

The Efficiency of The Natural Product

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ABSTRACT : *This research paper is written with the aim to investigate the efficiency of natural products, specially targeting on Taxol, Artemisinin, and Ginkgo Biloba. Those three drugs are the substances extracted from the natural products. While Taxol is mainly anti-cancer, Artemisinin is anti-malarial, and the Ginkgo Biloba is antioxidant. According to the several studies and database, the claim is that those natural product drugs are petty effective on treating specific disease. For the future expectations, there should be more clinical trials that identifying the safety, efficiency, optimal dosages and other treating diseases.*

KEY WORDS: *Taxol, Artemisinin, Ginkgo Biloba, natural product, efficiency.*

1.Introduction

A natural product is a chemical compound or substance that is isolated from a natural living organism. Over few centuries, the experts have done so many clinical researches on those natural sources, and mainly focus on the potential bioactive compound on medical uses. Eventually, the drug that made from those substances have gained the appeal by the U.S. Food and Drug Administration.

Based in the international hotspot research, there are three drugs Taxol, Artemisinin, and Ginkgo Biloba being chosen. The reason is due to their rough completion on clinical experiments and official approval, and their efficiencies have made them outstanding.

During this research, the main topic is exploring on exactly how efficient each drug is.

2.Taxol

2.1. Basic information about Paclitaxel

Paclitaxel is a natural product which is extracted from the Pacific yew. Currently, it is proved to be a microtubule-stabilizing drug that can be used for the treatment of

various cancers such as ovarian cancer, breast cancer and lung cancer. In 1963, American chemist M.C.Wani and Monre E.Wall at the Research Triangle Institute in North Carolina extracted the Paclitaxel from the Pacific yew. In 1971, with the help of Andre McPhail in Duke University, they identified the chemical structure of it and named it "Taxol". In 1979, Susan Horwitz and coworkers at Albert Einstein College of Medicine discovered the anti-tumor mechanism of Taxol, which attracted more biologists to discover the new method of fighting against cancer. Since the concentration of Paclitaxel is low in Pacific yew and the scarcity of the Pacific yew, scientists are finding the way to synthesis Paclitaxel in laboratory.

2.2 The history of finding Paclitaxel

In the early 1960's, the United States National Cancer Institute organized collection of plants from the U.S for evaluation as potential sources of anticancer drugs. Three-quarters of a pound of stem bark of the Pacific yew was collected in 1962 at a site 7 miles north of Packwood, Washington, in the Gifford Pinchot National Forest. Monre.Wall and Mansukh Wani at the Research Triangle Institute (RTI) was assigned to identify the active substance in Pacific yew, and in 1971, with the help of Andre. McPhail, they used X-ray crystallography to determine the chemical structure (figure 1)¹ of the Paclitaxel.

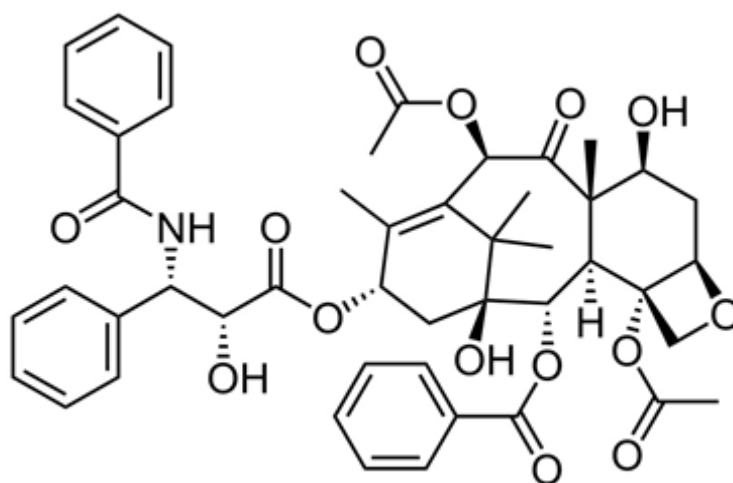


Figure 1. The chemical structure of Paclitaxel

¹ Figure 1 from Wikipedia

In 1979, Susan Horowitz and coworkers at Albert Einstein College of Medicine found that Paclitaxel can bind to the tubulin and can promote the tubulin assembling into microtubules and can block the microtubules from disassembling. In order for cells to properly divide microtubules must be dynamic to assemble and disassemble. Therefore, the Paclitaxel can stop the process of cancer cell division and growth. John Hopkins University and Albert Einstein College of Medicine both did the animal tests which had indicated that Paclitaxel might be useful against breast cancer.

