgG, or F-fragment; Glutathione; Heparin solution; Hydroxyethylbiguanide; Leukocyte extract; Mercuric ammonium chloride; Mercuric oxide; Mercurochrome (merbromin); Methylsalicylate; Placental extract; Polyinosinic-polycycytidylate; Procaine and other anaesthetics; Quinine bisulphate; Silver nitrate and silver protein solutions; Strychnine; Tocopherol; Undecylenic acid; Xenalazone; Zinc oxide; Zinc sulfate
Chemical Cauterizing or De-epithelializing Agents: Chlorinated water; Chromic acid; Cupric sulphate; Ethanol; Ether; Formalin; Hydrogen peroxide; Iodine, potassium iodide, sodium iodide, and/or ethyliodide in alcohol or water solution or as vapour; Lactic acid; Para-aminobenzene; Phenol; Silver nitrate; Trichloroacetic acid; Turpentine; Urea	**Antibiotics:** Chloramphenicol; Chlortetracycline; Cycloserine; Lysozyme; Neomycin; Optochin; Oxolinic acid; Penicillin; Streptomycin; Sulfadiazine; Tetracycline; Viomycin
Surgery: Argon laser; Conjunctival flap; Corneal incision; Keratocentesis; Massage; Tarsorrhaphy	**Systemic Agents:** Amphetamine; Antibiotics and antivirals; Autoinoculation of corneal isolate; Bee venom; Benzylbenzimidazone; Brewer's yeast; Campolon; Cowpox; smallpox and typhoid vaccines; Growth hormone; Iosprinosine; Lactoflavin; Levamisole; Liver extract; Milk injection; Panthesine; Quinacrine; Snake venom toxoid; Sodium bicarbonate; Sodium iodide; Thymostimulin; Transfer factor; Uric acid; Vitamins A, B1, B6, B12, C, D, niacin, riboflavin and paraaminobenzoate; Xenalamine; Whole blood injection
Radiation: Electric current; Radioactive cobalt; Radioactive strontium; Shortwaves; Ultrviolet light; without or with dyes; Visible light; X-rays	
Photoreactive Dyes: Fluorescein; Methylene blue; Neutral red; Proflavine; Rose Bengal; Scarlet red	
Enzymes: Chymotrypsin or trypsin; Hyaluronidase; Ribonuclease	
Antimetabolic Agents: Actinomycin; Benzylbenzimidazole; Puromycin; Carbocyclic oxetanocin G; Cytarabine; Diphenylsulfone; Ethionine; Ethyldeoxyuridine; Florenal; Fluorodeoxyuridine; Glucosamine; Iododeoxycytidine; 5-Mercaptouracil; Methisoprinol; Methylaminodeoxyuridine; Oxymethylmethyluracil; Parafluorophenylalanine; Propyldeoxyuridine; Reticulose; Riboazauracil; Riodxolate; Tromantadine; Tyrothricin	

JK was prescribed 3% acyclovir ointment one drop in the right eye five times a day for two weeks. A one-week review was scheduled. Upon one-week review, the right eye was no longer photophobic or painful, however vision was still poor. On examination, the cornea had healed apart from some fine punctate corneal staining. (Fig. 4) JK was advised to continue with acyclovir ointment five times a day and a review was scheduled for 2 weeks.

Upon the second review, there was a mild discomfort and foreign body sensation. Vision measured R: 6/7.5$^-$ and L: 6/7.5$^-$. Corneal examination was unremarkable aside from inferior punctate staining. This was considered to be a reaction to the acyclovir ointment. Acyclovir ointment was discontinued and JK was prescribed systane lubricants. Another review was organised for 2 weeks time. At the final optometric review, the cornea was clear and vision measured R and L 6/6.

DIFFERENTIAL DIAGNOSIS

Typically HSV epithelial keratitis is diagnosed from the distinguishing features of dendritic ulcers and reduced corneal sensitivity. These ulcers have a characteristic linear-branching appearance with terminal bulbs at the end and stain distinctly with fluorescein, Rose Bengal and Lissamine Green. Enlargement of the ulcer may occur, particularly with inappropriate steroid use, leading to a geographic ulcer.[5] Often in HSV related keratitis the corneal sensation is reduced due to the neural involvement of HSV. In one study, 80% of HSK cases showed a loss of corneal sensitivity.[6]

Careful clinical examination and history taking remains the most vital component for the accurate diagnosis of HSK. However, diagnosis can be further confirmed by laboratory investigation. Studies have shown that using a combination of polymerase chain reaction and immunohistochemistry increases the specificity for the diagnosis of HSK to 97%.[7,8]

The differential diagnoses for HSV epithelial keratitis include corneal abrasion, herpes zoster keratitis, acanthamoeba keratitis and keratitis medicamentosa. Each of these can mimic the appearance HSK with pseudo-dendrites; however these can be eliminated via clinical signs and history.[9] Corneal abrasions often present with a history of trauma and significant pain or irritation. In this case, JK did not have a history or trauma or significant pain. She was diagnosed with HSV epithelial keratitis in the right eye on the basis of the characteristic epithelial defect and positive history of previous herpes infection. However, no laboratory tests were performed.

Herpes zoster keratitis mainly affects elderly patients and presents with associated painful unilateral skin lesions on the forehead and nose which respect the mid-line. The pseudo-dendrites of zoster keratitis end in tapered ends without terminal bulbs and do not stain

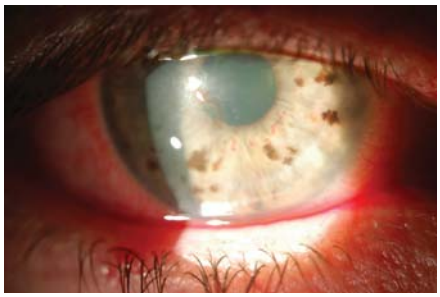

Figure 2. *Herpes simplex virus epithelial keratitis stained with rose Bengal*

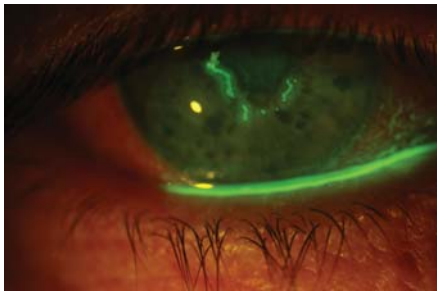

Figure 3. *Herpes simplex virus epithelial keratitis stained with Fluorescein*

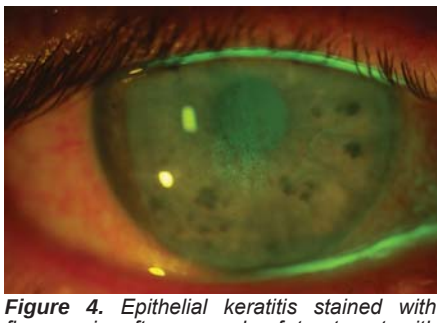

Figure 4. *Epithelial keratitis stained with fluoroscein after a week of treatment with acyclovir ointment*

well with fluorescein.[5,9] JK did not present with any skin lesions and her dendrites had clear terminal bulbs.

Acanthamoeba keratitis is often misdiagnosed as HSV due to the presence of pseudo-dentrites. Symptomatically, acanthamoeba keratitis can be differentiated from HSV because patients often present with severe pain and a history of contact lens wear, while keratitis medicamentosa presents with a history of toxicity reaction with certain topical medications.

THERAPEUTIC TREATMENT

JK was managed with acyclovir 3% ointment 5 times a day for 3 weeks. After 3 weeks keratitis was resolved and treatment was ceased.

The goal of HSV treatment, to shorten the course of herpetic eye disease, can be achieved by physical or chemical removal of viral particles, or the prevention of further viral replication. Currently there are many physical, chemical and antiviral agents available for the treatment of HSV. Historically, before the development of antiviral drugs, virus particles were removed with epithelial debridement and cauterization. In the early 1960s an antiviral drug, idoxuridine, was introduced and replaced debridement as the main therapy for ocular HSV.[10] There are currently 6 antiviral drugs with proven efficacy in ocular HSV: idoxuridine, vidarabine, trifluridine, acyclovir, famciclovir and valacyclovir.[11] In a systematic review, Wilhemus (2008) concluded that all currently available antiviral agents were essentially equal in the effective treatment of HSV. It was also proposed that antiviral nucleosides used in conjunction with debridement or interferon accelerated healing.[10]

Acyclovir

Topical acyclovir is currently the first drug of choice in the treatment for HSV epithelial keratitis. This is because action is specifically targeted at viral enzymes leading to relatively low toxicity.[12] Acyclovir is a guanine derivative that interacts exclusively with herpesvirus thymidine kinase producing a nucleoside which inhibits HSV DNA polymerase.[13] According to one study by Christophers et al., it was reported that drug resistance does not seem to be a significant problem, with only negligible incidences reported.[14]

Prolonged use of topical medications can result in toxic side effects, particularly when the drops are used for longer than 2 or 3 weeks at full dose. Effects can include allergic blepharodermatitis, follicular conjunctivitis, superficial punctate keratitis (SPK), toxic epithelial ulceration, lacrimal punctal occlusion, anterior segment ischemia, and interference with wound healing (Shearer & Bourne 1990).[15] After one week of treatment, JK had minimal toxic reaction with fine SPK. This was resolved once the treatment ceased.

Acyclovir is also available in oral form. Collum et al (1986) has shown that oral acyclovir at 400 mg five times per day provided a similar therapeutic result to 3% topical acyclovir.[16] Oral treatment provides a useful alternative if topical treatment is contraindicated or if patient compliance is an issue.

Alternative therapies

Alternative therapies for HSK include other topical, oral or intravenous nucleoside antivirals and interferon montherapy. If acyclovir resistance presents as a problem intravenous foscarnet may be considered.[17] Access to topical foscarnet in Australia is limited, however this may be an avenue for future enquiry. Interferon monotherapy was shown to have a similar efficacy to antiviral therapy. Furthermore, it was shown that combined interferon-nucleoside therapy yielded promising results.[18]

Although Ganciclovir is not yet available in Australia, it may provide an alternative therapy in the future. It has been shown to have similar properties and efficacy to acyclovir.[19]

Prophylactic treatment

Oral acyclovir has been suggested for prophylactic use to decrease the rate of recurrences in persistent ocular HSV disease. A 400 mg dose taken twice daily for one year showed a 45% lower risk of recurrence compared to placebo.[20-22] Recurrences in 12 patients is reported to have decreased from 39 in 2 years without treatment to 3 recurrences in 2 years with 200 mg twice a day.[23] However, this prophylactic benefit is only seen when treatment is maintained and therefore could present a significant financial burden. In this case, prophylactic management was not deemed necessary as it was JK's first ocular manifestation of ocular HSV. Prophylactic treatment may be reconsidered if there were frequent recurrences in the future.

As a part of management, JK should be made aware of the recurrent nature of HSV infections. She should be advised to return promptly if symptoms should recur. Prompt treatment will help to reduce the potential for corneal scarring.

DISCUSSION

HSV ocular disease is one of the leading infectious causes of corneal blindness in the Western Hemisphere.[24] A study in Rochester reported an annual incidence of ocular HSV cases at 20.7 per 100,000 people and a prevalence of 149 people per 100,000 population.[25] In another more recent study, Labetoulle et al. (2005) estimated a higher incidence of 31 per 100,000 people per year.[26]

Ocular HSV may manifest in the lids or conjunctiva, however, corneal disease remains most significant due to its potential for vision loss.[27] Epithelial keratitis is the most common manifestation of ocular HSV, making up approximately 70% to 80% of all cases.[25,26] Studies have estimated the prevalence of HSV epithelial keratitis to be approximately 15 to 20 per 100,000 people per year.[25,26]

HSV keratitis generally occurs as a unilateral condition. However, there are varying frequencies of bilateral ocular HSV reported in the literature due to the differing definitions of bilateral disease. Liesegang (2001) found bilateral involvement in 10-12% of cases.[28] Eight variations of human herpes viruses have been distinguished, namely, HSV-1, HSV-2, varicella zoster virus, cytomegalovirus, Epstein-Barr virus and human herpesvirus 6, 7, and 8 (Miyagawa et al. 1999).[29] Ocular manifestations of herpes are usually due to HSV-1 although HSV-2 may infect the eye as well (Khan & Pavan-Langston 2004).[11] HSV-1 has been found to be responsible for 78% to 98% of HSK cases in older children and adults (Hamrah et al. 2009).[24]

Infection or transmission of HSV is via direct contact with infected lesions or virus containing secretions.[11] Once infection has occurred, HSV can manifests as either active replicating infection (in non-neuronal cells) or latent infection (primarily in neuronal cells).[27] After initial infection the virus travels through the sensory nerves and establishes a site of latency, most commonly at the trigeminal ganglion. In this manner, HSV can remain dormant and undetected by the host immune system. During latency there is no active viral replication, however, small amounts of viral RNA called latency-associated transcripts are produced. LAT is thought to play an important role in the reactivation and recurrence of HSV infection.[27]

Ocular complications can manifest as a result of primary or recurrent infection, however, primary HSV infections are often asymptomatic.[28] In one study, recurrence rates of ocular HSV were estimated at approximately 10% at 1 year reaching over 60% at 20 years.[25] Vision loss in HSV infection is largely due to its recurrent nature (HEDS 2000). This is due to the increasing opportunities for corneal scarring with each recurring episode. Liesegang et al. (1989) found corneal scarring occurred in 18-28% of ocular HSV cases.[25]

Potential triggers for recurrent attacks have been suggested including: upper respiratory tract infection, fever, sunlight, seasonal conditions, emotional factors, psychological stress, trauma and menstruation. However, the HEDS group (2000) has suggested that these studies were unreliable.[21,22] Their study reported no correlation between psychological stress and recurrence. Furthermore, in their more recent study (HEDS 2001) they did not find any significant causal factors or triggers in ocular HSV recurrence.

Epithelial disease generally resolves, however sequelae include persistent punctate epithelial keratopathy, recurrent corneal erosions or granularity.[27] Damaged corneal nerve function can lead to neurotrophic keratopathy which can occur due to damaged corneal nerve function.[30] In advanced stages this leads to decreased visual acuity, stromal scarring, corneal neovascularisation and perforation.[30] It has been reported that 25% of people develop stromal keratitis or iritis after epithelial keratitis.[10] In addition to structural damage to the cornea, visual loss in ocular HSV can result from keratitis, uveitis, cataract or glaucoma.

CONCLUSION

HSV epithelial keratitis is a manageable corneal infection. The prognosis with immediate and appropriate treatment is generally good. Treatment is aimed at minimising corneal scarring and subsequent vision loss. HSV epithelial keratitis can resolve spontaneously within 1-2 weeks. With antiviral therapy healing time speeds up to 7-10 days. Several factors have been reported to delay the healing such as: large epithelial defects, longer duration of symptoms, peripheral location of defect, presence of stromal inflammation and viral resistance.[18] In this case, JK's episode of HSV epithelial keratitis was uncomplicated and responded well to therapy. This was JK's first ocular manifestation of ocular HSV.

