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Review Article

Obstacles in Phytopharmaceutical Drug Discovery and the Urgent Need for Regulatory and Funding System Reformation

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Abstract

The global healthcare industry particularly the pharmaceutical industry faces challenges such as toxicity, food residues and microbial resistance. Therefore, the industry has to be transformed towards phytopharmaceuticals to alleviate adverse effects. However, the natural product drug discovery faces stringent regulatory issues, pharmaceutical monopoly and funding constraints. Therefore, the formulation of favorable laws and regulations, is vital, to spur the industry to enable the discoveries of phytopharmaceutical; that may initiate the bioeconomy of tropical countries; especially the poor ones in Asia.

Keywords: Natural Product Drug Discovery; Favorable Regulation; Funding

Abbreviations

The use of natural product or herbs in the treatment of mankind, has been practiced by Siddha masters for thousands of years. However, in the middle of 20th centuries, where chemically synthesized drug was at dominance, the natural therapy has been placed in a limelight. Due to the adverse effects and the development of microbial resistance, in the chemically synthesized medication systems; the global healthcare systems have been forced to revert to the natural product therapy gradually.

Majority of illness and ailment that requires oral medication is well treated without side effects; by ethnomedicine or herbs. Approximately 80% of world's population including developed countries, depends completely or partially on herbal medicine to cure ailment [15]. The combination of these herbs was efficacious in treating ailments that are not easily treated with pharmaceuticals.

Natural product as a source of drug

The plant base medication has been the main source of drug for centuries although the use was replaced by pharmaceuticals in the middle of 20th century. However, in the last few decades herbal medicine is emerging again as an important medical system to complement the allopathic system of medicine [1]; accepted in Malaysia hospitals lately.

The use of whole plant and its extracts have been in practice by Siddha masters for ages. Currently, with the advancement in chemistry and contemporary extraction methods and identification systems; the bioactive compounds were succesfully isolated and separated for direct use; or as a lead for semisynthesis of a compound of higher activity with lower toxicity [6].

The advantages of tropical countries and the threats to the bioresources

The tropical rainforest is inhabited by a widely bio-diversed species of flora of up to 500,000 species, in which 95% of the medicinal values are still yet to be investigated [10,11] and they belong to angiosperms category of flowering and fruiting plant with seeds. The Asean countries harbours the majority of these medicinal plants; to benefit from bioeconomy project. Therefore, its timely to execute a continous drug discovery acitivities.

The untapped flora has to be utilized by the modern science to discover cure for ailments such as cancer and other diseases yet to be healed. The Siddhars or saints of Siddha medicine via their wisdom and supernatural power has outline 4448 diseases; that will affect human in the present and future; whereby only less than 2000 of these diseases, are familiar to the modern allopathic sci-

entist and specialist. Therefore, there is a wide range of bioactive compounds to be discovered; to cure unknown diseases that are known to the Siddha masters only.

Apart from Asia, the remaining part of the world that may benefit from their natural resources of the tropical rainforest are shown in Figure 1. Hence, it's a fortune; particularly to the poor economies, to tap the multi-billion-dollar bioeconomy industry for their economic transformation.

Nevertheless, the excessive deforestration and burning is a great threat as bioresources may vanish much earlier than the drug discovery enforcement. Recently, the area of Amazon forests burned was 259,000 square km or twice the size of peninsular Malaysia. The greens are estimated to produce 20% of global oxygen for all being on earth. It is believed that the burned cleared land is for the cultivation of corn and soybean for livestock farming; to add to the already worsening global warning. International Union for the Conservation of Nature (IUCN) has estimated that 28,000 species of animal, fish and plants are at the brink of extinction [9]. Figure 1 below shows the countries mainly developing nations; that can benefit by venturing into the eveready drug resources.

Figure 1: The world tropical map below shows the countries that harbours tropical rainforest.