2.3. How Taxol/Paclitaxel kills cancer cells

Microtubules are polymers of tubulin that form part of the cytoskeleton and provide structure and shape to eukaryotic cells. During the mitosis of the cell, spindle microtubules is a critical structure of helping the kinetochores divide and move to both side of the cell. The separation of kinetochores depends on the attachment of the spindle microtubules and the kinetochores. (figure 2)²

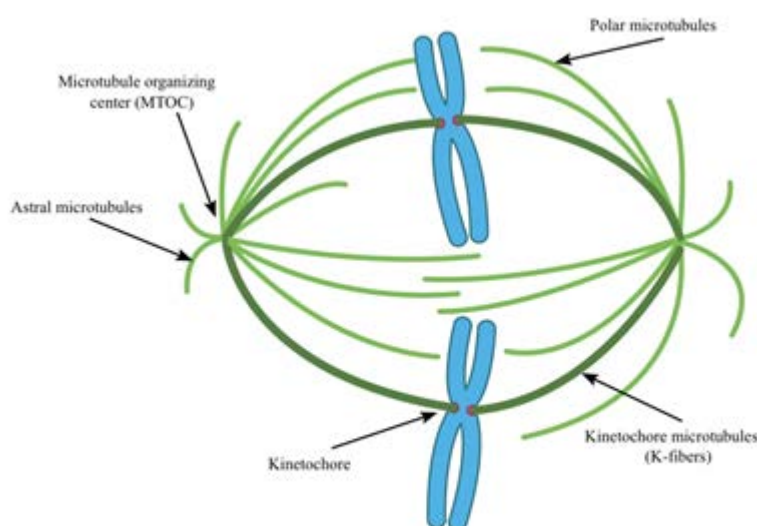


Figure 2. The attachment of the spindle microtubules and the kinetochores.

When the spindle microtubules disassemble, the microtubules monomers break and bend outwards. With the microtubules monomers consistently breaking, the

² Figure 2 from Wikipedia

Dam-I complex will take shape of a circular structure in the root of the bending region of the microtubules monomers, attaching to the kinetochores and then transforms the bend of the microtubules monomers into tension which can pull the replicated pairs of sister chromatids to both poles of the mitotic spindle³. The protein that forms the spindle microtubules is called tubulin. There are two types of tubulin: α -tubulin and β -tubulin. Paclitaxel can tightly combine with β -tubulin and induce the polymerization of these two proteins. The polymerized complex is called the dimer, which can assemble the spindle microtubules. Therefore, the Paclitaxel appears in the spindle microtubules and prevent it from disassembling. If the microtubules do not disassemble, there will not be the tension that can pull the sister chromatids to both poles of the cell, which can lead to the cell division stop in G2-M period and can inhibit the division of the cells. Generally, it is believed that inhibition will lead to the cell apoptosis, which indicates the effect of Paclitaxel on cancer cells.

Cancer cells are a kind of cells that can replicate without bound and can easily metastasis. Paclitaxel can inhibit the cancer cells dividing and promote to the apoptosis. Therefore, it can be used for the treatment of cancer. It is widely used in ovarian cancer, breast cancer, lung cancer and some kind of head and neck cancer. There is still more treatment of cancer that Paclitaxel can apply to under exploring, such as gastroesophageal cancer, endometrial cancer, cervical cancer and prostate cancer.

2.4 Paclitaxel in Breast cancer

In breast cancer treatment, Paclitaxel is a widely used drug with an overall response rate of 25%. However, resistance occurs frequently and the evasion mechanisms remain unclear. Tumor recurrence occurs in 30% of node-negative and up to 70% in node-positive breast cancer patients. Several recent studies suggest that paclitaxel (5, 6) both kills and activates tumor cells thereby increasing chemoresistance and metastasis. The goal of this study was to delineate the mechanisms underlying relapse-associated metastasis possibly driven by paclitaxel therapy.⁴

In vitro experiment, Paclitaxel is infused in nutrient solution with human breast cancer cell BCap37. The cell cycle distribution analysis showed that after treatment with paclitaxel (100nmol/L) for 3 hours, the percentage ratio of cells in G2 /M phase was increased. At 48 hours, the percentage of G2 /M cells was 55.5 %. The sub-diploid peak (Sub-G1), also known as the apoptosis peak, indicated that the DNA degraded. At 72 h, the cells in sub-G1 phase accounted for 9.2%. It is also reported that the Bcl-2 gene participate in the induction of Paclitaxel. The protein

³ Beth A. Weaver William Bement. "How Taxol/Paclitaxel kills cancer cells." Mol Biol Cell.2014 Sep 15;25(18)

⁴ Paclitaxel as First-Line Treatment for Metastatic Breast Cancer. April 1, 1997

that the Bcl-2 gene encodes can inhibit apoptosis in lymphocyte and non - lymphocyte tissues. The vitro experiment showed that after paclitaxel (100nmol/L) treatment, the expression of Bcl-2 protein decreased at 3, 12 and 24 hours, which means that the inhibition of apoptosis is suppressed and the cells continue to divide in an unregulated manner.