Author's background

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Growth Inhibition and Cell Cycle Arrest Effects of Oolong Tea Polyphenol Extract on Human Hepatoma and Prostate Cancer Cells

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ABSTRACT

The antioxidant activities of polyphenolic antioxidants in green tea, jasmine, pu-erh and Oolong tea were compared. The anti-proliferative effects of tea polyphenol extract on human prostate cancer cells DU145, hepatocellular carcinoma cells HepG2 and hepatic carcinoma cells WRL68 were evaluated. Results indicated that, Oolong tea exhibited the highest antioxidant activities compared to other teas. The growth of cancer cells was efficiently suppressed by the polyphenolic components in the extract after 48 h of incubation, showing dose dependency. According to the results of MTT assay, IC_{50} was 45.8 μg/mL in DU145, 31.2 μg/mL in HepG2 and 18.8 μg/mL in WRL68, respectively. Higher concentration of Oolong tea polyphenol extract (over IC_{50}) induced typical apoptosis morphological changes, and triggered cell cycle arrest at S phase and G2/M phase in DU145 cells, S phase in HepG2 cells and G2/M phase in WRL68 cells, respectively. The apoptosis inducing effects were confirmed by Annexin V/PI and JC-1 flow cytometry analyses. After Oolong tea polyphenol treatment (at concentration equal to IC_{80}), the proportion of early apoptotic cells increased from 4.18 to slightly over 75% in HepG2 cells, 7.5 to 45.61% in WRL68 cells and 2.78 to 9.68% in DU145 cells, respectively. Collapse of mitochondrial membrane potential was observed in all three types of cancer cells, indicating one of the earliest features of apoptosis. In conclusion, higher concentration (over IC_{50}) of Oolong tea polyphenols extract could efficiently inhibit or slow down the growth of human hepatoma and prostate cancer cells, via the induction of cell cycle arrest and apoptosis.

Keywords: *Oolong tea, antioxidant, cell proliferation, cell cycle, apoptosis*

INTRODUCTION

Tea, derived from the leaves of *Camellia sinensis* plant, is one of the most popular beverages consumed all over the world.[1] According to different manufacturing procedures, tea is generally classified into three categories; i.e. the un-fermented green tea, the semi-fermented Oolong tea and the fully fermented black tea. Flavan-3-ols, namely catechins, is the primary polyphenolic antioxidant in green tea, which includes (−)-Epigallocatechin-3-gallate (EGCG), (−)-Epicatechin-3-gallate (ECG), (−)-Epigallocatechin (EGC) and (−)-Epicatechin (EC).[1] Theaflavins and thearubigins have been reported to be the major bioactive constituents in black tea.[2] The former compound consists of group of theaflavin (TF1), theaflavin-3-monogallate (TF2A), theaflavin-3' -monogallate (TF2B), and theaflain-3, 3'-digallate (TF3).[3] Bioactive ingredients like gallic acid, caffeine, theobromine and other polyphenols in tea are isolated and identified as well.[4]

The abounding polyphenolic antioxidants in tea are generally thought to be responsible for the reputed health beneficial effects on human, like the reduction of risk of cancer and cardiovascular disease,[5, 6] the control of body weight [7, 8] and a newly reported genoprotective function.[9] Tea polyphenols can exert beneficial health effects on bone density, dental cavities, kidney stone[10] and neurodegenerative diseases (Alzheimer's and Parkinson's diseases) etc.[11] Extensive evidences indicate that free radicals are the major contributors to aging and degenerative diseases of aging, such as cancer, cataract, cardiovascular disease, immune system decline and brain dysfunction.[12] By scavenging free radicals, antioxidants play a vital role in cell proliferation inhibition via modulation of cell-signaling pathway, such as the interruption of cell cycle regulation, inhibition of proliferation and induction of apoptosis etc.[13,14]

Apoptosis cell death can be characterized by morphological and biochemical changes, such as cytoplasm shrinkage, chromatin condensation, DNA degradation and the formation of apoptotic bodies etc.[15] According to literal reports, apoptosis involves several molecular pathways: (a). extrinsic pathway that involves transmembrane receptor-mediated interactions, in which the receptor consists of TNF-α/RNFR1, FasL/FasR, Apo2L/DR4, Apo2L/Dr5 and Apo3L/Dr3;[16] (b). intrinsic pathway (namely mitochondrial pathway), which involves the collapse of mitochondrial membrane potential and the release of pro-apoptosis proteins, such as cytochrome c, HtrA2/Omi and Smac/DIABLO, AIF, endonuclease G and CAD;[17] (c). perforin/granzyme pathway that involves secretion of the perforin accompany with the release of cytoplasmic granules into target cell;[18] (d). execution pathway, the last step of apoptosis that involves the activation of caspase 3 and the degradation of DNA by endonucleases.[19]

There have been extensive literatures about tea polyphenolic antioxidants and their anti-proliferative effects on various cancer cells.[20-23] To evaluate the growth inhibitory effects of tea polyphenols on human hepatoma and prostate cancer cells, the antioxidant activities of different

teas were compared and the anti-proliferative effects were further studied by investigating cell viability, cell-cycle distribution and apoptosis induction.

MATERIALS AND METHODS

Materials and Chemicals

Samples of Rickshaw® (Unilever Hong Kong Ltd., Hong Kong SAR, PR China) green tea, pu-erh, jasmine and Oolong tea were purchased from local supermarket. Standard vitamin C, 2,6-Dichlorophenol indophenol (DCPIP), (−)-epigallocatechin-3-gallate (EGCG), 3-(4,5-dimethylthiazol-2-yl)-2,5–diphenyl tetrazolium bromide (MTT),5,5',6,6'-tetrachloro-1,1',3,3'-tetraethylbenzimidazol carbocyanine iodide (JC-1), carbonyl cyanide-chlorophenylhydrazone (CCCP), Annexin V-GFP and prodium iodide (PI) were purchased from Sigma Chemical Corporation. All chemicals used were analytical grade.

Tea and tea polyphenols extract preparation

Different types of tea leaves (4g) were brewed with 150 mL distilled water at 100°C for 4, 8, 12, 16 and 20 min, respectively. Water extracts were filtrated through filter paper and stored at -20°C before usage. For tea polyphenols extraction, water extracts were filtrated through 0.22 µm filter paper and concentrated with a rotary evaporator, followed by freeze-drying. The crude extracts were stored at -20°C until further use.

Antioxidant activities assay

The antioxidant activities of various types of tea were assayed by DCPIP (2,6-Dichlorophenol indophenol) titration and colorimetric method. For the former assay, 1 mL DCPIP (0.025%) was titrated with water extract of tea until the color of DCPIP solution changed from dark blue to colorless. For the colorimetric analysis, 100 µl DCPIP (0.05%) was added by 100 µl antioxidant with different concentrations and immediately mixed for 5 seconds. The absorbance was monitored at 595 nm with a UV- VIS spectrophotometer.

Cell culture

Three human cell lines including prostate carcinoma cell line (DU145), hepatocellular carcinoma cell line (HepG2) and hepatic carcinoma cell line (WRL68) were used. They were purchased from the American Type Culture Collection (Rockville, MD, USA). Cells were cultivated in medium consists of 10% heat-inactivated fetal bovine serum (Gibco BRL, Gaithersburg, MD, USA), 100 units/mL penicillin (Rotex, Germany) and 100 µg/mL streptomycin. Cells were incubated at 37°C in a humidified atmosphere of 5% CO_2 in air.

Cell viability assay

To investigate the cytotoxicity of tea polyphenols extract, cells were subjected to MTT assay according to the method described by Li *et al*.[24] In brief, 5×10^3 cells in 200 µl medium were seeded into 96-well plate and incubated at 37°C for 24 h. Then cells were exposed to 100 µl tea polyphenols extract (0-100 µg/mL), followed by addition of 10 µl MTT dye solution. Cells were further incubated for 4 h, and then 100 µl DMSO was added to dissolve the formazan crystals. The absorbance was monitor at 570 nm with a microplate reader (Model 550, Bio-Rad, USA).

Cell morphological changes

Cancer cells were incubated with different concentrations of tea polyphenols extract (equal to IC_{20}, IC_{50} and IC_{80}) for 48 h. After incubation, cells were collected and stained with fluorescent dye Hoechst 33342 (5 µg/mL) for 20 min. The dyed cells were observed by fluorescent microscope (Zeiss Axioskop, Mikron Instruments, NY, USA) at wavelength range between 365 and 460 nm.

Cell cycle distribution analysis

Cell cycle analysis was performed by propidium iodide (PI) staining assay described by Fong *et al* with slight modification.[25] After 48 h of tea polyphenols extract exposure, cells were subsequently collected and fixed in 70% ethanol overnight at 4°C. After washing, cells were stained with DNA staining solution consists of 150 µg/mL PI, 5 µg/mL RNAse A, 0.1% NP-40 and 0.1% trisodium citrate for 40 min. The percentage of cells in sub-G1, G_1 phase, S phase and G_2/M phase were monitored under flow cytometer (Becton Dickinson Mountain View, CA, USA) with wavelength from 488 nm to 630 nm. Results were further analyzed by Modfit LT™ software (Verity Software House, Inc., Topsham, ME, USA).

Annexin V/ propidium iodide flow cytometry assay

To assess apoptosis cells, Annexin V/ propidium iodide (PI) test was performed as described by Wilkins *et al* with minor revision.[26] In brief, after 48 h of treatment, cells were pretreated with 0.5% Triton X100, and then incubated with 20 µl binding buffer and 5 µl Annexin V-GFP at 25°C in dark for 15 min. Cells were subsequently stained with 2 µl PI (1 mg/mL) and monitored under a flow cytometer. For positive control, cells were treated with 50 µM CCCP. Results were analyzed by WinMDI software (Joseph Trotter, Scripps Research Institute, La Jolla, CA, USA).

JC-1 mitochondrial membrane potential assessment

Mitochondrial membrane potential was measured by JC-1 reagent according to the method of Mathur *et al.* with slight modification.[27] Briefly, tea polyphenols treated cells were washed with PBS and subsequently added by 2 µl JC-1 (1 mg/mL), then followed by an additional incubation at 37°C in dark for 20 min. Cells were washed twice with ice-cold PBS and assayed using flow cytometer. The protonophore CCCP, an uncoupler of oxidative phosphorylation, is capable of abolishing the mitochondrial electrochemical gradient.[28] For positive control, cells were treated with different concentrations of CCCP (25, 50 and 100 µM). Results were analyzed by CellQuest software (Becton Dickinson Immunocytometry System, San Jose, CA, USA).

Statistical analysis

Data were expressed as mean ± standard deviation (SD) of three parallel measurements. Parametric ANOVA method was applied to represent significant difference with 95% confidence interval.

RESULTS AND DISSCUSSION

Antioxidant activities of different teas

The antioxidant activities of green, pu-erh, jasmine and Oolong teas gradually increased with the brew time, as fewer volumes of teas were needed to reduce the DCPIP solution (Fig. 1). In this work, 12 to 16 min of brew time appeared to be sufficient enough to extract most of the polyphenolic antioxidants in various types of tea, since the antioxidant activities remained the same as brew time further increased.

Interestingly, the antioxidant activity of Oolong tea was apparently higher than other teas over the entire brewing period, and the antioxidative capacities decreased in the order: Oolong > green tea > jasmine > pu-erh (Fig. 1). Polyphenols have been suggested to be the main antioxidants in tea and play a crucial role in the antioxidative reaction of tea.[29,30] The potent antioxidant activities in Oolong tea should be attributed to its abounding antioxidants. Moreover, the size and thickness of Oolong tealeaves were relatively smaller and thinner compared to others. Thus, the greater surface area of Oolong tealeaves might as well contribute to the higher efficiency in the extraction of polyphenolic antioxidants. Assay of infrared spectrum also showed relatively higher content of polyphenols in Oolong tea than others (data not shown), which were in accordance with the DCPIP results. Nonetheless, green tea has been reported to possess higher DPPH radical scavenging activities than Oolong tea,[31] while simultaneous HPLC determination suggested higher catechins content in green tea than Oolong tea.[32] Results of relevant researches on tea antioxidants might vary with species, season, preparation procedures and analysis methods involved etc.

The antioxidant activities of Oolong tea and the purified epigallocatechin gallate (EGCG) solution were further compared by colorimetric method, with vitamin C as reference. As shown in Figure 2, Oolong tea exhibited slightly higher antioxidative potential than the purified EGCG solution. Neilson *et al*. indicated that the majority of catechins in Oolong tea is EGCG, followed by EGC, ECG and EC.[33] Results obtained in this work might be attributed to the higher content of other polyphenols with smaller molecular weight in Oolong tea.[34]

Oolong tea polyphenols induce growth inhibition and morphological changes

Results of cytotoxicity of Oolong tea polyphenols on cancer cells were shown in Figure 3 and Table 1. As demonstrated in Figure 3, cell growth of HepG2, WRL68 and DU145 cells were efficiently inhibited, showing a clear dose-dependent response. Lower concentration of Oolong tea polyphenols (< 20 μg/mL) suppressed cancer cells proliferation, while higher concentration induced obviously cytotoxic effects. After 48 h exposure to Oolong tea polyphenols, the IC_{50} was 45.8 (HepG2 cells), 31.2 (WRL68 cells) and 18.8 μg/mL (DU145 cells), respectively (Table 1). It indicated that human prostate carcinoma cell (DU145) was more cytotoxic sensitive to Oolong tea extract than two hepatoma cancer cells.

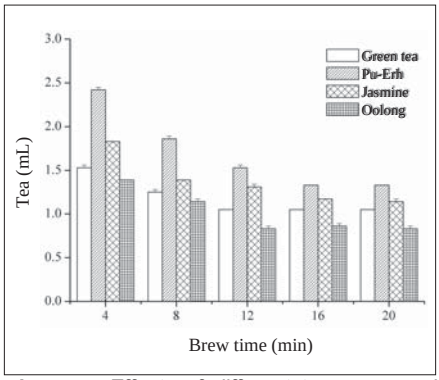

Figure 1. *Effects of different teas prepared from different brew time on the DCPIP reducing activities. Data were expressed as mean ± standard deviation (SD) of three independent experiments.*

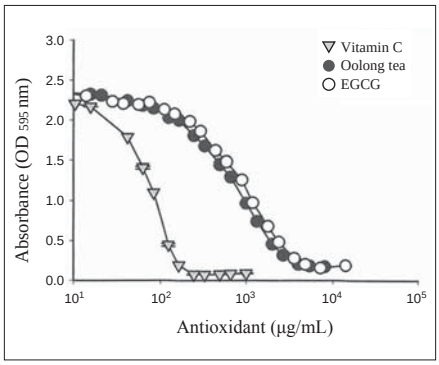

Figure 2. *DCPIP reducing activities of Vitamin C, Oolong tea and EGCG. EGCG: epigallocatechin gallate; Data were expressed as mean ± standard deviation (SD) of three independent experiments.*

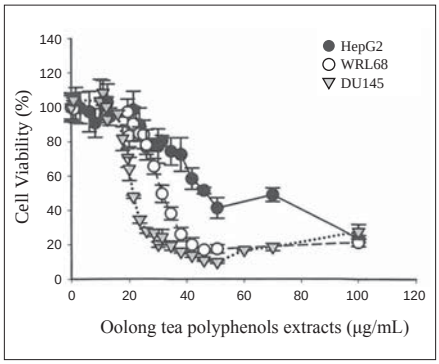

Figure 3. *Effects of Oolong tea polyphenols extract on cell viability of HepG2, WRL68 and DU145 cells. HepG2: human hepatocellular carcinoma cell line, WRL68: human hepatic carcinoma cell line, DDU145: human prostate carcinoma cell line; Cells were exposed to different concentrations of Oolong tea polyphenols extract for 48 h treatment. Data were expressed as mean ± standard deviation (SD) of three independent experiments.*

Cells morphological changes were illustrated in Figure 4. Apparent morphological changes were not observed in three types of cancer cells at lower concentration (equal to IC_{20} of Oolong polyphenols extract). Nonetheless, as concentration increased up to IC_{50} and IC_{80}, the shrinkage of cytoplasm, the condensation of chromatin, the fragmentation of nuclear and the formation of apoptotic bodies etc. were observed in cancer cells. These features represented the most characteristic morphological changes during apoptosis process.[15,16] Moreover, cellular DNA and RNA were differentially stained for the DNA and RNA content evaluation. As concentration of Oolong tea polyphenols extract increased up to IC_{50} and IC_{80}, the proportion of DNA was largely decreased in prostate cancer cell DU145 cells (Fig. 4A). In cancer cells undergoing apoptosis process, cellular DNA are gradually cleaved by endogenous ribonucleases and finally the mono- and oligo-nucleosome DNA fractions are formed.[16] Meanwhile, cellular RNA remains intact as being segregated from DNA,[35] which results in the increase of RNA proportion in apoptotic cells.

