Looking at Luteolin:The Anticancer Compound

by Theresa Stephen

ccording to the Breast Cancer Foundation Malaysia, 1 in 19 women in Malaysia are at risk of breast cancer with Chinese women at the highest risk followed by Indian women and Malay women. Breast cancer is also the second leading cause of cancer deaths among women worldwide, right after lung cancer.

Cancer is a group of cells that have grown inexplicably, damaging healthy tissues surrounding it. This group of cancer cells would form a lump, which is called a tumour. A malignant tumour present in the breast is known as breast cancer.

In an effort to contribute to breast cancer research, University of Cyberjaya's Head of Pharmaceutical Technology and Industry Department, Associate Professor. Ts. Dr. Liew Kai Bin and his team work on discovering the anticancer property of Luteolin, originally found in plants such as the species Reseda luteola.

"Luteolin is a plant extract that can be found in many plants such as fruits, vegetables, and medicinal herbs. It is a natural flavonoid with anti-cancer properties. However, its use is limited due to its solubility and bioavailability. It would be a waste if we do not explore the potential of the natural extracts by overcoming its limitations," he says.

He was also driven to conduct this research as many anti-cancer drugs used today in chemotherapy are either chemically synthesised or extracted from plants with high side effects. The high risk of serious side effects often time complicates the chemotherapy process. The goal is to develop a compound with high anti-cancer effects and low side effects.

His research titled, "Development of Luteolin Loaded Folate Decorated Vitamin E TPGS—Poloxamer Long Circulating Micelle for Multi-Drug Resistant Breast Cancer Smart Targeting", investigates the effects of different concentrations of Vitamin E TPGS (a synthetic water-soluble version of vitamin E) and other polymers in enhancing the solubility and absorption of Luteolin to better target highly resistant forms of breast cancer cells.

Luteolin is a yellow, crystalline polyphenolic flavonoid that is present in fruits and vegetables like apples, carrots, celery, cabbage, green peppers, and dandelion leaves. Aside from its use in modern medicine, herbal traditions around the globe also use luteolin-rich plants to strengthen the immune system, relieve inflammation, and combat cancer.

As luteolin has limited solubility and low bioavailability, its extract is not clinically appealing to become a practical product. As such, Dr. Liew's research tries to manipulate the extract using 2 polymers, Vitamin E TPGS and Poloxamer, to form nanomicelles. Nanomicelles are used in the process of targeted drug delivery in the body which allows a greater depth of tissue penetration and increases the bioavailability of the drugs. When the nanomicelles are encapsulated with luteolin, the extract's solubility and bioavailability become greatly enhanced.

"Breast cancer cells are full of folate receptors. By including folate in the nanomicelles, it would increase its ability to perform targeted drug delivery to breast cancer cells. As micelles are nano-sized, they are easily solubilised and absorbed into the body," says Dr. Liew.

Needless to say, the process is more complex than that. Cancer cells have their own defence mechanism to reject foreign particles such as anti-cancer drugs from their membrane to protect them from being dissolved. This makes the anti-cancer agents less effective in killing cancer cells.

This is where the effectiveness of polymers – Poloxamer and Vitamin E TPGS – come to play. Poloxamer is reported to accumulate in multi-drug resistance cancer cells which increases the targeting and success rate of cancer treatment. Vitamin E TPGS on the other hand has also been reported to increase the circulating time inside the body and can also overcome multidrug resistance. With the encapsulation of Luteolin in Vitamin E-TPGS Poloxamer micelle, the solubility and bioavailability can be enhanced and the accumulation in multi-drug resistance cancer cells can be increased.

While it is important to produce a drug that can kill cancer cells, it is important to note the side effects it may cause. For a medicine to work, its molecules must bind to the right receptor to exert pharmacological action. For example, when a person who suffers a heart-related disease takes their prescribed medicine, it should be able to bind to the heart or the blood vessel controlling the dilation and constriction. However, when the molecules bind to other receptors in other organs, the person would then suffer side effects.

The anti-cancer medicines in the market work like non-specific missiles that hit both cancer cells as well as healthy cells, causing side effects. Therefore, there is a need for smart targeting drugs, a newer generation of medicine that is able to target cancer cells more specifically. In 2021, Dr. Liew managed to secure a Fundamental Research Grant Scheme (FRGS) award of RM144,300 from the Ministry of Higher Education for his research. His co-researchers include Associate Professor Dr. Shairvzah Ahmad Hisham, Deputy Dean of Academic Affairs of the Faculty of Pharmacy, Professor Dr. Shamima Abdul Rahman, Postgraduate Coordinator of the Faculty of Pharmacy, Associate Professor Dr. Chan Siok Yee from Universiti Sains Malaysia, Dr. Masriana Hassan from Universiti Putra Malaysia and Dr. Riyanto Teguh Widodo from University Malaya.

"Besides producing a scientific publication, I hope to produce a new practical natural-based anticancer product that can be used in the clinical setting. As cancer is still a major healthcare concern that takes the lives of many every year, I hope to be able to produce a highly effective, lowcost product with minimum side effects made accessible for patients," says Dr. Liew.