2.5 Clinical application of Paclitaxel

2.5.1 Ovarian Cancer

Paclitaxel is a front-line agent for ovarian cancer chemotherapy, along with the platinum agents. Although Paclitaxel has been used in clinical treatment for nearly 20 years, scientists are still finding the efficacious paclitaxel dosing strategy in ovarian cancer. In a Canadian-European trial, it came to the conclusion that compared to the 24-hour infusion schedules for paclitaxel in recurrent ovarian cancer, 3-hour infusion has the equivalent efficacy with reduced bone marrow toxicity and increased incidence of neuropathy. Therefore, for its less cost and convenience, 3-hour infusion became the new standard of paclitaxel treatment. In early ovarian cancer, it is suggested to use three cycles of paclitaxel at 175 mg/m² for three hours. In advanced ovarian cancer treatment, it is highly recommended to use paclitaxel with carboplatin, a better tolerated platinum compound. Intravenous (IV) carboplatin is widely used around the world with paclitaxel to the treatment of ovarian cancer.

2.5.2 Lung Cancer

For the treatment of non-small-cell lung cancer, apart from the use of paclitaxel with carboplatin, the addition of bevacizumab also has benefits. It is proved that the addition of bevacizumab to a standard, platin-based, two-agent chemotherapy regimen conferred a significant improvement in overall survival, progression-free survival, and response rate in patients with non-squamous-cell carcinoma and a good performance status.⁵

2.5.3 Breast Cancer

⁵ Alan Sandler, M.D., Robert Gray, Ph.D., Michael C. Perry, M.D., Julie Brahmer, M.D., Joan H. Schiller, M.D., Afshin Dowlati, M.D., Rogerio Lilenbaum, M.D., and David H. Johnson, M.D.. "Paclitaxel-Carboplatin Alone or with Bevacizumab for Non-small-Cell Lung Cancer." *New England Journal of Medicine*. 14.Dec 2006.

At the current time, docetaxel is the preferred taxane for many clinicians treating patients with breast cancer. In most experiment, the potentially most optimal Taxane schedules is dose-dense therapy, which is under active investigation, suggesting administering AC followed by paclitaxel every 2 weeks. One optional neoadjuvant therapy is to give weekly paclitaxel monotherapy followed by four cycles of FAC. ⁶In addition, paclitaxel and doc-etaxel is also a method to the treatment of breast cancer.

2.6 Latest investigation of Paclitaxel

In 2017, George Karagiannis et al. found that paclitaxel promotes breast cancer metastasis by increasing the tumor metastasis microenvironment. ⁷ A month later, Tsonwin Hai found that in addition to helping cancer cells escape from their primary foci, paclitaxel also acted directly on the lungs, changing the lung microenvironment and helping cancer cells colonize in the lungs ⁸. In 2018, Loanna Keklikoglou and Michele De Palma of ecole Polytechnique Federale De Lausanne have identified another mechanism by which paclitaxel promotes tumor metastasis. They found that paclitaxel and doxorubicin, two commonly used chemotherapy drugs, can promote the release of exosomes from tumors, change the microenvironment in the lung, and promote lung metastasis of breast cancer. The paper is published in Nature Cell Biology. ⁹The researchers noted, however, that the survival rates of the mice under various treatment conditions were not examined in the study, and it was unclear whether the tumor metastasis caused by the chemotherapy would affect the survival time of the model mice. The clinical team behind the study also said: "Our results should not prevent patients from receiving neoadjuvant chemotherapy. As multiple clinical trials show, it remains an essential treatment for many invasive breast cancers."