Oolong tea polyphenols induce cell cycle arrest

To investigate whether cell growth inhibitory effects involved the induction of cell cycle arrest, cells were subjected to cell cycle distribution analysis. As shown in Figure 5, Oolong tea polyphenols exposure caused an obviously increase in the proportion of sub-G1 phase in all three types of cells, which from 2.05 to 16.43% (about 8-fold) in DU145, 11.37 to 30.4% (around 3-fold) in HepG2 and 27.1 to 38.41% in WRL68 cells, respectively. Accumulation of cell population at sub-G1 phase represents the appearance of apoptotic cells that with DNA content less than 2*n*.[36]

Table 1. Growth inhibition effects of Oolong tea polyphenols extract on cancer cells

	Cell viability (%)	HepG2(μg/mL)	WRL68(μg/mL)	DU145(μg/mL)
IC_{20}	80	25.8	25.8	12.5
IC_{50}	50	45.8	31.2	18.8
IC_{80}	20	100	41.6	24.0

Cell cycle distribution assay revealed that, lower concentration of Oolong tea polyphenols (IC_{20}) would not trigger obvious cell cycle arrest, while higher concentrations (over IC_{50}) induced different increase trends in the proportion of S and (or) G2/M phase in three types of cancer cells. Incubation with 18.8 and 24 μg/mL Oolong tea extract obviously elevated the S and G2/M percentage and decreased the G1 proportion in prostate DU145 cancer cells (Fig. 5A), demonstrating the transition between the late S and early G2/M phase were partly blocked by Oolong tea polyphenols. Moreover, higher concentration of tea polyphenols (45.8 μg/mL, IC_{50}) treatment increased HepG2 cells population in S phase, from 24.5 in control up to 31.9% (Fig. 5B). For WRL68 cells, 41.6 μg/mL (IC_{80}) of tea polyphenols treatment increased G2/M phase ratio from 12.8 to 21.5%, accompanied with decreased G1 and S phase population (Fig. 5C).

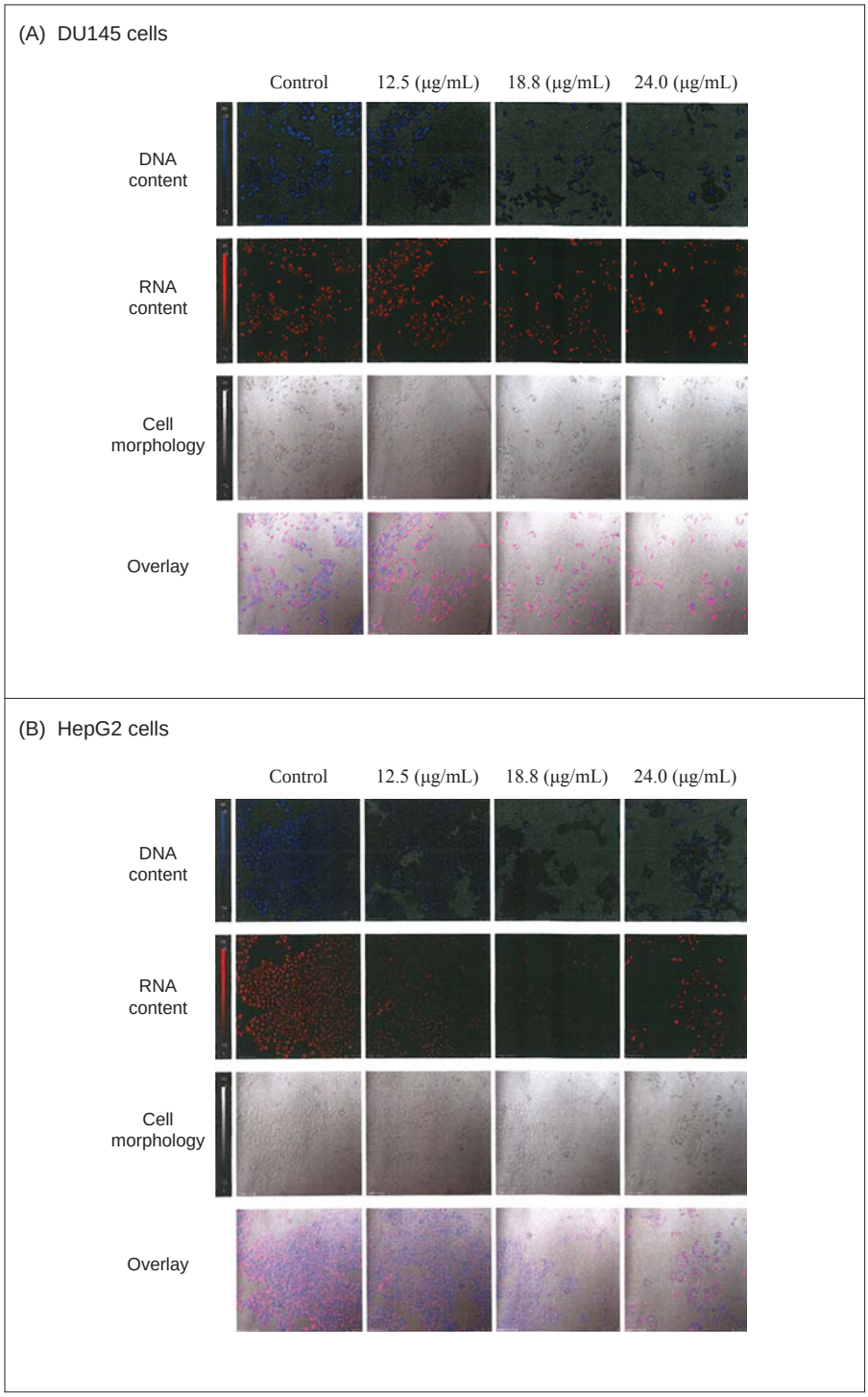

Figure 4. *Effects of Oolong tea polyphenols extract on cell morphology. Cells were exposed to different concentrations of Oolong tea polyphenols extract for 48 h treatment. Cell morphology was observed at 200 × magnifications.*

Epigallocatechin gallatein in tea has been reported to inhibit the growth of hepatoma cells by blocking the process of cell cycle at G1 phase, via the molecular pathway of p53 expression activation and p21 expression up-regulation.[22,37] By inducing cyclin kinase inhibitor that inhibits the cyclin-cyclin-dependent kinase complexes operative in the G1 phase, EGCG induced cell cycle arrest at G1 phase in human prostate carcinoma cells as well.[23] Different results might attribute to different cell lines and treatment conditions like concentration and time etc. To further investigate the molecular mechanisms of cell-cycle arrest in this work, more research works would be focused on the expression of relevant proteins that involved in the transition.[38,39]

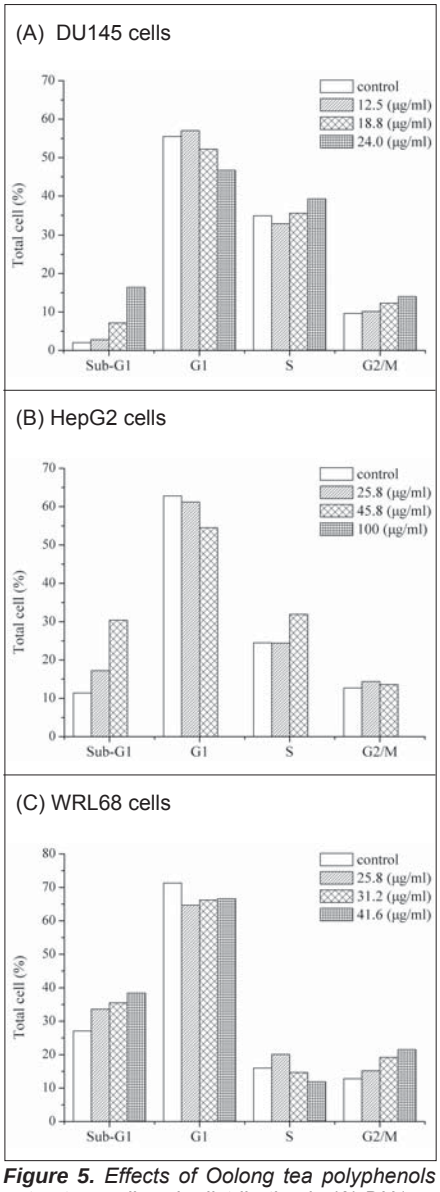

Figure 5. *Effects of Oolong tea polyphenols extract on cell-cycle distribution in (A) DU145, (B) HepG2 and (C) WRL68 cells. Cells were exposed to different concentrations of Oolong tea polyphenols extract for 48 h treatment. Results were representative of two independent experiments.*

Apoptosis-inducing effect assayed by Annexin V/PI staining

During the early process of apoptosis, the phosphatidylserine (PS) transfers from the inner plasma membrane to the outer cell surface,[15,16] then the exposed PS can be bonded by Annexin V, a phospholipid-binding protein with high affinity to phosphatidylserine.[40] At the initial stage of apoptosis, cell membrane remains intact and cells are PI dye exclusive; when necrosis occurs, cell membrane loses its integrity and cells are stained by PI.[15] Apoptosis were assessed by Annexin V/propidium iodide (PI) method using flow cytometry, in which damaged cells were recognized as Annexin V negative and PI positive, live cells were both Annexin V and PI negative, apoptotic cells were Annexin V positive and PI negative, while necrotic cells were both Annexin V and PI positive, respectively.

After treatment with 24 μg/mL (IC_{80}) Oolong tea polyphenols for 48 h, the population of apoptotic cells (Annexin V positive and PI negative) was slightly increased from 2.78 to 9.68% in DU145 cells. Meanwhile, same treatment dramatically increased the ratio of necrosis cells (both Annexi V and PI positive), from 4.76 in control up to 24.07% (Fig. 6A). For HepG2 cells, after 100 μg/mL (IC_{80}) tea polyphenols treatment, the proportion of apoptotic cells significantly increased up to slightly over 75%, from the initial level of 4.18% in control (Fig. 6B). When incubated with 41.6 μg/mL (IC_{80}) of Oolong tea polyphenols, the proportion of apoptosis increased from 7.5 to 45.61% in WRL68 cells as well (Fig. 6C). The increased percentage of Annexin V positive and PI negative cells indicated the early apoptosis-inducting effects of Oolong tea polyphenols at concentrations over IC_{50}.

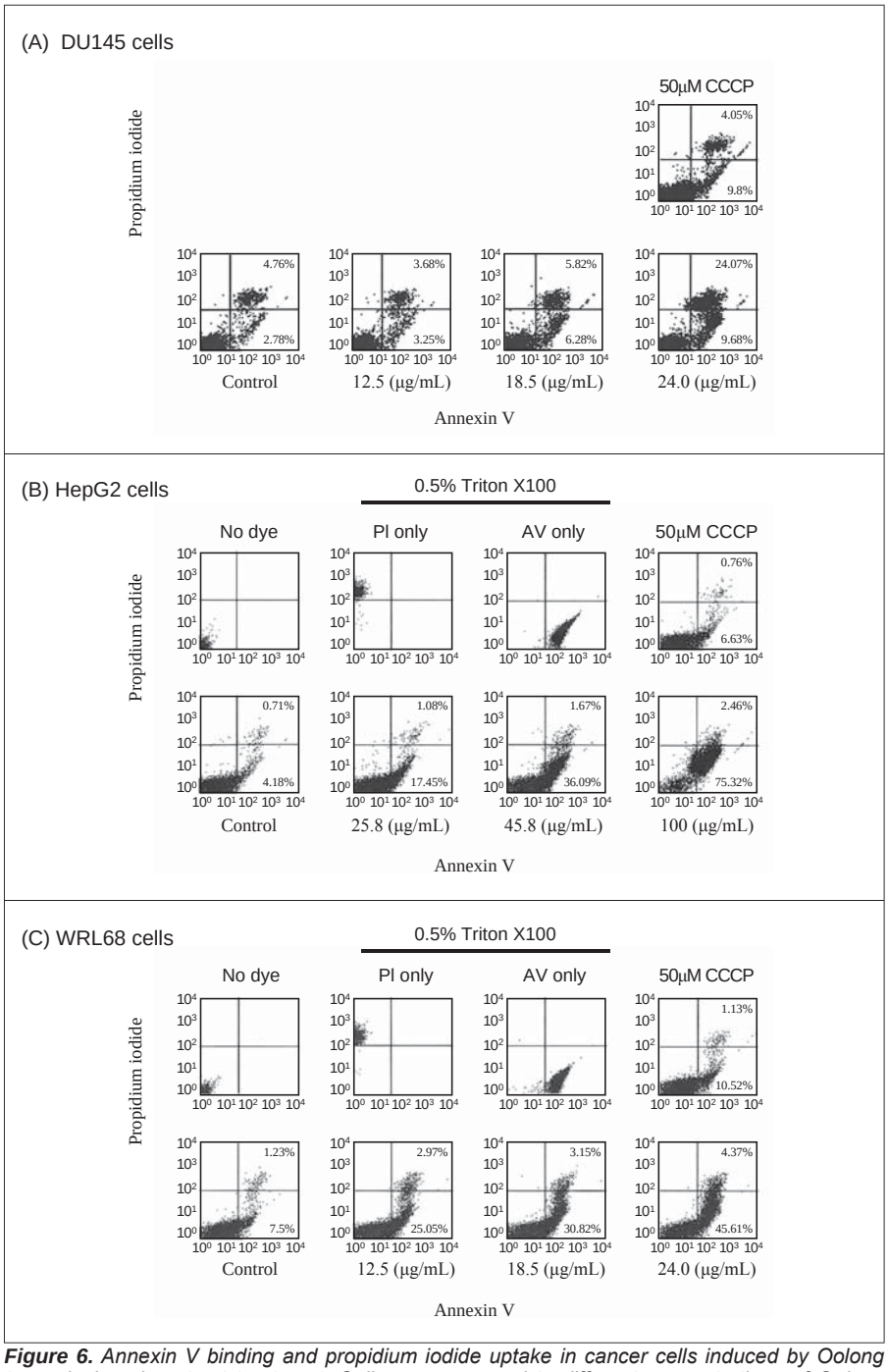

Figure 6. *Annexin V binding and propidium iodide uptake in cancer cells induced by Oolong tea polyphenols extract treatment. Cells were exposed to different concentrations of Oolong tea polyphenols extract for 48 h treatment. Results were representative of two independent experiments.*

Collapse of mitochondrial membrane potential

The loss of mitochondrial membrane potential (MMP) is thought to be one of the earliest events of the apoptosis caspase cascade, in which once MMP collapses, apoptosis occurs irreversibly.[15,16] The changes of mitochondrial membrane potential were assayed by JC-1 regent, whose monomer form exits in the cytosol with green fluorescence while the aggregate stays in the mitochondria with red fluorescence signal in healthy cells. As apoptosis occurs, JC-1 regent presents mainly as monomer in cells. Thus, reduction of MMP can be represents as the shift of JC-1 fluorescence from red to green as well as the decrease in the ratio of red and green fluorescence intensity.