"We have completed the first phase of the research which is the formulation stage. The next phase would be to test the product in cell lines and animal models. We have partnered with the Malaysian Nuclear Agency to provide us with its facilities to conduct the animal study which will take 1 year to complete. If the second phase is completed with positive outcomes, there is a high possibility that this product can enter into the clinical phase for cancer prevention. We're confident that the product will make a great impact on anticancer therapy and look forward to completing the research for the greater good."

Side effects of cancer drugs

There are different kinds of side effects patients deal with when taking cancer drugs, and these side effects vary from person to person. Some of the side effects of breast cancer treatment include nausea or vomiting, diarrhoea, constipation, arm swelling, shortness of breath, and breast skin irritation.

Chemotherapy is the use of anticancer drugs to destroy cancer cells. Patients who undergo chemotherapy usually face side effects on a shortterm basis, which would go once treatment has finished. However, some of these side effects are severe, like a drop in the number of platelets.

This can lead to bruising easily, nosebleeds, and bleeding gums. Chemotherapy patients also have an increased risk of getting an infection, which can be lifethreatening if treatment is not done quickly.

Though most chemotherapy side effects are temporary, there are also patients who suffer late side effects such as early menopause, infertility, and heart and lung problems.

In fact, some chemo drugs may also increase the risk of developing a second cancer, especially if one receives higher doses of chemo over a longer period.

Breast cancer – the world's most prevalent cancer

The three main parts of the breast are the lobules, ducts, and connective tissue. The lobules are the glands that produce milk, and the ducts are tubes that carry milk to the nipple. The connective tissue surrounds and holds everything together.

The most common types of breast cancer are known as:

- 1. Invasive ductal carcinoma. This is when the cancer cells begin in the ducts and then grow outside the ducts into other parts of the breast tissue.
- 2. Invasive lobular carcinoma. Cancer cells begin in the lobules and then spread from the lobules to the breast tissues that are close by.

In both types, invasive cancer cells can spread to other parts of the body, a term known as metastasize.

Breast cancer is one of the 5 most common cancers in Malaysia. According to Cancer Research Malaysia, 2.3 million women were diagnosed with breast cancer in 2020, resulting in 685,000 deaths globally. More Asian women succumbed to the disease compared to the rest of the world as breast cancer continues to rise rapidly in the region.

In countries with high-income economies and in some Malaysian private hospitals, 9 out of 10 breast cancer patients survive for as long as 10 years. However, the stats reduce to 5 out of 10 in some parts of Malaysia due to late detection and poor or delayed access to treatment.



Source: National Breast Cancer Foundation, Inc. (America)

Breast cancer prevention

The importance of breast cancer screening cannot be overstated. Cancers detected at an early stage have a higher chance of being cured. Doctors recommend that women get mammograms every 2 years if they are above the age of 50. However, each woman has different risk factors and may require to be screened at a younger age.



Women are also encouraged to perform regular breast selfexaminations. The best chance of a long-term recovery from cancer is when the cancer has not yet spread. In order to reduce the risk of breast cancer, it is also advised to avoid alcohol or drink in moderation. Alcohol increases the risk by damaging DNA in cells. In fact, compared to women who don't drink at all, women who have 3 alcoholic drinks weekly have a 15 percent higher risk of breast cancer. It is also important to exercise at least 30 minutes on most days of the week. Research has found that women who exercise have an improved quality of life and fewer side effects during treatment.

Challenges faced by male breast cancer patients

Both men and women are born with a small amount of breast tissue. While women begin developing more breast tissue during puberty, men do not. Despite the differences in breast tissue size, the risk of developing breast cancer is still eminent.

Male breast cancer commonly occurs in older men, though it can happen to men at any age. Some of the symptoms include:

- A painless lump or thickening in the breast tissue
- Changes to the skin texture on the breast
- Changes to the nipple, such as redness or scaling, or a nipple that begins to turn inward
- Discharge from nipple

Aside from the gruelling process of surgery, chemotherapy, or radiotherapy, men also face stigmatisation due to this disease as it is a typical "women's disease". A study found that men diagnosed with breast cancer experienced social isolation as some do not know how to deal with a man having breast cancer. As it is a rare cancer, men would undergo therapy surrounded by other breast cancer patients who are female. An exchange of similar experiences to gain support is difficult to find, especially in these settings.



Associate Professor Ts. Dr. Liew Kai Bin, Head of Department, Pharmaceutical Technology and Industry

Upon obtaining his PhD at University Sains Malaysia, Dr. Liew served as a community and industrial pharmacist in various pharmaceutical-related fields, including product development, bioequivalence study, analytical chemistry, regulatory affairs and public health pharmacy before joining academia.

He has published over 80 publications in international journals and book chapters and has been awarded national and international grants that are worth more than RM500,000. Dr. Liew has been repeatedly invited as a speaker to deliver speeches in various countries such as Japan, India, and Indonesia. He has also supervised research projects for both undergraduate and postgraduate pharmacy students. Dr. Liew's research product has won several awards, including Best Innovation, Gold and Silver Awards in international exhibitions, including the Malaysia Technology Expo and International Innovation and Technology Expo.

Apart from teaching and doing research, he is also actively involved in community service and professional development programmes. He has also counselled public health campaigns organised by pharmacy students. Dr. Liew was the organising chairman for a few international workshops and seminars during his tenure at UCSI University. He was also awarded the Best New Lecturer by UCSI University in 2015.