2.7 Conclusion

⁶ "Decetaxel and Paclitaxel in the treatment of Breast cancer: A review of clinical experience." The oncologist

⁷ Karagiannis G S, Pastoriza J M, Wang Y, et al. "Neoadjuvant chemotherapy induces breast cancer matastasis through a TMEM-mediated mechanism[J]." Science translational medicine, 2017, 9(397)

⁸ Chang Y S, Jalgaonkar S P, Middle J D, et al. "Stress-inducible gene Atf3 in the noncancer host cells contributes to chemotherapy-exacerbated breast cancer metastasis[J]." Proceedings of the National Academy of Sciences, 2017, 114(34)

⁹ Keklikoglou I, Cianciaruso C, Guc E, et al. "Chemotherapy elicits pro-matastatic extracellular vesicles in breast cancer models[J]." Nature Cell Biology, 2018:1

In general, paclitaxel that extracted from the pacific yew can be widely used in cancer treatment. Its unique mechanism of promoting the tubulin polymerization and prevention of microtubules disassembling make it a useful drug of killing cancer cells. In different cancers, it has different use strategies. In ovarian cancer, it is used along with the platinum agents and 3-hour infusion can be a relatively optimal dose. In lung cancer, the use of paclitaxel with carboplatin and bevacizumab can have benefits. In breast cancer, there are different strategies under investigation, among which the dose-dense therapy can be a potentially optimal method. In the latest discovery of paclitaxel, it suggests that the paclitaxel may promote the metastasis of cancer cells when killing them. But it was unclear whether the tumor metastasis caused by the chemotherapy would affect the survival time of the model mice.

3.Artemisinin

3.1 Introduction

3.1.1 Artemisinin

Artemisinin is the substance that is extracted from the plant *Artemisia annua* (sweet wormwood).

Artemisinin and its derivatives are potent drugs known for rapidly reducing the number of malaria parasites in the blood of malaria patients, and these recognized drugs for malaria include highly resistant strains.

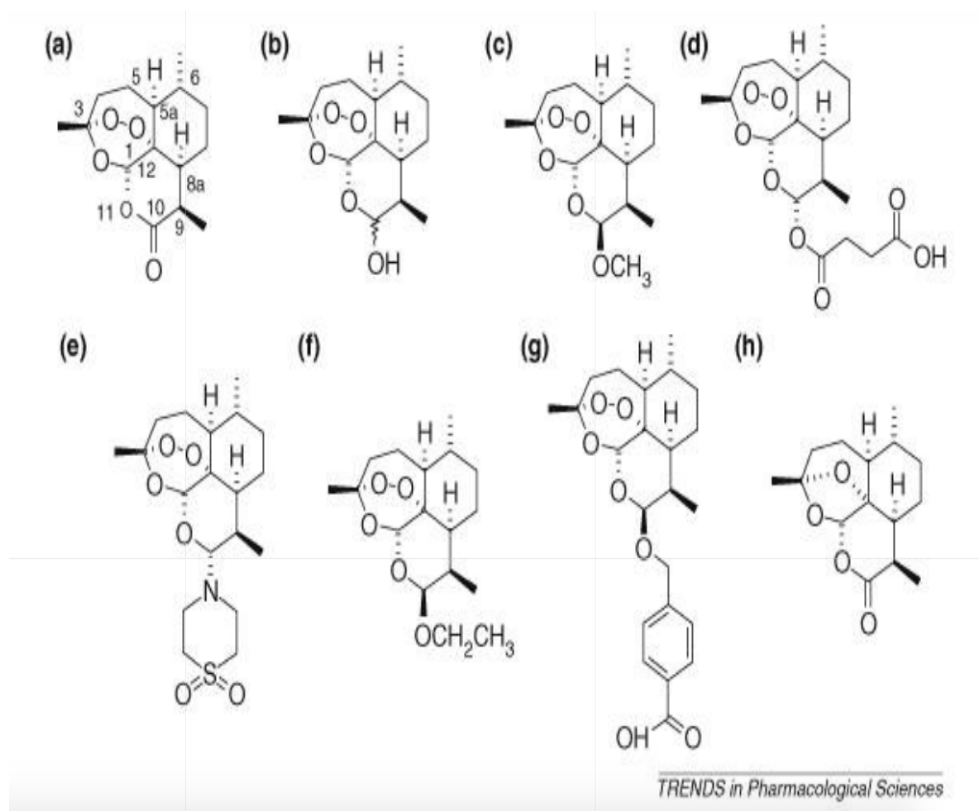


Figure 3. Chemical structures of artemisinin

In the figure above, “Artemisinin (a) isolated in crystalline form in 1973 from *Artemisia annua* and derivatives dihydroartemisinin (DHA) (b), artemether (c), artesunate (d) and arteether (f) were first prepared by Chinese scientists in the 1970s. Artemisone (e), representative of a new class of artemisinin known as amino-artemisinins, is curative in clinical trials at one-third the dose regimen of artesunate. It is characterized by low toxicity. Artelinate (g) was prepared at the Walter Reed Army Institute of Research, but was withdrawn because of toxicity concerns. Deoxyartemisinin (h), lacking the peroxide bridge, is biologically inert.”¹⁰

3.1.2 ACT

¹⁰ Krishna, Sanjeev, et al. “Artemisinins: Their Growing Importance in Medicine.” *Trends in Pharmacological Sciences*, Published By Elsevier In Association With The International Union Of Pharmacology, Oct. 2008, www.ncbi.nlm.nih.gov/pmc/articles/PMC2758403/figure/fig1/.