As indicated in Figure 7, red fluorescence gradually shifted to greenish signal in all cancer cells with the increasing concentrations of Oolong tea polyphenols extract, demonstrating the dose-dependent mitochondrial membrane potential attenuation. According to the results of software analysis, the most significant changes were obtained in HepG2 cells. 100 μg/mL Oolong tea polyphenols treatment significantly elevated the percentage of green fluorescence from 39.13 to 91.12%, resulted in a decrease in the red to green fluorescence intensity ratio from 1.56 to 0.10. The MMP was observed to be collapsed as well in prostate cells DU145, as the red

and green fluorescence signal ratio decreased from 12.3 to 1.9. A slight increase in greenish cells population was as well obtained in WRL68 cells (from 72.29 to 81.61%), which was accompanied with the decrease of JC-1 dimer to JC-1 monomer fluorescence ratio (from 0.38 to 0.16). Collapse of MMP further confirmed the apoptosis-inducing effects of Oolong tea polyphenols.

Mitochondrial apoptosis pathway induced by tea polyphenols has been widely studied, which involved series of biochemical changes, like the collapse of MMP, the release of cytochrome C into the cytosol, and the active expression of caspase-3 and caspase -9 proteins etc.[41-43] In this work, the apoptosis caused by Oolong tea polyphenols might also involved the mitochondrial pathway; yet, further research works should be performed. Other molecular mechanisms of anti-proliferative effects of tea polyphenols on various cancer cells have been extensively reported as well. Epigallocatechin gallate has been reported to cause the reactive oxygen species (ROS)-related apoptosis in human hepatoma cancer cells and lymphoblastoid B cells.[41,42] By elevating Fas/APO-1 and its two ligands, membrane-bound Fas ligand (mFasL) and soluble Fas ligand (sFasL), as well as Bax protein expression, EGCG induced the Fas/FasL apoptosis pathway in human HepG2 cells.[37] Moreover, Epigallocatechin gallate also exerted cell cytotoxicity on colon cancer cells HT-29 by activating AMP-activated protein kinase (AMPK) and inhibiting COX-2 expression; the triggering of AMPK was in association with the decrease of vascular endothelial growth factor (VEGF) and glucose transporter etc.[44]

CONCLUSIONS

Increased brew time contributed to higher activities of polyphenolic antioxidants in various teas, and the Oolong tea exhibited the most potent antioxidant activities towards DCPIP than other teas. Thus, effects of Oolong tea polyphenols on different cancer cells proliferation were subsequently analyzed. Results indicated that, higher concentrations of Oolong tea polyphenols (over IC_{50}) exerted efficient growth inhibitory effects on human prostate cancer cells DU145, hepatoma cells HepG2 and WRL68. The anti-proliferative effects were mainly due to cell cycle arrest at S and (or) G2/M phase and apoptosis in various cancer cells. The apoptosis involved the collapse of mitochondrial membrane potential, indicated the Oolong tea polyphenols might triggered the mitochondrial apoptosis pathway. Further research works are needed to reveal the molecular mechanisms of cell-cycle arrest and apoptosis induced by Oolong tea polyphenols.

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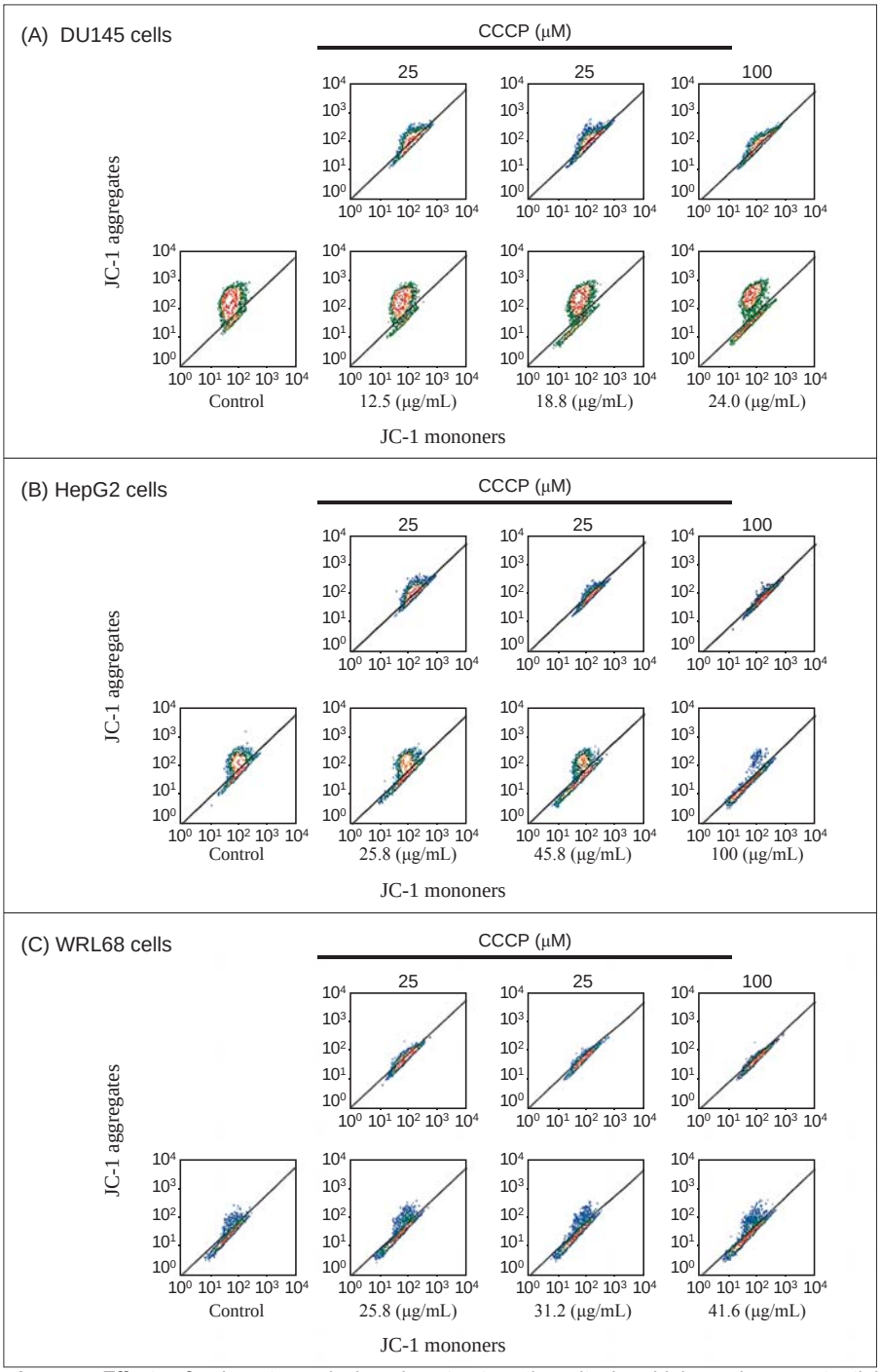

Figure 7. *Effects of oolong tea polyphenols extract on the mitochondrial membrane potential (MMP) of (A) DU145, (B) HepG2 and (C) WRL68 cells. Cells were exposed to different concentrations of Oolong tea polyphenols extract for 48 h treatment. Results were representative of two independent experiments.*

Author's background

LEE On-Ki, *is a gifted student from a secondary school. She was picked at the age of 15 by the Hong Kong New Generation Cultural Association to work on her project under Dr CHEUNG Hon-Yeung's supervision in City University of Hong Kong.* ***YANG Mei*** *is a postgraduate student, currently doing her MSc degree in Guangzhou and will join Dr Cheung's research team in this summer.* ***Dr. CHEUNG Hon-Yeung,*** *who is an associate professor of Pharmaceutics at the City University of Hong Kong, is a manufacturing pharmacist and biotechnologist. He has published more than 200 papers and articles in many prestigious international journals. He is frequently interviewed by TV and the media. He can be contacted through his email address: bhhonyun@cityu.edu.hk*

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Biological Activities and Functions of *Camellia sinensis* (Tea)

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Botanical Names: Variety (1) *Camellia sinensis* (L.) O. Kuntze. (tea); Variety (2) *Camellia sinensis var. assamica* (J. Masters) Kitam. (Assam tea)

Old Names: *Thea bohea, Thea sinensis* and *Thea viridis*

Plant Family: Theaceae

Chinese Name: 茶 (Cha)

Other names: white tea, green tea, oolong, pu-erh tea

Part Used: leaves, stems, twigs

Common uses: beverage (around the world), dietary supplement to maintain health (U.S.), traditional Chinese medicine to prevent cancers, improve mental alertness aid in weight loss and treat asthma (functioning as a bronchodilator), angina pectoris, peripheral vascular disease, and coronary artery disease.

ABSTRACT

Tea is an infusion of leaves (or stems/twigs) of the *Camellia sinensis* plant. It is a very popular drink in the world with a history of more than four thousand years. Tea contains abundant polyphenols (catechins), tannins, flavonols, and methylxanthines (caffeine, theophylline, theobromine). Polyphenolic flavonoids in tea are potent antioxidants with various biological activities and functions and the chemopreventive effect of green tea is attributed to these polyphenolic compounds, which have been shown to inhibit tumor proliferation. A large number of studies have demonstrated its beneficial effect on human health. This review attempts to address a general introduction of both bioactive ingredients and various biological activities of tea extracts. In addition, potential drawbacks of tea consumption regarding adverse effects and drug interactions are also mentioned. In summary, daily tea consumption is a recommended behavior to prevent a variety of health disorders though some safety issues should be noted.

Keywords: *Camellia sinensis, tea, green tea, polyphenol, flavonoid, catechin*

Contraindications:

Harmful effect of green tea has not been reported. Like coffee the caffeine, interferes with the absorption of certain medications. Hence, should not be used by pregnant women.

Undesirable effects:

Caffeine in tea may have unwanted effects on a person's sleep patterns. Breastfeeding women are advised to avoid drinking green tea.[81] Excessive consumption of black tea and oolong tea (3-14 liters/day) for the elderly may lead to hypokalemia.[84-86]

Interactions:

Tea has been found to influence the therapeutic effects of β-blockers, *β*-Lactam antibiotics, birth control medications, blood-thinning medications, clozapine, diazepam, doxorubicin, lithium, lorazepam, MAO inhibitors and tamoxifen.

INTRODUCTION

Tea is one of the most popular beverages around the world. There are a number of teas, including white tea, green tea, oolong and black tea which are all derived from the plant *Camellia sinensis* with different processing methods. For example, white tea is made from growth buds and young leaves under minimal oxidation while green tea is produced with more mature tea leaves which are not oxidized. Oolong tea is made from wilted, bruised leaves that are partially oxidized. Black tea is produced using wilted, bruised, rolled tea leaves through full oxidation. All teas contain a lot of bioactive chemicals, and polyphenol ingredients have been widely studied due to their potential health benefits, which may be an important reason for the popularity of tea in many cultures.

DESCRIPTION AND IDENTIFICATION:

Camellia sinensis is of the genus Camellia in the family Theaceae. Generally speaking, there are two major varieties that represent this species; namely *Camellia sinensis* var. sinensis (L.) Kuntze (Fig. 1) and *Camellia sinensis*

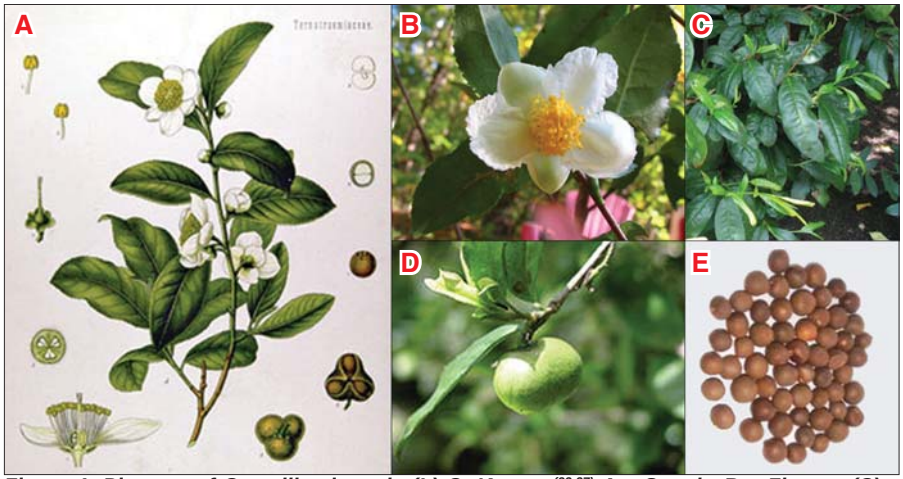

Figure 1. Pictures of Camellia sinensis (L) O. Kuntze.[22-27] A = Stetch; B = Flower; (C) = Leaves; (D) = Flower blub; E = Seeds

var. assamica (J. Masters) Kitam. The first variety, also called Chinese *Camellia sinensis* favors tropical and subtropical climate, moisture and high altitude. It is native to mainland China, South and Southeast Asia. It is a small-leaved bush with multiple stems. Most popular teas, especially Chinese and Taiwanese fine teas, are yielded from the Chinese variety. It is usually trimmed to below two metres (six feet) when cultivated for its leaves. It is an evergreen shrub or small tree having a strong taproot. The flowers have 7-8 yellow-white petals, 2.5–4 cm in diameter. The seeds can be pressed to yield tea oil, a sweetish seasoning and cooking oil that should not be confused with tea tree oil which originates from the leaves of a different plant that is used for medical and cosmetic purposes. The leaves are between 4–15 cm long and 2–5 cm broad. Short white hairs on the underside of the young, light green leaves are evident. Older leaves are deeper green. Differing tea qualities are produced by different leaf ages. They differ in their chemical compositions.[1]

The second variety, also called Assamese variety, is native to north-east India, Myanmar, Vietnam and South China. It is a single stemmed tree with large leaves. It can grow to 3 meters in height. But for easy harvesting, it is usually trimmed short. When compared with the Chinese variety, it has a shorter life span. All Assam teas and most Ceylon teas are derived from this plant. The assam plant produces malty, earthy drinks, unlike the generally flowery yield of the Chinese variety. It is commonly used for producing black tea. In addition, there are also another variety, named *Camillia sinensis* var. waldenae, which is found on Sunset Peak and Tai Mo Shan in Hong Kong. It is also distributed in Guangxi Province, China.[2-3]

BIOACTIVE CONSTITUENTS

Bioactive compounds in tea are mainly composed of flavonoids, caffeine and fluoride, which have been discovered with various methods.[10,65-68] Flavonoids, known as potent antioxidants, are abundant in various types of tea, and tea has been an important source of flavonoids in the US diets.[72] The bitter taste of tea is attributed to this class of compounds. As flavonoids may bring potential health benefits, most attention has been paid on their constituents in tea. Catechins is group of flavonol monomers mainly found in tea. In both white and green tea, which are made from fresh tea leaves, colorless and water soluble catechins largely include epicatechin (EC), epicatechingallate (ECG), epigallocatechin (EGC) and epigallocatechin gallate (EGCG)(Fig.2-4).[21,28-30] However, various methods of tea processing may affect the polyphenol content in tea. Oolong tea and black tea, for example contain much lower amount of catechins comparing with white tea and green tea, but the contents of theaflains and thearubigins are higher in oolong tea and black tea due to extended oxidation process (Fig. 5)[31]. Besides, saponins, caffeine, and tannins are also present in tea.[10, 65-68]