The fiasco of livestock farming

There is an urgent need for paradigm shift towards stopping meat consumption as the livestock farming is contributing to serious global warming from methane emission. It has also contributed mainly to anti-microbial resistance (AMR) whereby 75% of the antibiotics and other pharmaceuticals are consumed. An estimated of 75% of global corn and soybean is consumed by livestock for meat conversion at a very inefficient ratio, whereby 30kg feed required to convert to 1kg meat. The commodity could have been fed to millions of starving mankind in the world. The production and sourcing of meat is one of the major causes of global warming, land and water pollution and destruction of environment [4,5].

Bioactive compound identification and stages in drug discovery

The extraction of bioactive compounds from plants is simple but the separation and identification of different compounds from the group alkaloids, flavanoids, terpenoids, phenolic compounds and others are very complex and tedious. Very often they are in minute amounts varying from micrograms to nanogram. In addition, the same compound may vary widely dependent on geographical location, climatic conditions, soil fertility, irrigation, pest infestation and other factors [11].

As far as funding for these activities in Malaysia, these researches have been funded to the government linked institutions, like research institutes and universities. Nevertheless, most of these research findings are halted at the level of in-vitro bioassays and laboratory animals; without the completion till a novel drug is developed. Figure 2 shows the processes involved in the drug discovery system.

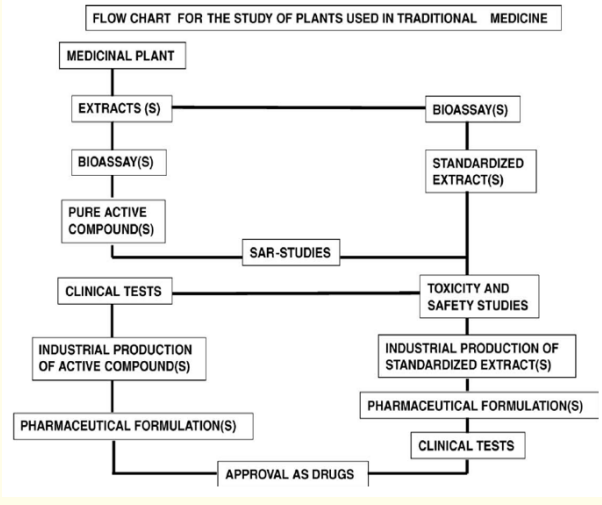

Figure 2: The flow chart below shows all the processes that a bio active extract goes through prior to development of a pure drug and extract-based drug.

As illustrated above; in spite of the toxicity and safety studies completed; researchers are halted from progressing towards dosage validation, efficacy, adverse effects and others due to funding issues.

Apparently, global drug discovery system has been monopolized by the Federal Drug Authority (FDA) based in United States of America (USA); for approval of novel compound; including chemically synthesized drugs. The FDA system of one compound approval out of thousands submitted; with billions in expenditure and waiting period of 10 years minimum; is neither feasible and nor viable [6].

The monopolistic strategy was tactically designed to hinder tropical countries and developing economies to venture into this multi-billion-dollar bioeconomy. Therefore, tropical countries should omit the engagement with FDA and formulate their customized systems for drug discovery with minimal cost and fast approval. FDA is aware that if natural compounds is allowed to thrive, the pharmaceutical industry and the petrochemical industries which produces the lead compounds for chemical drug synthesis; has to wind up.

Seemingly, there are many diseases untreatable in allopathy; is being treated in naturopathy which awaits the identification of the active compounds for pure drug development. For instance, the extensively studied curcumin from *Curcuma longa* is a broad spectrum antibiotic efficacious on resistant bacteria and this compound is yet to be accepted as an antibiotic till today in medical and veterinary practices [8]. Similarly, an anti-pox virus compound from the neem leave, *Azadirachta Indica*; namely nimbin and nimbidin is not developed into drug, though the use for smallpox and fowl pox treatment have been in practice for millennium in India [14].

In spite of the use of vaccines to control viral and bacterial diseases; many factors such as host, environment and the vaccines itself; failed to initiate effective immunity and its action not immediate and requires weeks to months. Therefore, Tamil Nadu state in India has been medicating and recuperating patients with the extract from *Andrographis paniculata*; for dengue virus and many other unknown viral infections with fever; for immediate action. Andrographolides, the active ingredient responsible, is yet to be investigated or developed into drug.