ACT (artemisinin-based combination therapy) combines the artemisinin derivative with a partner drug. While the artemisinin compounds are reducing the number of parasites in the first three days of treatment, the partner drug is the drug that eliminates the residual parasites.

The efficiency of the ACT has pursued it to become the first-line treatment for simple *Plasmodium falciparum* and chloroquine-resistant vivax malaria.

3.2 Uses

3.2.1 Antimalarial

Artemisinin and its derivatives can rapidly reduce the number of malaria parasites in the blood of malaria patients with a rate of 10,000 per erythrocytic cycle, resulting in rapid clinical responses.

Due to the feature of being water-insoluble, the carbonyl group of artemisinin was reduced to obtain DHA and its derivatives such as the water-soluble artesunate and oil-soluble artemether and arteether, which show greater antimalarial activity.

3.2.1.1 Malaria

Malaria is a life-threatening disease caused by the transmitting of the parasites through biting. With the symptoms of fever, headache, and chill, if the patient is not quickly treated, then it may become several illnesses that lead to death.

3.2.1.2 Danger of malaria

According to the data reported by WHO states that “there were about 212 million new cases of malaria worldwide in 2015. First of all, the majority 90% of the case come from African, followed by the Southeast Asia region with 7%, and the last part is 2 % in the Eastern Mediterranean region. As a result, the Malaria burden led to an estimate of 429,000 malaria deaths. Specifically, children under 5 years of age are particularly vulnerable to malaria, infection, and death. In 2015, malaria killed about 303,000 minors worldwide”.¹¹

3.2.2 Schistosomiasis

Other than treating malaria, artemisinin also can solve some phylogenetically unrelated parasitic infections such as schistosomiasis.

11 “Fact Sheet: World Malaria Report 2016.” World Health Organization, World Health Organization, 21 Feb. 2017, www.who.int/malaria/media/world-malaria-report-2016/en/.

Schistosomiasis is helminthiasis that affects more than 200 million people and returning travelers in the tropics. Treatment relies mainly on single-agent praziquantel. But, Praziquantel does not kill developing schistosomiasis, leading to frequent treatment failures and reinfection. Therefore, new drugs are urgently needed.

According to the PubMed database for publications with the search terms "artemisinin" and "schistosomiasis", reviewed their anti-schistosomiasis activities in vivo and patients, and selected animal studies and human clinical trial reports. *Mansonia*, *Schistosoma japonicum*, and *Schistosoma japonicum* have been tested in mice, rabbits, hamsters, and dogs. These artemisinin derivatives greatly reduce the incidence of helminths by causing oxidative and metabolic stress, which leads to morphological damage and reduced parasite fertility.

3.2.3 AntiCancer

Recently, the artemisinin has also shown strong and extensive anticancer properties in cell lines and animal models. Like other natural products, ARS acts on tumors in a variety of specific ways and exhibits cytotoxic effects. Cellular responses of ARS and its derivatives (dihydroartemisinin, artesunate, artemisinin, artemisinin) to cancer cells include oxidative stress response of reactive oxygen species and nitric oxide, DNA damage and repair, various modes of cell death, Inhibition of angiogenesis and tumor-related signal transduction pathways, and signal sensors.

ARS drugs are still being tested in pre and early clinical studies. Several published case reports and phase I/II trials have shown the clinical anticancer activity of these compounds. So it is not recommended until controlled clinical trials demonstrate the safety of unapproved combination therapy.

3.3. History

A project leading to the discovery of artemisinin was initiated at the request of North Korean leaders who suffered severe soldier losses due to malaria during the Vietnam War. Chairman Mao and Premier Zhou called for urgent solutions to find effective antimalarial drugs. Beginning in 1975, thirty scientific research units and medical and pharmacology schools formed the "Qinghaosu Research Collaborative Group", to systematically work in inactivating the Qinghao plants and took only 6 years to form a certified drug from a Chinese traditional medicinal herb. And another 15 years finished the evolution from Qinghaosu to derivatives, combinations, large scale production, and marketing.