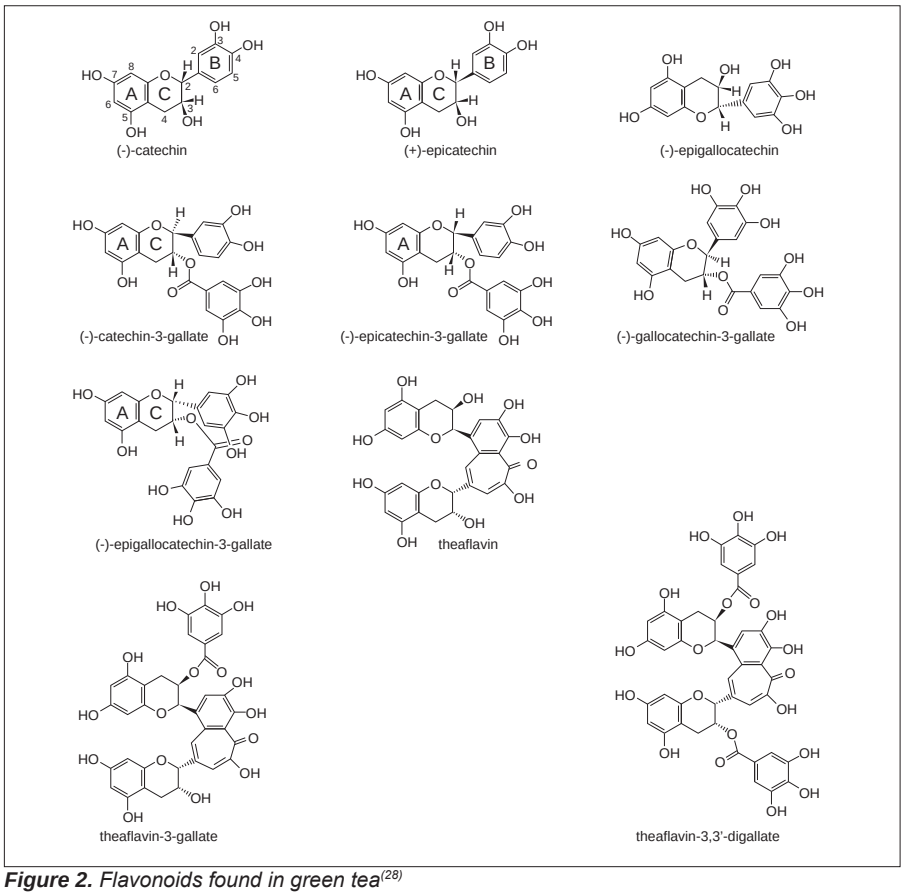

Figure 2. *Flavonoids found in green tea*[28]

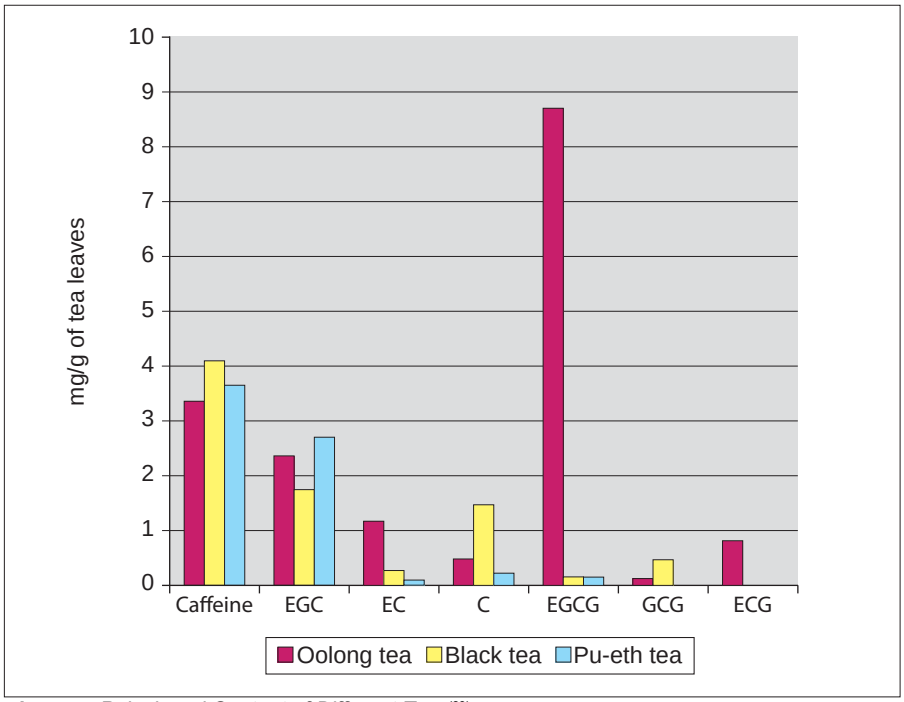

Figure 3. *Polyphenol Content of Different Teas*[29]

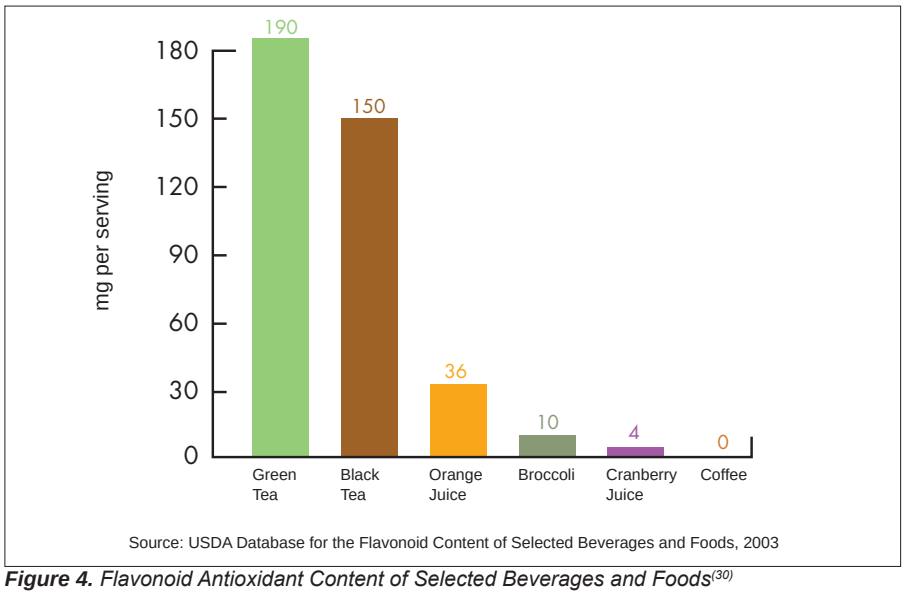

Figure 4. *Flavonoid Antioxidant Content of Selected Beverages and Foods*[30]

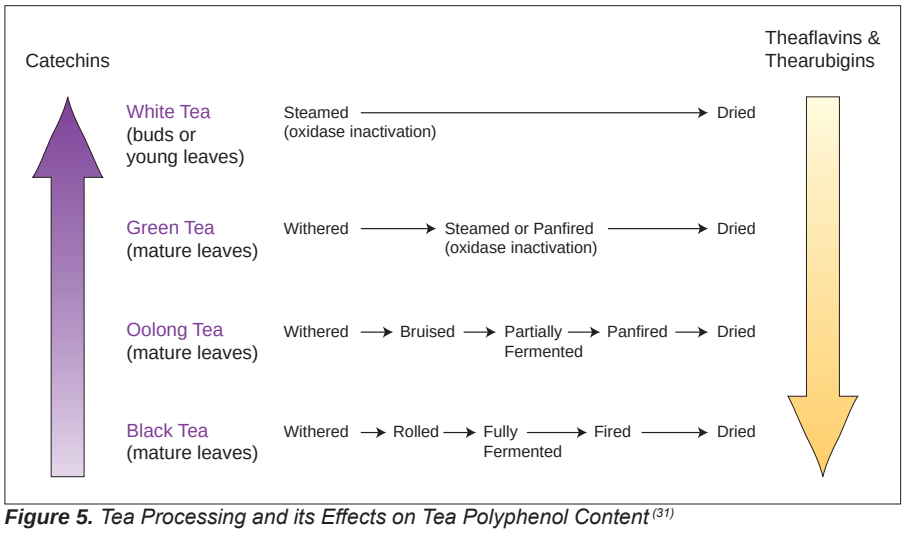

Figure 5. *Tea Processing and its Effects on Tea Polyphenol Content*[31]

IDENTIFICATION, ISOLATION AND PURIFICATION OF BIOACTIVE COMPONENTS IN TEA

Procedure for isolation and purification of caffeine and other polyphenolic compounds is well documented in literature. More recently, caffeine (3,7-dihydro-1,3,7-trimethyl-1H-purine-2,6-dione) was isolated from *C. sinensis* by Mohammed and Al-Bayati (2009) using a liquid-liquid extraction method and it was detected on thin layer chromatography (TLC) plates. In their study, both Fourier transform infrared (FTIR) spectrometer and High performance liquid chromatography (HPLC) analyses were applied to determine the purity of extracted caffeine.[68] Catechin compounds had also been recovered from Korean tea using solvent extraction.[69] Chinese green tea was 114.65% higher in catechin compounds than that extracted from the Korean green tea.[70] Isolation and characterization of polyphenol oxidase from Indian tea leaf was done by Halder *et al*. (1998).[71]

PHARMACOLOGICAL ACTIVITIES:

Effects on oxidative stress

It was reported that black tea extract (BTE) could prevent the oxidative stress administered to human red blood cees and completely inhibited the lipid peroxidation occurred both in pure erythrocyte membrane and whole red blood cells. Meanwhile, when compared to free catechins, black tea seemed to be a better protecting agent against various types of oxidative stress.[4] BTE was also found effective in preserving and restoring skeletal health by reducing the number of active osteoclasts. The reduced oxidative stress of mononuclear cells, serum levels of bone resorbing cytokines, osteoclast differentiation factor, and resorption markers were steadily linked with BTE supplementation, and it is suggested that BTE has both protective and restorative actions against ovariectomy-induced mononuclear cell oxidative stress and associated bone loss.[8]

Chemo-protective activity

The chemopreventive activity of tea aqueous extracts and selected constituent pure polyphenols using a battery of *in vitro* marker systems relevant for the prevention of cancer was evaluated. The bioactive compounds found in tea including (−)epigallocatechin gallate (EGCG), quercetin (Q), gallicacid (GA), green tea (GT, *C. sinensis*), ardisia tea (AT, *Ardisia compressa*) and mate tea (MT, *Ilexpara guariensis*) extracts were tested for their effects.[56-59] *In vitro* cytotoxicity testing using HepG2 cells, TPA-induced ornithine decarboxylase (ODC) and quinonereductase (QR) activities were also evaluated. Using the *Saccharomyces cerevisiae* yeast system, the topoisomerase inhibitory activity was also tested. MT, AT and GT are cytotoxic to the HepG2cells, with MT demonstrating dominant cytotoxicity. In addition, EGCG showed greater cytotoxicity than Q and GA against HepG2cells. Q showed the greatest inhibition (82%) of TPA induced ODC activity, with 25 μM (IC50 = 11.90 μM). The cellular target of MT, AT, EGCG, Q and GA was Topoisomerase II, but not topoisomerase I. The overall chemo-preventive activity of AT and MT extracts may be attributed to the cytotoxic activity and the inhibition of topoisomerase II. Thus, ardisia and mate teas may share a public health benefit as chemo-preventive agents.[6]

Effects on metabolic syndrome (lipid lowering activity, obesity & slimming effects)

The effect of consuming tea alone or tea supplemented with vitamin E on reduced plasma low-density lipoprotein (LDL) cholesterol concentrations, LDL oxidation, and early altherosclerosis in male Syrian hamsters was studied. The incorporation of vitamin E into the LDL molecule favors the anti- oxidant action of vitamin E. The hamsters fed with the vitamin E diet compared to the different concentrations of tea had significantly lower plasma LDL cholesterol concentrations, –18% ($p < 0.007$), –17% ($p < 0.02$), and –24% ($p < 0.0001$), respectively.[7] According to Ramadan *et al.* (2009), both black and green teas may have beneficial effects against the risks of the metabolic syndrome and cardiovascular disease as shown in rat models of human obesity

and diabetes.[39] Through improving lipid metabolism, oolong tea could decrease body fat content and reduce body weight. Oolong tea may prevent obesity through regular consumption.[40-43] In fact, it also increases the metabolic rate and fat oxidation in men.[82]

Anti-inflammatory activity

Methanol-water (1:1) extract of dried tea (*C. sinensis*) root extract (TRE) was found to possess anti-inflammatory, analgesic and antipyretic activities at 1/10th of its LD50 dose of 100 mg/kg i.p. Tea root extract produced the anti-inflammatory activity by inhibiting both the cyclo-oxygenase and lypooxygenase pathways of arachidonic acid metabolism in rats. Peritoneal cell count and the number of macrophages in normal mice were also enhanced by TRE. These activities of TRE may be due to the saponins present in TRE.[10]

Neuromuscular-blocking action

The neuromuscular-blocking action of botulinum neurotoxin types A, B, and E in the mouse phrenic nerve-diaphragm preparations was investigated with the thearubigin fraction of black tea. The neuromuscular-blocking action of botulinum neurotoxin was counteracted by thearubigin fraction when mixed with each toxin. [11]

DNA effect

It was found that green tea extract, in cell culture at a dose of 10 mg/L did not protect Jurkat cells against H_2O_2-induced DNA damage. Evaluation of the DNA damage by the Comet assay was dose-dependent. Without any protective effect exerted by the extract, however, it reached a plateau at 75 mmol/L. The DNA repair process was unaffected by supplementation completed within 2 hours.[12]

Immunomodulatory effect

IL-2, and IL-10 production from mixed lymphocyte proliferation were performed to determine the effects of tea on the transplant-related immune function *in vitro* lymphocyte proliferation tests using phytohemagglutinin mixed lymphocytes culture assay. It was also found that tea had immunosuppressive effects and decreased alloresponsiveness in the culture. A decrease in IL-2 production mediates the immunosuppressive effect of tea.[13]

Antiviral activity

Administration of epigallocatechin-3-gallate to Hep2 cells in culture, produced a therapeutic effect. It was found to be effective when added to the cells during the transition from the early to the late phase of viral infection. This suggests that the polyphenol inhibits one or more late steps in viral infection.[14]

Antibacterial activity

Alcohol extract of black tea was found to have an inhibitory effect on *Salmonella typhi* and *Salmonella paratyphi A*.[15] In order to prevent usual livestock intestinal diseases, the employment of *C. sinensis* (L.) whole plant extract as a food supplement in livestock nutrition has been suggested. It has been reported that *C. sinensis* (L.) whole plant extract is able to reduce the number of some potential pathogenic bacteria in piglet gut and hence might improve animal health.[16] It has also antibacterial effects on alpha hemolytic *Streptococcus* like *S. mutans* and *S. sanguinis*.[48] It also inhibits biofilm formation.[49]

Antispasmodic activity

The tannin fraction of the dried entire plant of *C. sinensis* and its hot water extract were active on the rabbit and rat intestines vs. barium induced contractions and pilocarpine-induced spasms.[17]

Hepatoprotective and antioxidant activity

Water extracts of black tea (*C. sinensis*) were studied in sodium oxalate treated rats showing hepatoprotective and antioxidant effects. Administration of 100 mg/kg body weight sodium oxalate induced lipid peroxidation in rats. Serum and tissue levels of malondialdehyde, catalase activity, aspartate transaminase (AST) and alanine transaminase (ALT) as well as serum vitamin C content in the normal, control and experimental rats after 10 and 20 days of tea administration was monitored to assess the protective effect of black tea. It was observed that the serum and tissue levels of malondialdehyde, as well as AST and ALT activities lowers significantly ($p<0.05$) after tea administration in a dose dependent manner. Serum level of malondialdehyde was reduced from 47.855±1.050 to 32.186±0.882 nm/h, AST activity from 59±2.95 to 31±1.40 IU and ALT activity from 39±2.51 to 25±1.25 IU after 10 days of administration of 200 mg/kg body weight of tea extract. Besides, an increase in serum catalase activity from 7 to 10% and serum vitamin C level was increased from 45.39±9.75 to 79.11±5.13 mg/100 ml following administration of 200 mg/Kg body weight of tea for 10 days. The same trend was observed in the tissues. There was a significant increase in serum vitamin C level and the activity of catalase in both the serum, liver and the kidney ($p<0.05$) after prolonged tea administration for 20 days. Also, significant reductions ($p<0.05$) in the serum and tissue levels of malondialdehyde and transaminase activities (AST and ALT) were also observed.[18]

Anti-diabetic activity

A strong glucose lowering effect of the aqueous green leaf extract of *C. sinensis* (450 mg kg-1) was shown after oral administration in rats. Two hours after glucose loading, the decrease of glycemia had reached to 30% of the control value. In the presence of tea extract, the amount of glucose absorbed in a segment jejunum *in situ* was 9.2±0.2 mg vs. 14.11±0.91 mg in control rats during 2 h ($p<0.05$). The significant anti-hyperglycemic effect of the aqueous extract of tea may be caused in part by the reduction of intestinal glucose absorption.[19] Like green tea, black tea also showed anti-diabetic effects.[38,43,46]

Anti-cataract activity

The incidence of selenite cataract *in vivo* was reduced following tea administration in culture to enucleated rat lens. A single subcutaneous injection of sodium selenite induced *in vivo* cataract in 9-day-old rats of both control and treated groups. Intraperitoneal injection with tea extract prior to selenite challenge in treated rats was continued for 2 consecutive days thereafter. Slit lamp examination was employed to evaluate the cataract incidence on 16 postnatal days. There was a positive modulation of biochemical parameters. The tea extract acted primarily by preserving the antioxidant defense system as indicated by the results.[20]

Anti-genotoxic effect

Two anabolic steroids Trenbolone and Methyltestosterone in cultured human lymphocytes, both in absence and presence of metabolic activation was used to induce genotoxic damage. The results of the study of Gupta *et al.* (2009) proved the antigenotoxic potential of green tea extract due to its polyphenol content. [21]

Anti-coronary heart disease

Tea polyphenols act as antioxidants *in vitro* by scavenging reactive oxygen and nitrogen species and chelating redox active transition metal ions. Hence, tea may reduce the risk of a variety of illnesses, including cancer and coronary heart disease based on epidemiologic observations and laboratory studies (Fig. 6).[21,36,73]

Anti-Parkinsonism

Green tea polyphenols (GTP) and EGCG were reported to prevent oxidative stress induced by 6-hydroxydopamin (6-OHDA) in cell signaling pathways through inhibiting oxidized 6-OHDA scavenging reactive oxygen species (ROS), counteracting undesirable effect of 6-OHDA on both PKC and ERK1/2, attenuating NF-κB translocation to the nucleus, modulating the expression of cell cycle genes and inhibiting the generation of peroxynitrite (ONOO-) (Fig. 7).[32] All the findings suggest that GTP/EGCG possesses neuro-protective effects, and GTP/EGCG treatment is supposed to prevent the pathogenesis of Parkinson's disease (PD).

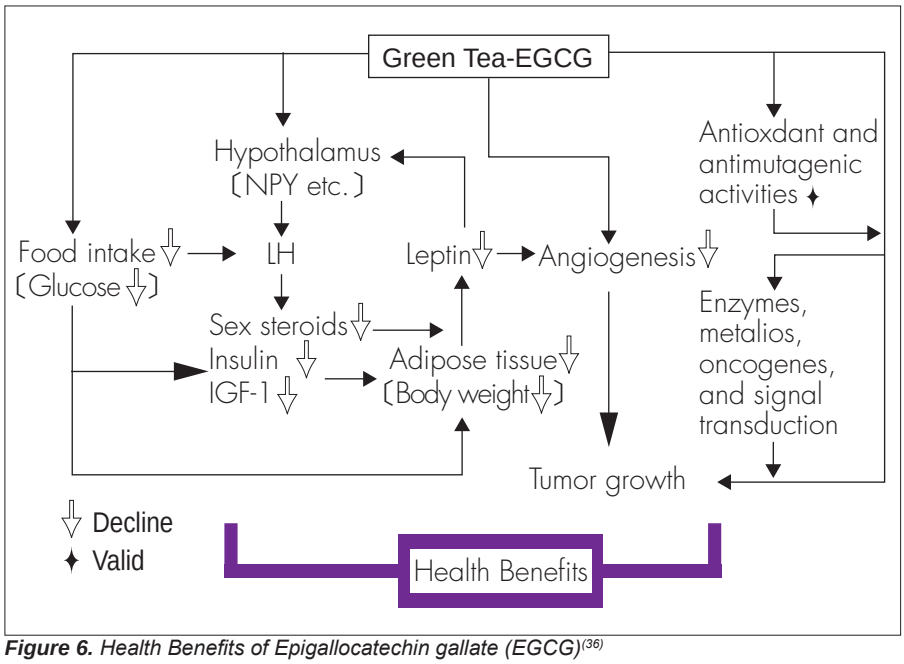

Figure 6. *Health Benefits of Epigallocatechin gallate (EGCG)[36]*

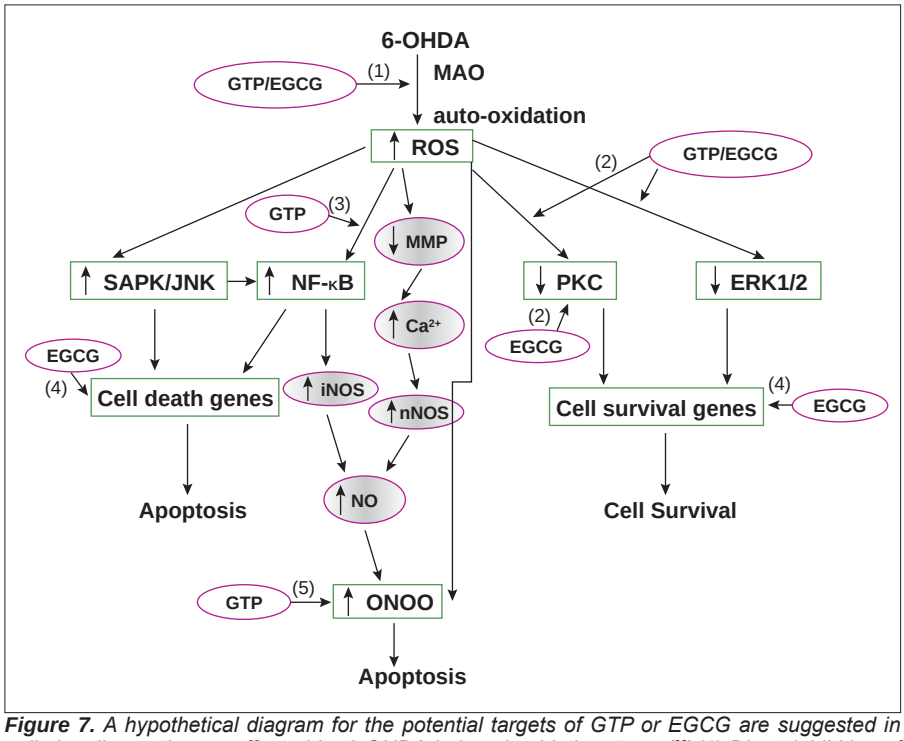

Figure 7. *A hypothetical diagram for the potential targets of GTP or EGCG are suggested in cell signaling pathways affected by 6-OHDA-induced oxidative stress.[32] (1) Direct inhibition of oxidized 6-OHDA and/or scavenging of ROS; (2) inhibiting the negative effect of 6-OHDA on both PKC and ERK1/2, and EGCG can direct phosphorylative activation of PKC; (3) attenuating NF-κB translocation to the nucleus, and inhibiting it activation; (4) modulating the expression of cell death and cell cycle genes; (5) modulating the intracellular NO level and inhibiting the generation of peroxynitrite ($ONOO^-$).*

Transcriptional activation of redox sensitive genes

Intracellular kinase cascades leading to increased NO, ROS or peroxynitrite levels are known to be activated by isoflavones, estrogens and other polyphenols. Dissociation and nuclear translocation of the redox sensitive transcription factor Nrf2 resulted from the modification of cysteine residues on Keap-1. To enhance eNOS expression, this in turn binds to an antioxidant response element (ARE) or electrophile response element (EpRE) in the promoter region of target genes (e.g. phase II and antioxidant enzymes NQO1, HO-1, GPx) whilst estrogen receptors bind to estrogen response elements (ERE)(Fig. 8).[33-35]

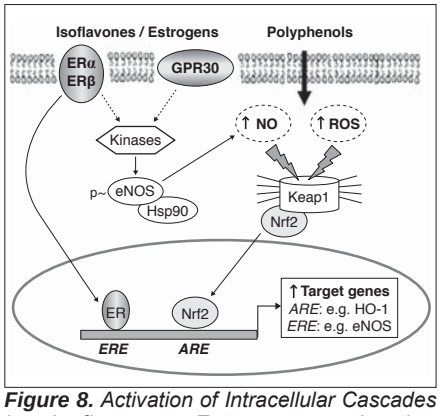

Figure 8. *Activation of Intracellular Cascades by Isoflavones, Estrogens, and other Polyphenols[33-35]*

Nitric oxide as a mediator of polyphenol induced transcriptional activation of antioxidant genes. Isoflavones, estrogens and other polyphenols activate intracellular kinase cascades, leading to acute activation of eNOS and NO and/or ROS generation. Increased NO, ROS or peroxynitrite levels will modify cysteine residues on Keap-1 leading to dissociation and nuclear translocation of the redox sensitive transcription factor Nrf2. Nrf2 binds to the antioxidant response element (ARE) or electrophile response element (EpRE) in the promoter region of target genes (e.g. phase II

and antioxidant enzymes NQO1, HO-1, GPx) whilst estrogen receptors bind to estrogen response element (ERE) to enhance eNOS expression. Induction of other antioxidant genes such as MnSOD may involve rapid phosphorylation of ERK1/2 and IκB and translocation of the p50 subunit of NF-κB to the nucleus and transactivation of MnSOD expression. [33-35]

Anti-diarrheal effects and prevention of gastrointestinal disorders

The effect of a hot water extract of black tea on both upper gastrointestinal transit and diarrhea was investigated using conventional rodent models of diarrhea. Results showed that black tea extract possesses antidiarrheal activity in all models.[44] Meanwhile, drinking unfractionated green tea is also simple and beneficial way to prevent gastrointestinal disorders since tea catechins are well absorbed in the gastrointestinal tract and they interact synergistically in their disease-modifying actions.[50]

Diuretic

The efficacy of Sri Lankan black tea differs with the agroclimatic elevation of production. It possesses mild oral diuretic activity.[45]

Aphrodisiac/sexual stimulant

Ratnasooriya and Fernando (2008) found that black tea brew (BTB) of *C. sinensis* can acts as a quick acting, safe, oral aphrodisiac which may also be useful in certain forms of sexual inadequacies such as premature ejaculation and impaired libido and other sexual functions.[47]

Anti-cariogenic

Studies carried out by Ferrazzano *et al.* (2009) on green, oolong and black tea indicate that tea polyphenols exert an anti-caries effect via an anti-microbial mode-of-action, and galloyl esters of (-)-epicatechin, (-)-epigallocatechin and (-)-gallocatechin show increasing antibacterial activities.[48] It was also found that volatile components of *C. sinensis* could inhibit the growth and biofilm formation by oral streptococci *in vitro*.[49]

Anti-cancer and anti-carcinogenic activity

Teas have been found to have anti-cancer activity in a variety of laboratory and animal studies, which is largely attributed to the strong antioxidant properties of their polyphenol compound, preventing cells from damages caused by reactive oxygen species or suppressing tumor cell proliferation. For example, green tea polyphenols were reported to inhibit proliferation of breast cancer cells both *in vivo* and *in vitro*.[84] Ravindranath et al. (2009) showed the differential growth suppression of human melanoma cells by tea epicatechins.[85] Male populations in Far-East countries where large quantities of green tea are consumed on regular basis were found to have the lowest incidence of prostate cancer (PCa).[51-52] and PCa chemopreventive effects of green tea seemed to be mediated by its polyphenolic constituents, especially EGCG, with multiple targets.[53] The effect of EGCG on cancer stem cells ($CD44^+CD133^+$) isolated from human prostate cancer cell lines were examined by Tang *et al* (2010)(Fig. 9).[54] The data indicates that human prostate cancer cell lines possess a small population of CSCs which are responsive to EGCG treatment. It was also demonstrated that EGCG could inhibit the formation of primary and secondary tumor spheroids and cell viability of human prostate cancer stem cells (Fig. 10).[54] Tang et al (2010) reported that EGCG inhibits the expression of XIAP and Bcl-2 and induces caspase-3 activation in human prostate cancer stem cells (Fig. 11).[54] Furthermore, EGCG inhibits the expression of epithelial-mesenchymal transition marker (EMT) in human prostate cancer stem cells (Fig. 12).[54]

Besides, other bioactive compounds have anti-cancer activity as well. The cytototoxic and apoptogenic effects of tea root extract (TRE) and its steroidal saponins (TS1 and TS2), were investigated on both human cell lines and cells from leukemia patients. It was found that TRE, TS1 and TS2 could significantly decreased cell count, and TRE could cause apoptosis. However, for normal white blood cells, TRE didn't lead to cell count reduction and cytotoxicity.[5]

Antithrombotic effects

Reduced production of platelet activation by inhibition of various molecular mechanisms of platelet aggregation has been manifested in various experiments.[74-79]

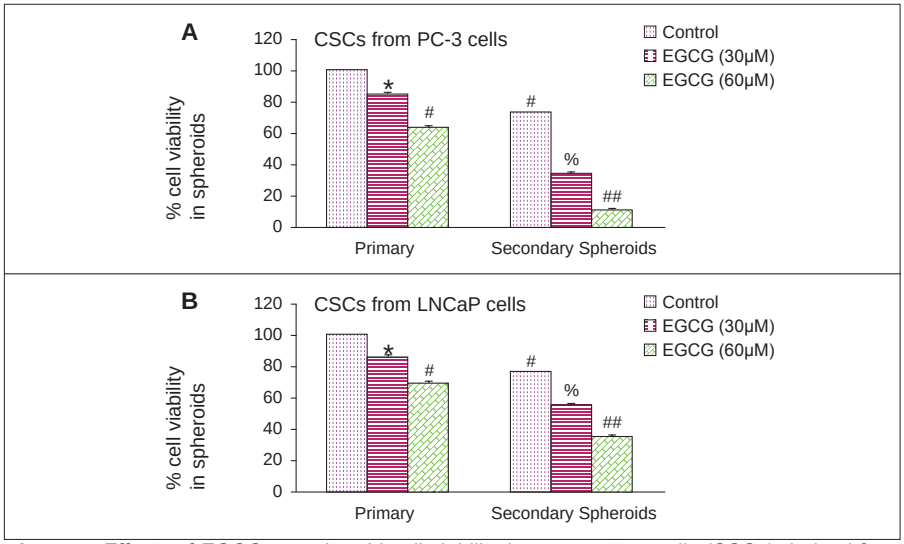

Figure 9. *Effects of EGCG on spheroid cell viability in cancer stem cells (CSCs) derived from human prostate cancer cell lines. (A), The CSCs were enriched from PC-3 cells, and grown in suspension in keratinocyte serum-free medium supplemented with B27, 10 ng/ml EGF, and 10 ng/ml basic fibroblast growth factor (Invitrogen). Prostate CSCs were re-seeded in suspension and treated with EGCG (0-60 μM) for 7 days. The spheroids were dissociated with Accutase (Innovative Cell Technologies, Inc.), and sieved through a 40-μm filter. Cell viability was measured by trypan blue assay. For secondary sphere formation, CSCs were reseeded and treated with EGCG for 7 days. Data represent mean ± SD. *, #, % or ## = significantly different from control, P < 0.05. (B), Prostate cancer stem cells were isolated from LNCaP cells, seeded in suspension and treated with EGCG (0-60 μM) for 7 days. At the end of incubation period, spheroids were dissociated with Accutase (Innovative Cell Technologies, Inc.), and sieved through a 40-μm filter. Cell viability was measured by trypan blue assay. Data represent mean ± SD. *, #, % or ## = significantly different from control, P < 0.05.*[54]