Nonetheless, this significant finding and the apparent delay in the reporting of relevant studies may be due to several factors. First, this project was initially a secret military project. Second, Western journals dominated Chinese academia hindered the publication of scientific data by, especially during the Cultural Revolution.

Finally, limited English communication skills may also play a role. In fact, a large number of papers on artemisinin and related topics have been published in Chinese journals.

Next, the origin of the ACT. As early as the 1980s, since all three antimalarial drugs developed in early China were combination drugs, initial efforts focused on this strategy. In the late 1970s, the first widely used drug ACT was invented by pairing the existing drug mefloquine with artesunate. Then in the early 1990s, artesunate-mefloquine (ASMQ) was used to treat malaria in Cambodia, Thailand border province, because the existing mefloquine treatment in these areas has failed, and it successfully cured almost 100% of infected patients.

3.4. Efficiency

According to data, there has been a significant reduction in the global malaria burden over the past 15 years, and increased access to ACT in malaria-endemic countries is the key. Between 2010 and 2017, it is estimated that countries will purchase 2.74 billion ACT, and approximately 62 % of these purchases are for the public sector.

“Between 2010 and 2015, the incidence rate of malaria (new malaria cases) in the global and African regions decreased by 21%. Over the same period, malaria mortality rates are estimated to have fallen by 29% globally and 31% in Africa. The burden of malaria in other areas has been greatly reduced. Since 2010, malaria mortality has decreased by 58% in the Western Pacific, 46% in Southeast Asia, 37% in the Americas, and 6% in the eastern Mediterranean. In 2015, there was no malaria in Europe: all 53 countries in the region reported zero locally acquired malaria cases for at least one year. Malaria mortality among children under five years of age was estimated to have decreased by 35% between 2010 and 2015.”¹²

3.5. Side Effects

The possible side effects of using artemisinin include skin rash, nausea, vomiting, tremors, and liver issues. However, while many anti-malaria drugs can cause psychological side effects, there is no explicit evidence on artemisinin cause psychological side effects, that's also one reason so many people choose it once it was invented.

3.6. Resistance

¹² “Fact Sheet: World Malaria Report 2016.” World Health Organization, World Health Organization, 21 Feb. 2017, www.who.int/malaria/media/world-malaria-report-2016/en/.

3.6.1 Partial resistance

Artemisinin resistance usually refers to delayed removal of malaria parasites from the bloodstream after treatment with ACT. More precisely, the delay gap should be named as "partial resistance", because recent studies have shown that the mechanism of parasite resistance to artemisinin compounds affects humans only at one stage of the malaria parasite cycle: the ring stage. In such a way, the time limit and cycle-specific function can be emphasized by this name.

Although the ACT was doing well in the first decades, however, by the mid-2000s, it was clear that the artesunate could no longer bear the resistance from *P. falciparum* toward mefloquine. By upregulating the multidrug resistance gene encoding the mutant transporter PfMDR1, parasites can extract drugs from their cytoplasmic targets and eliminate them into the digestive juice, so many of the parasites can survive elimination by mefloquine. By 2008, ASMQ had failed in about 20% of patients in this region of Southeast Asia. Only artemisinin resistance rarely leads to treatment failure. But in fact, the resistance of Plasmodium to ACT partner drugs may lead to treatment failure (whether or not artemisinin is partially resistant). Therefore, in the GMS regions, some ACTs that have been identified as resistant to artemisinin and ACT partners have failed.

3.6.2 Mutation

At the end of 2013, researchers had an amazing discovery: the Kelch 13 (K13) mutation in the propeller domain is associated with delayed parasite clearance in vivo and in vitro. This finding allows researchers to accurately map and monitor the geographical distribution of resistance. In many cases, it can also be a mechanism for drawing resistance retrospectively.

3.6.3 Controlling plan

The efficacy of the ACT was evaluated by the Therapeutic Efficacy Study (TES). Regular conduct of such studies in the same location can identify early declines in drug efficacy and provide evidence to guide national malaria treatment policies.

WHO is working with national malaria programs, research institutions, and other partners to map the distribution of artemisinin resistance and partner resistance within and outside the GMS, because they can become the early warning signals or used to study whether ACT treatment failure is a result of drug resistance.

Additionally, WHO, in collaboration with national malaria plans and partners, developed the Strategy for malaria elimination in the Greater Mekong Subregion (2015–2030). The strategy urges immediate action, calls for the eradication of all human malaria in the GMS by 2030, and prioritizes areas where multidrug-resistant malaria parasites have been identified.