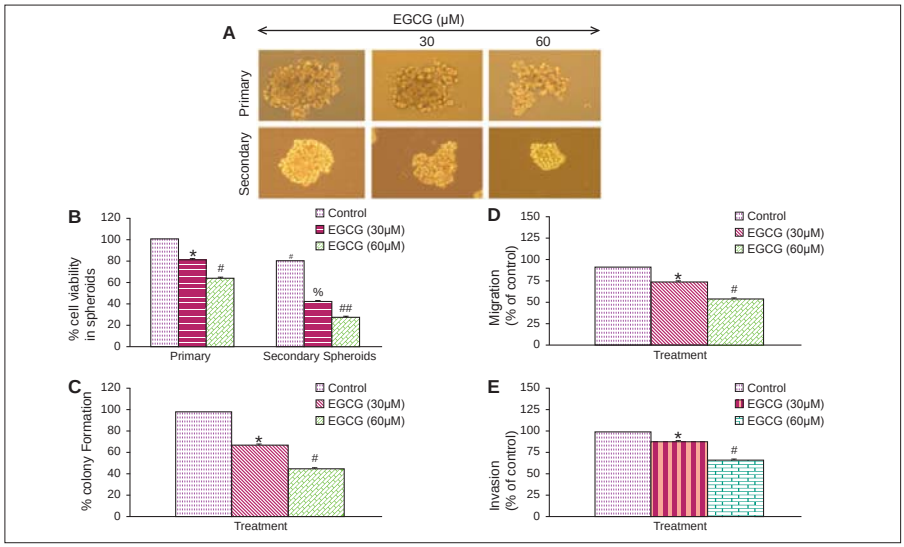

Figure 10. *Effects of EGCG on tumor spheroids and cell viability of prostate cancer stem cells (CSCs). (A), Prostate CSCs were seeded in suspension and treated with EGCG (0-60 μM) for 7 days. Pictures of spheroids formed in suspension were taken by a microscope. (B), Prostate CSCs were seeded in suspension and treated with EGCG (0-60 μM) for 7 days. At the end of incubation period, all the spheroids were collected and resuspended. Cell viability was measured by trypan blue assay. Data represent mean ± SD. *, #, % or ## = significantly different from control, P < 0.05. (c), EGCG inhibits colony formation by prostate CSCs. Prostate CSCs were seeded in soft agar and treated with various doses of EGCG and incubated at 4°C for 21 days. At the end of incubation period, colonies were counted. Data represent mean ± SD. * or # = significantly different from respective controls, P < 0.05. (D), Transwell migration assay. Prostate CSCs were plated in the top chamber of the transwell and treated with EGCG (0-60 μM) for 24 h. Cells migrated to the lower chambered were fixed with methanol, stained with crystal violet and counted. Data represent mean ± SD. * or # = significantly different from respective controls, P < 0.05. (E) Matrigel invasion assay. Prostate CSCs were plated onto the Matrigel-coated membrane in the top chamber of the transwell and treated with EGCG (0-60 μM) for 48 h. Cells invaded to the lower chambered were fixed with methanol, stained with crystal violet and counted. Data represent mean ± SD. * or # = significantly different from respective controls, P < 0.05.*[54]

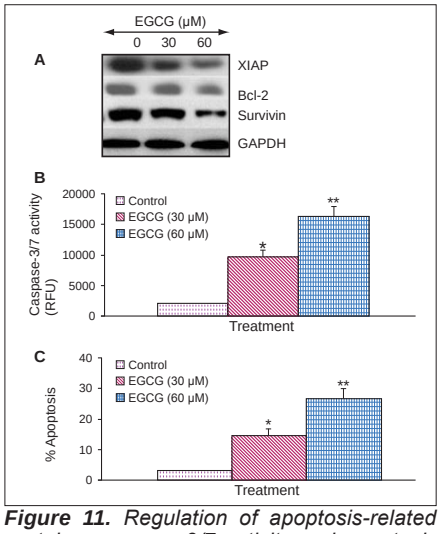

Figure 11. *Regulation of apoptosis-related proteins, caspase-3/7 activity and apoptosis by EGCG on CSCs derived from human primary prostate tumors. (A), Regulation of apoptosis-related proteins. Prostate CSCs from primary tumors were treated with EGCG (0-60 μM) for 48 h. The Western blot analyses were performed to examine the expression of XIAP, Bcl-2 and survivin, and GAPDH. (B), Regulation of caspase-3/7 activity by EGCG. Prostate CSCs were treated with EGCG (0-60 μM) for 24 h, and caspase-3/7 activity was measured as per manufacturer's instructions. Data represent mean ± SD. * or ** = significantly different from control, P < 0.05. (C), Regulation of apoptosis by EGCG. Prostate CSCs were treated with EGCG (0-60 μM) for 48 h, and apoptosis was measured by TUNEL assay. Data represent mean ± SD. * or ** = significantly different from control, P < 0.05.*[54]

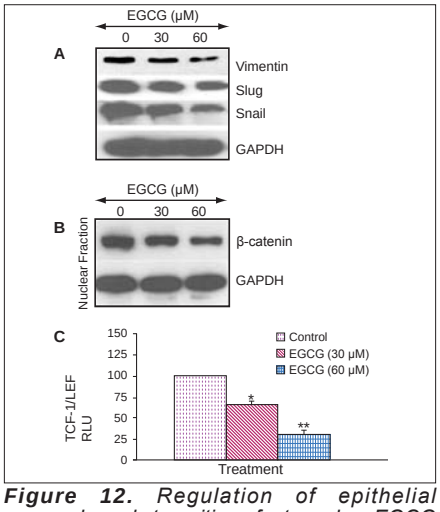

Figure 12. *Regulation of epithelial mesenchymal transition factors by EGCG in prostate cancer stem cells isolated from primary tumors. (A), Prostate CSCs were treated with EGCG (0-60 μM) for 48 h. At the end of incubation period, the expression of vimentin, slug, and snail was measured by the Western blot analysis. (B), Effects of EGCG on the expression of nuclear β-catenin. Prostate CSCs were treated with EGCG (0-60 μM) for 48 h. At the end of incubation period, cells were harvested and nuclear fractions were prepared. The expression of β-catenin and GAPDH was measured by was measured by the Western blot analysis. (c), Effects of EGCG on TCF-1/LEF activity. Prostate CSCs were transduced with lentiviral Top-dGFP-reporter (pRLR.sm-18.ppt). Transduced CSCs were treated with EGCG (0-60) for 3 days and the GFP fluorescence was measured. Data represent mean ± SD. * or ** = significantly different from control, P < 0.05.*[54]

Anti-aging

In the study of Murase *et al.* (2008) it was suggests that tea consumption combined with habitual exercises might prevent a decline in physical function associated with human aging.[4,8,40-43,80-82]

Anti-leukemia

The study of Zhang *et al.* (2008) suggests that a higher intake of green tea is associated with a reduced risk of adult leukemia.[83]

SAFETY

Tea as a food item is generally considered safe by the US Food and Drug Administration and so far no maximal safety level established.[81] Li *et al*. (2011) reported that both acute and subchronic toxicity of tea towards animals is very low.[37] However, safety issues regarding adverse effects and drug interactions of teas have emerged in recent years. No harmful effect has been reported for tea consumption on all parameters measured by Ramadan *et al.* (2009), except that the high dose of both tea extracts significantly decreased the spleen weight:body weight ratio and induced lymphopenia.[39] Though, there were reports of genotoxic effects of EGCG at higher concentrations, there are other compounds in the green tea extract known to counteract such actions.[60-67]

SIDE EFFECTS/CONTRAINDICATIONS

Green tea contains caffeine in small amounts (if brewed for two to three minutes, an average of 20 to 30 mg per cup) Caffeine may have unwanted effects on a person's sleep patterns. Breastfeeding women are advised to avoid drinking green tea.[81]

ADVERSE EFFECTS

An excessive consumption of oolong tea and black tea (3-14 liters/day) for the elderly may lead to hypokalemia which has been related with caffeine toxicity.[84,85] For healthy adults supplement with up to 1200 mg/day of EGCG over 1-4 weeks, adverse effects were observed including excess intestinal gas, nausea, heartburn, stomach ache, dizziness, headache and muscle pain.[86,87]

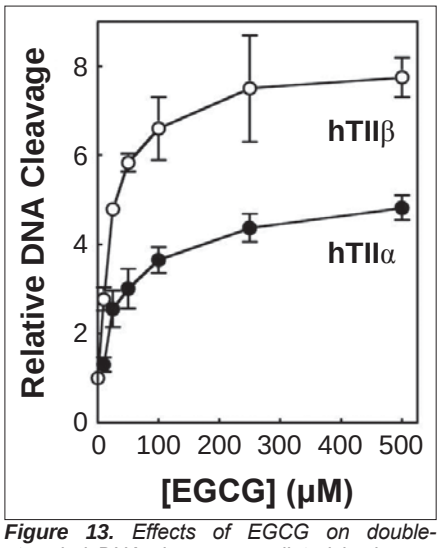

Figure 13. *Effects of EGCG on double-stranded DNA cleavage mediated by human topoisomerase IIα and β. Data for DNA cleavage mediated by topoisomerase IIα (hTIIα; closed circles) and topoisomerase IIβ (hTIIβ; open circles) in the presence of 0–500 μM EGCG are shown. Levels of cleavage were compared to those in the absence of compounds (set to 1.0). Error bars represent standard deviations for three independent experiments.*[65]

It has been reported at high concentrations of catechins showed genotoxic effects in mammalian cells.[60-64] Results of a study by Bandele and Osheroff (2008) showed that EGCG is a strong redox dependent factor of the cleavage of human topoisomerase II (Fig. 13).[65] However, their results also showed that there was no DNA intercalation observed at concentrations of the extract up to 200 μg/mL due to the possibility that tannins and other compounds in the extract inhibit topoisomerase II-DNA binding.[65-67]

DRUG INTERACTIONS

Tea was found to influence the therapeutic effects of some drugs. For example, green tea may reduce bacterial resistance to *β*-lactam antibiotic treatment and increase their effectiveness. However, after drinking green tea, the anti-psychotic effects of the medication clozapine may be reduced. The actions of adenosine (a medication given in the hospital for an irregular heart rhythm) may be inhibited by green tea.[55] The sedative effects of benzodiazepines, such as diazepam and lorazepam (medications commonly used to treat anxiety) have been shown to be reduced by caffeine from green tea.[55] Green tea could also make warfarin ineffective since it contains vitamin K. Blood levels of lithium (a medication used to treat manic/depression) has been shown to be decreased by taking green tea. Meanwhile, green tea could strengthen effects of certain drugs as well. The effectiveness of chemotherapy medications specifically doxorubicin and tamoxifen increased in laboratory tests when combined with green tea. However, there have been reports of both green and black tea extracts causing prostate cancer cells less sensitive to chemotherapy drugs due to stimulation of a certain gene. Therefore, people should not drink black and green tea as well as their extracts while receiving chemotherapy for prostate cancer in particular.[55]

In addition, several drugs can impair the metabolism of caffeine, increasing the potential for adverse effects caused by caffeine. Aspirin should not be mixed with green tea because they both prevent platelets from clotting, thus, increasing the risk of bleeding. Oral contraceptives may increase the stimulating effects of caffeine because it can prolong the amount of time caffeine stays in the body. Phenylpropanolamine (an ingredient used in weight loss products and many over-the-counter prescription cough and cold medications) in combination with caffeine (including caffeine from green tea) can cause mania and a severe increase in blood pressure.[55]

It was reported that green tea may cause agitation, tremors, insomnia, and weight loss when taking together with ephedrine. When taking together with MAOIs (medications used to treat depression like phenelzine and tranylcypromine), green tea may cause a severe increase in blood pressure, called “hypertensive crisis”.[55]

CONCLUSIONS

Tea has diverse biological activities benefiting human health, which are mainly contributed by its bioactive compounds, especially polyphenols. It is a promising herb that offers a lot of health benefits yet to be discovered. Possible applications of this beverage in the prevention of pathogenesis of dental caries has been suggested based on the anti-cariogenic effects against alpha-haemolytic streptococci due to the polyphenolic components in cocoa, coffee, and tea.[48] Clinical trials should be employed on green tea catechins which could be developed for prevention and/or intervention of prostate cancer.[51-52] Adhami *et al*. (2003) suggested that there are multiple targets for PCa chemoprevention by green tea. Hence, further studies to identify novel pathways that may be modulated by green tea or its polyphenolic constituents could be further exploited for prevention and/or treatment of PCa.[53] It is also recommended that the combination of bioactive dietary agents with complementary activities is beneficial for prostate cancer prevention and/or treatment since carcinogenesis is a complex process.[54]

However, its potential safety issues associated with adverse effects and drug interactions should not be ignored in daily consumption. Adverse effects caused by tea may largely result from caffeine present in many tea products. In addition, polyphenols and tannins of tea might also bind to proteins in reversible or irreversible ways to form covalent or non-covalent linkages, which may be one of important reasons to explain the phenomena thus affecting the effectiveness of certain drugs, or even leading to undesirable effects. Therefore, more and more attention has been focused on the study of the interactions between tea extracts and drugs, which may be contributory to guide the proper use of both drugs and tea, or discover new functions of tea.

Author’s background

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Hong Kong Pharmacy Conference 2011: Against the Breaking Wave

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After the successful Hong Kong Pharmacy Conference conducted in Hong Kong Convention and Exhibition Centre (HKCEC) in 2010, the 23rd Hong Kong Pharmacy Conference was again successfully held in HKCEC on 26th February, 2011 and 27th February, 2011. This year, we had more than 400 local participants attending the Conference and thirty participants coming from Macau, Thailand and Australia.

The Conference theme this year was "Against The Breaking Wave". This theme was created with the imagery of pharmacy profession as a big ship. Pharmacists working in different sectors are sailors providing different functions for this ship. Pharmacist leaders are the captains to guide the direction; pharmacists working in pharmaceutical industry and pharmacists doing research projects are sailors working in the engine room to provide kinetics to the ship; pharmacists working in government authority are engineers supporting every component of the ship to make sure it functions properly; frontline pharmacists working in hospitals and community pharmacies are service providers giving best services to our passengers (patients); pharmacists working in universities are trainers who develop potential sailors to sustain the sailing of the ship. Missing any single role above , the ship won't be able to get to the right destination. The breaking wave is any cleft interrupting our way. However with all pharmacists joining hands, the ship is able to conquer the breaking wave like what mentioned in the Chinese theme: "同舟共濟 乘風破浪".

Being the chief captain of the conference this year, Ms. Iris Cheng, Chairlady of Hong Kong Pharmacy Conference Organizing Committee 2011 and President of the Practising Pharmacists Association of Hong Kong, had led the organizing committee to prepare for the Conference since March 2010. The organizing committee indeed encountered several breaking waves during the preparation of the conference, including changes of theme speakers, uncertainty of the venue and also two black rainstorms and one signal 8 typhoon! We had ridden against the breaking waves and the ship had set sail.

In the opening ceremony on 26th February 2011, we were honoured to have Dr. Joseph Lee, JP, SBS, Legislative Council Member; Ms Linda Woo, Chief Pharmacist, Department of Health; Prof Joan Zhou, Associate Director, School of Pharmacy, the Chinese University of Hong Kong (CUHK); Ms. Teresa Ngan, Senior Pharmacist, Hospital Authority; Mr. So Yiu Wah, President of the Society of Hospital Pharmacists of Hong Kong; Mr. Benjamin Kwong, President of the Pharmaceutical Society of Hong Kong and Ms. Iris Cheng, Chairlady of Hong Kong Pharmacy Conference 2011, to mark the opening of the conference with a specially designed wheel.

Following the opening ceremony, the conference began with the opening speeches given by Ms. Iris Cheng and Dr. Joseph Lee. Subsequently, we were privileged to have Dr. Sian Griffiths, Director, School of Public Health, CUHK, to give the first theme speech about the role of pharmacists in primary health care. Dr. Man Li Tse from the Hong Kong Poison Information Centre then provided us a constructive talk about the emerging drugs of abuse. In the past conferences, we seldom had chances to hear the request from our patients. This year, we invited Mr. KP Tsang, Chairman of Alliance for Patients' Mutual Help Organizations, to give us an overview of what patients want from us nowadays. Thanks to the conference sponsors which had invited three honourable speakers Dr. Raymond Wong, Dr. Thomas Yau and Prof. Kenneth Lee to give us lectures respectively about the new thrombopoetin receptor agonists for immune thrombocytopenia and antiangiogenic agent for metastatic renal cell carcinoma before the conference dinner and a sharing about a pharmacoeconomic analysis of a new pneumococcal vaccine before lunch on the second day.

As the conference has already been held for 23 years, pharmacists who have participated in previous conferences should know that Pharmacy Conference is not only an event to update pharmacists with up-to-date knowledge and share academic ideas, but is also a place for fraternity. The conference dinner is thus an important part of the conference to serve this purpose. Practising pharmacists, interns, and students from CUHK worked together to give us a wonderful and entertaining drama at the beginning of the conference dinner. I'm sure audiences should have felt their enthusiasm and were amused by their funny performance. Pharmacists joining the conference dinner were asked to make a boat by simple tools in the game part. Even in this simple game, every table showed the talent of creativity and the spirit of union. With challenging games, exciting lucky draws and delicious meal, the conference dinner ended with a familiar song with the same name as the conference theme 乘風破浪.

The second day (27th February, 2011) of the conference as usual involved three concurrent sessions which provide valuable knowledge to our participants. The three concurrent sessions each carried a theme namely Information Technology, Education and Clinical. Pharmacist experts from each area including speakers coming from Mainland China and Columbus have come to share their valuable experiences. Young pharmacists together introduced the latest and useful tools in our handheld devices and another group of pharmacists also shared their experiences of the visiting pharmacist service at elderly home.

From the establishment of a new

pharmacy school in the University of Hong Kong (HKU) in 2009, this was the first time to have pharmacy students from HKU joining our conference. Students from CUHK and HKU together gave us an inspiring debate on whether to accept master degree as the minimum qualifying degree for practicing pharmacists in Hong Kong. Audiences and judges were all impressed by the talented new blood of the pharmacy profession. In a burst of applause from the audiences, the curtain of Hong Kong Pharmacy Conference 2011 dropped.

For better preparation of the next Pharmacy Conference in 2012, the organizing committee appreciates any feedback from fellow pharmacists. If you have any interested topics or any other comments regarding the conference, please feel free to tell us by sending e-mail to the following address hkpharmacyconference@gmail.com. For more information about Hong Kong Pharmacy Conference, please visit our official website www.pharmacyconference.org

Look forward to seeing you in Hong Kong Pharmacy Conference 2012!

Author's background

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Photo Captions of the Annual Conference of Pharmaceutical Society of Hong Kong (2011)

Representatives from the six organizations (from left): Prof Joan Zhou, Associate Director, School of Pharmacy, CUHK; Ms. Linda Woo, Chief Pharmacist, Department of Health; Mr. Yiu-Wah So, President of the Society of Hospital Pharmacists of Hong Kong; Dr Joseph Lee, JP, SBS, Panel on Health Services, Legislative Council; Mr. Benjamin Kwong, President of the Pharmaceutical Society of Hong Kong; Ms. Teresa Ngan, Senior Pharmacist, Hospital Authority; Ms. Iris Chang, President of the Practising Pharmacists Association of Hong Kong

Opening ceremony

Conference Dinner

Organization Committee: Cheers!

NEW PRODUCTS

ONGLYZA®
(Bristol-Myers Squibb)

Active Ingredient:
Saxagliptin

Presentations:
Saxagliptin 5 mg film-coated tablets (as hydrochloride)

Pharmacological Properties:
Saxagliptin is a highly potent (Ki: 1.3 nM), selective, reversible, competitive, DPP-4 inhibitor. In type 2 diabetes, saxagliptin can inhibit DPP-4 enzyme activity for a 24-hour period. After an oral glucose load, this DPP-4 inhibition resulted in a 2-to 3-fold increase in active incretin hormones, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), decreased glucagon and increased glucose-dependent beta-cell responsiveness, which resulted in higher insulin and C-peptide. Saxagliptin improves glycaemic control by reducing fasting and postprandial glucose.

Indications:
Saxagliptin is indicated for type 2 diabetes mellitus to improve glycaemic control as add-on combination therapy with metformin, a thiazolidinedione or a sulphonylurea.

Dosage And Administration:
Saxagliptin 5mg once daily as add-on combination therapy and can be taken with or without a meal at any time of the day. A double dose should not be taken on the same day.

Contraindications:
Hypersensitivity to the active substance or the excipients.

Precautions:
Should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis and it has not been studied in combination with insulin.
It is not recommended for patients with moderate to severe renal impairment .
Caution with moderate hepatic impairment, and not recommended in severe hepatic impaired patients.
Sulphonylureas are known to cause hypoglycaemia therefore a lower dose of sulphonylurea may be required.
Not to be used in patients with serious hypersensitivity reaction to a DPP4 inhibitor.
Skin disorders, such as blistering, ulceration or rash should be monitored.
Lactose intolerance.

Pregnancy:
There are no data from the use of saxagliptin in pregnant women. Studies in animals have shown reproductive toxicity at high doses. The potential risk for humans is unknown therefore should not be used during pregnancy unless clearly necessary.

Drug Interactions:
The metabolism of saxagliptin is primarily mediated by cytochrome P450 3A4/5 (CYP3A4/5). In healthy subjects, neither the pharmacokinetics of saxagliptin and its major metabolite, were meaningfully altered by metformin, glibenclamide, pioglitazone, digoxin, simvastatin, omeprazole, antacids or famotidine. In addition, saxagliptin did not meaningfully alter the pharmacokinetics of metformin, glibenclamide, pioglitazone, digoxin, simvastatin, diltiazem or ketoconazole.

Moderate inhibitor of CYP3A4/5 diltiazem, increased the C_{max} and AUC of saxagliptin by 63% and 2.1-fold, respectively, and the corresponding values for the active metabolite were decreased by 44 and 34%, respectively.

Potent inhibitor of CYP3A4/5 ketoconazole, increased the C_{max} and AUC of saxagliptin by 62% and 2.5-fold, respectively, and the corresponding values for the active metabolite were decreased by 95% and 88%, respectively.

Potent CYP3A4/5 inducer rifampicin, reduced C_{max} and AUC of saxagliptin by 53% and 76%, respectively. The exposure of the active metabolite and the plasma DPP4 activity inhibition over a dose interval were not influenced by rifampicin

CYP3A4/5 inducers, other than rifampicin (such as carbamazepine, dexamethasone, phenobarbital and phenytoin) have not been studied and may result in decreased plasma concentration of saxagliptin and increased concentration of its major metabolite. Glycaemic control should be carefully assessed when concomitantly used with a potent CYP3A4 inducer.

Side Effects:
Dizziness, fatigue, dyspepsia, myalgia, upper respiratory tract infection and upper urinary tract infections.

Forensic Classification:
P1S1S3

Valdoxan®
(Servier)

Active Ingredient:
Agomelatine.

Presentation:
25 mg film-coated tablet

Pharmacological Properties:
Agomelatine is a melatonergic agonist (MT_1 and MT_2 receptors) and $5\text{-}HT_{2C}$ antagonist. Binding studies indicate that agomelatine has no effect on monoamine uptake and no affinity for α, β adrenergic, histaminergic, cholinergic, dopaminergic and benzodiazepine receptors.
Agomelatine resynchronises circadian rhythms in animal models of circadian rhythm disruption. Agomelatine increases noradrenaline and dopamine release specifically in the frontal cortex and has no influence on the extracellular levels of serotonin.

Indications:
Treatment of major depressive episodes in adults

Dosage & Administration:
The recommended dose is 25 mg once daily taken orally at bedtime.
After two weeks of treatment, if there is no improvement of symptoms, the dose may be increased to 50 mg once daily, i.e. two 25 mg tablets, taken together at bedtime.
Valdoxan tablets may be taken with or without food.
No dosage tapering is needed on treatment discontinuation.

Contraindications:
Hepatic impairment (i.e. cirrhosis or active liver disease)
Concomitant use of potent CYP1A2 inhibitors (e.g. fluvoxamine, ciprofloxacin)

Precautions:
Valdoxan is not recommended in the treatment of depression in patients under 18 years of age.
Valdoxan should not be used for the treatment of major depressive episodes in elderly patients with dementia.
Valdoxan should be used with caution in patients with a history of mania or hypomania and should be discontinued if a patient develops manic symptoms.
Patients with a history of suicide-related events or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known Combination with potent CYP1A2 inhibitors is contraindicated to be at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment.

Liver function tests should be performed in all patients: at initiation of treatment and then periodically after around six weeks (end of acute phase), after around twelve and twenty four weeks (end of maintenance phase) and thereafter when clinically indicated.
Caution should be exercised when valdoxan is administered to patients who consume substantial quantities of alcohol or are treated with medicinal products associated with risk of hepatic injury.
Valdoxan contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Drug Interactions:
Co-administration of Valdoxan with potent CYP1A2 inhibitors (e.g. fluvoxamine, ciprofloxacin) is contraindicated.
Combination of agomelatine with oestrogens (moderate CYP1A2 inhibitors) results in a several fold increased exposure of agomelatine.
Caution should be exercised when prescribing agomelatine with other moderate CYP1A2 inhibitors (e.g. propranolol, grepafloxacin, enoxacin) until more experience has been gained.

Side Effects:
Adverse reactions were usually mild or moderate and occurred within the first two weeks of treatment. The most common adverse reactions were nausea and dizziness.
These adverse reactions were usually transient and did not generally lead to cessation of therapy.
Other common side effects include headache, dizziness, somnolence, insomnia, migraine, nausea, diarrhoea, constipation, upper abdominal pain, hyperhidrosis, back pain, fatigue, increases (>3 times the upper limit of the normal range) in ALAT and/or ASAT (i.e. 1.1% on agomelatine 25/50 mg vs 0.7% on placebo).

Forensic Classification:
P1S1S3

Active Ingredient:
Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine

Presentation:
GARDASIL* is a recombinant, quadrivalent vaccine that protects against Human Papillomavirus (HPV).
GARDASIL is a sterile preparation for intramuscular administration. Each 0.5-mL dose contains HPV 6 L1 protein, HPV 11 L1 protein, HPV 16 L1 protein, and HPV 18 L1 protein.

Indications:
Girls and Women
GARDASIL is a vaccine indicated in girls and women from the age of 9 years through 45 years for the prevention of the following diseases caused by Human Papillomavirus (HPV) types included in the vaccine:
- Cervical, vulvar, and vaginal cancer caused by HPV types 16 and 18
- Genital warts (condyloma acuminata) caused by HPV types 6 and 11

And the following precancerous or dysplastic lesions caused by HPV types 6, 11, 16, and 18:
- Cervical intraepithelial neoplasia (CIN) grade 2/3 and Cervical adenocarcinoma *in situ* (AIS)
- Cervical intraepithelial neoplasia (CIN) grade 1
- Vulvar intraepithelial neoplasia (VIN) grade 2 and grade 3
- Vaginal intraepithelial neoplasia (VaIN) grade 2 and grade 3

Boys and Men
GARDASIL is indicated in males from the age of 9 through 15 years for the prevention of genital warts (condyloma acuminata) caused by HPV types 6 and 11.

Dosage and Administration
Dosage
GARDASIL should be administered intramuscularly as 3 separate 0.5-mL doses according to the following schedule:

First dose: at elected date
Second dose: 2 months after the first dose
Third dose: 6 months after the first dose (See Immunogenicity, Schedule Flexibility)

Paediatric population: There is no experience with the use of Gardasil in children below 9 years of age.

Drug Interactions:
Use with Other Vaccines
Results from clinical studies indicate that GARDASIL may be administered concomitantly (at a separate injection site) with Hepatitis B vaccine (recombinant), Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine, Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (Tdap), and Diphtheria, Tetanus, Pertussis (acellular, component) and Poliomyelitis (inactivated) Vaccine, (adsorbed, reduced antigen(s) content).

Use with Common Medications
In clinical studies for girls and women (aged 16 to 26 years), 11.9%, 9.5%, 6.9%, and 4.3% of individuals used analgesics, anti-inflammatory drugs, antibiotics, and vitamin preparations, respectively. In a clinical study in women (aged 24 to 45 years), 30.6%, 20.2%, 11.6%, and 7.5% of individuals used analgesics, anti-inflammatory drugs, antibiotics, and vitamin preparations, respectively. Conversely in a clinical study in boys and men (aged 16 to 26 years), 10.3%, 7.8%, 6.8%, 3.4% and 2.6% of individuals used analgesics, anti-inflammatory drugs, antibiotics, antihistamines, and vitamin preparations, respectively. The efficacy, immunogenicity, and safety of the vaccine were not impacted by the use of these medications.

Use with Hormonal Contraceptives
In clinical studies, 50.2% of women (aged 16 to 45 years) who received GARDASIL used hormonal contraceptives. Use of hormonal contraceptives did not appear to affect the immune responses to GARDASIL.

Use with Steroids
In clinical studies for girls and women (aged 16 to 26 years), 1.7% (n = 158), 0.6% (n = 56), and 1.0% (n = 89) of individuals used inhaled, topical, and parenteral immunosuppressants, respectively. In a clinical study in women (aged 24 to 45 years), 1.4% (n = 27) used corticosteroids for systemic use. In a clinical study in boys and men (aged 16 to 26 years), 1.0% (n = 21) used corticosteroids for systemic use. The corticosteroids for all individuals were administered close to the time of administration of a dose of GARDASIL. These medicines did not appear to affect the immune responses to GARDASIL. Very few individuals in the clinical studies were taking steroids, and the amount of immunosuppression is presumed to have been low.

Use with Systemic Immunosuppressive Medications
There are no data on the concomitant use of potent immunosuppressants with GARDASIL. Individuals receiving therapy with immunosuppressive agents (systemic doses of corticosteroids, antimetabolites, alkylating agents, cytotoxic agents) may not respond optimally to active immunization.

Forensic Classification:
P1S1S3

Pfizer

LIPITOR®

atorvastatin calcium – crystalline form

Power to do more

More Evidence across More Patient Types

Moderate Risk

Hypertension

36% RRR

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

Diabetes

37% RRR

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

High Risk

CHD

59% RRR

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

CHD

22% additional RRR

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

Highest Risk

ACS

16% RRR

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

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

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