Under the technical guidance of WHO, all countries in the GMS have developed national malaria elimination plans. As countries implement these plans, WHO is providing ongoing technical support through its five national offices for global marine ecosystems, regional offices in New Delhi and Manila, and the organization's headquarters in Geneva.

In the long run, current emergency actions will save substantial money and improve the sustainability and public health impact of global malaria interventions.

3.6.4 Funding

The generous contributions of many donors, including the Australian Department of Foreign Affairs and Trade, the Bill & Melinda Gates Foundation, the Global Fund to Fight AIDS, Tuberculosis, and Malaria (Global Fund), the UK Department for International Development and the US Agency for International Development.

In response to partial resistance to artemisinin, the Global Fund launched the Regional Artemisinin-resistance Initiative (RAI) in 2013. Funding provided through this initiative enables countries to purchase and distribute long-lasting insecticidal nets (LLINs), rapid diagnostic testing, and quality-assured drugs. In 2017, the Global Fund announced the expansion of RAI (RAI2E) and invested an additional \$242 million between 2018 and 2020.

3.7. Current Updates

3.7.1 Hearing loss

A recently published study in PNAS entitled "Unconventional secretory pathway activation restores hair cell mechanotransduction in a USH3A model", suggests that artemisinin can help inner ear sensory cells recognize and transport essential proteins to specialized membranes.

The ability to hear depends on the ability of the protein to reach the outer membrane of the sensory cell of the inner ear. But in some types of hereditary hearing loss, protein mutations prevent them from reaching these membranes. The sensory cells of the inner ear have hairy protrusions on their surface and are therefore called "hair cells". Hair cells convert vibration caused by sound and movement into electrical signals, which are transmitted through nerves and converted into hearing and balance information in the brain. The mutant form of this protein, *clarin1*, prevents hair cells from recognizing and transporting it to membranes necessary for hearing through typical intracellular pathways. Instead, most mutant *clarin1* proteins are trapped, ineffective in hair cells, and detrimental to cell survival.

Surprisingly, the team found that artemisinin restored the function of sensory cells in the inner ear of genetically engineered zebrafish, thereby restoring hearing and balance, thus providing the necessary hearing proteins for humans.

3.7.2 COVID

Chemists at the Max Planck Institute of Colloids and Interfaces (Potsdam, Germany) collaborated with virologists at Freie Universität Berlin have found in laboratory studies that aqueous and ethanolic extracts of specially bred sweet wormwood plants (*A. annua*) are active against the new coronavirus that has caused the Conorivus. And they have begun the human clinical trials to test the efficacy of both teas and coffee containing *A. annuas* as well as the anti-malaria drug artesunate are about to begin at the University of Kentucky's academic medical center.

Although the trial has not ended, some people began to call these substances COVID Organics. The scientist replied, "In recent weeks we have been asked over and over again to say something about Covid Organics. We have tried to get hold of some. Unfortunately, we weren't able to get hold of any samples. I think it's a real shame. If it really works, it would be great to be able to test it. As far as we know, there have not been any scientific studies so far.."13

3.8. Future Expectancy

- Effective isolation & Effective disease prevention
- While the molecular studies have shown that partial artemisinin resistance has emerged independently in several locations in the GMS, this can cause rapid expansion and important public health consequences.
- Strengthen drug market regulation
- The substandard ACT could be another reason for resistance.
- Tracking the spread of artemisinin resistance
- Using K13 mutations as molecular markers
- Since the pace of resistance development in parasites depends heavily on the genetic backgrounds of the parasites, this network is particularly pertinent given the diverse nature of drug histories and regimens in different countries.

13 (www.dw.com), Deutsche Welle. "Germany: Scientists Test Artemisia Plant against Coronavirus: DW: 25.06.2020." DW.COM, 25 June 2020, www.dw.com/en/germany-scientists-test-artemisia-plant-against-coronavirus/a-53944514

- It might help understanding whether partial resistance to artemisinin will further develop to affect other stages of the parasite and become fully resistant
- Further study on antimalarial drugs
- Because while the resistance is growing, we need to avoid total reliance on artemisinin as our last line of defense
- More clinical trials on the use of artemisinin
- No clinical evidence to provide convincing evidence of its therapeutic value for schistosomiasis.

4. Ginkgo Biloba

4.1 Introduction

Ginkgo biloba tree is one of the oldest living trees among the world, and it is referred to as the living fossil. The tree is originated from China. It was grown in the temple garden in China and Japan since ancient time, and it can tolerate cold weather and polluted air especially in urban area which make it widely grown in Asian. The ginkgo was used as a traditional Chinese medicine for centuries and it was popular in many countries. Scientific evidence has suggested that the concentrated or purified extracts of Ginkgo biloba leaves may provide protection against some neural and vascular damage.²¹ EGb-761 is a special extract from Ginkgo biloba tree's leaves. Its effect on a wide range of diseases or disorders has been studied for years.

4.2 Composition of EGb-761

It contains 24% of flavanol and 6% of terpene trilactones, and the terpene trilactones are mainly composed of Ginkgolides and Bilobalide. Some of the constituents of the Ginkgo biloba are not present or present with a very small amount in EGb-761. The ginkgolic acid and steroids occur with less than 1% concentration.

4.3 Ginkgo and oxidative effect

The ginkgo leaf extract has antioxidant property which is applied to the therapy of chronic diseases. It can be directly used to scavenge the free radicals such as the reactive oxygen species or inhibit their formations or inhibit its formations.²² The ginkgo leaf extract can remove reactive oxygen species such as hydroxyl radical, peroxy radical, nitric oxide radical, super oxide anion radical, hydrogen

peroxide, and ferryl ions species.²⁷ The ginkgo leaves extract can also increase the antioxidant ion activities such as superoxide dismutase, to work as an antioxidant.

4.4 Ginkgo and Cerebral ischemic injury

The human brain requires large amount of energy, which is provided by nutrients and oxygen from the body. As the brain does not store sufficient energy for functioning, interruption of glucose and oxygen supplies may lead to irreversible neurogenetic damage, which results in permanent disabilities. Ischemic stroke is a common cardiovascular disease(CVD) caused by blockage of arteries and fresh blood from heart could not reach the brain and its cells will die after few minutes. Ischemic stroke accounts for 69.6% of incident strokes and 77.8% of prevalent strokes.³⁸ The stroke is mainly caused by atherosclerosis, a process of gradual cholesterol deposition. The process narrows the artery and the blood cells may form blood clots that block the artery to form thrombosis.¹²

The ginkgo leaf extract has cardioprotective effects by acting as a antioxidant. It reduces the release of free radicals and lipid peroxidation causing tissue damage. The ginkgo leaf extract also increases the coronary blood flow through an antiplatelet activity by ginkgolide B.²³ Ginkgolide B is proved to reduce 50% to 60% of the production of reactive oxygen species, which can be used to treat various diseases.²⁸ The flavonoids from the leaves can improve contractile functions by increasing the release of catecholamines from endogenous liver tissue.

4.5 Ginkgo biloba and Alzheimer

In traditional Chinese medicine, the ginkgo leaves have been believed to have memory enhancing property. Multiple studies have been done to show the relation of the standardize ginkgo biloba extract and the memory impairment such as Alzheimer disease. Some experiment had shown that there may be moderate positive effect on cognition decline if large dose of ginkgo is taken, whereas the majority of studies did not show a difference in taking a placebo and taking ginkgoes.²⁹ The outcomes varied among the studies, and they failed to show any clear patterns of benefits for patients. It might be beneficial to take ginkgo extracts combined with conventional medicine with help of medic, but relying on herb medicines only may not be recommended.

4.6 The side effects of Ginkgo biloba

The Ginkgo biloba extract has very high medical value, but the ginkgolic acid (GA) present is proved to be highly allergenic and cytotoxic. Ginkgo biloba may cause severe side effects such as allergic skin reactions, headaches and digestive problems.³⁹ Patients with epilepsy or diabetes should only take ginkgo biloba with the help of the medical professions. People with bleeding disorders or taking supplements or medications related to blood clotting such as aspirin should avoid taking the ginkgo biloba, as it may affect blood clotting.

It concerns people that recent studies have reported that ginkgo biloba extract increased the risk of liver cancer of rodents.¹⁹ A study done on the data collected by National Center for Health Statistics compared the ginkgo and alcohol intake by samples of people and the liver enzymes from blood. There is no significant difference in the level of liver enzyme and Bilirubin between consumer and non-consumer in both males and females. The results show that the ginkgo biloba does not affect the same enzyme as alcohol does to liver function. The study has limitations that it does not show the relations of cause and effect and the sample size over 600 people may be too small to detect the liver injury.

5. Conclusion

In general, there are some natural products that have been proved to be effective in the treatment of certain diseases and have been used in clinical treatment. For these products, diverse clinical trials are expected to discover more information about them, such as the side effects and optimal doses. However, there are more natural products are being explored and the scientists are still finding their function in the treatment of disease.

6. Acknowledgement

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