Unfortunately, the intellectual property (IP) of Curcuma longa and Azadirachta in India was owned by USA, before it was depatented and reserved as the property of India lately. As a result, Malaysian government, via Forest Research Institute of Malaysia (FRIM) has imposed a strict law of IP ownership; on foreign researchers conducting natural product studies in our forest.

Undoubtedly, the infinite compound synthesized by tropical flora has all the therapeutic effects such as anti-bacterial, anti-viral, anti-parasitic, anti-fungal, antioxidant, anti-inflammatory, immunostimulant and most importantly anti-cancer; whereby majority of these selected herbs are much more superior to the chemical drugs in terms of efficacy and safety. Table 1 illustrates the superiority of naturopathy in treating common non-communicable diseases (NCD) of mankind with permanent cure and without lifelong medication.

Disease	Allopathic treatment	Remarks	Naturopathy treatment	Remarks
Hypertension	Lifelong medication	Disease not cured and kept in control only. Lifelong medication leads to kidney failure	Complete resolution in 3 months	Disease cured completely and herbal medication halted. No side effects as selected nutraceuticals used.
Hypercholesterolemia	Lifelong medication		Complete resolution in 3 months	
Diabetes	Lifelong medication		Complete resolution in 3 months	

Table 1: The comparison of efficacy and side effects; of diseases treated with naturopathy and allopathy.

The abovementioned 3 conditions are the source diseases that leads to other complications. In naturopathic system of medicine, the use of herbal medication for most diseases are resolved and medication discontinued in 3 month; with strict diet and exercise disciplines. Lifelong medication is rarely practiced, as even medicine is regarded as poison, if consumed in a long run. These conditions in combination, in both veterinary and medical fields; may risk patient with severe complication; and they are closely related to the type of diet and obesity management. Table 2 compares the presence of metabolic diseases between animals on basically meat and roughage diets.

The data in table 2 clearly highlights the consequences of meat-based diet in animal; which could be applied for human diseases today. All those metabollic diseases are important in medical field

Diseases	Meat based diet (Cat and Dog)	Roughage based diet (Ruminant)
Diabetes	+	-
Hypertension	+	-
Hypercholesterolemia	+	-
Kidney failure	+	-
Cancers	+	-

Table 2: The comparison of important diseases of animals based on diet.

+: Present and/or Important -: Absent and/or not important.

today and should enlighten mankind on the selection of their diet carefully; especially in the presence of toxic compounds [7]; and preservatives in processed meat [3]. The lifespan of animals on roughage diet like cattle, is 30 years without these diseases; whereas the pet dies within an average of 10 years; due to kidney failures mainly. Therefore, the pet feed ingredients has to be transformed to grain based diet with minimal or null animal source protein.

With regards to the deadly disease; cancer; the herbal combination used is effective to halt tumor spread and kill cancer cells without dreadful side effects; observed in chemical chemotherapeutics. Siddha and Ayurveda practitioners currently, able to cure cancers patients up to stage three, with strict food and lifestyle modification. Stage four is not treatable as per in the allopathic practice.

The mammalian systems, namely human, livestock and pet; have 80% to 90% genetic similarity [12], as well as disease conditions. Therefore, these similarities could be exploited to reduce the time required for clinical trials on human; by evaluating it in pet for substantial cost and time reduction; thus enhance drug development and approval; by National Pharmaceutical and Regulatory Authority (NPRA), Malaysia and not FDA. Consequently, the customized NPRA system of drug scrutinization and approval could be extended to Asean and other countries, to gradually replace FDA.

Funding constraints and the complexity of clinical trials

Currently, the FDA system of drug discovery and approval was designed to suppress the entry of non-financially sound companies and countries. The time required for a novel compound upon discovery in the laboratory with laboratory animal studies; to phase 1 clinical trial is 10 to 15 years. Furthermore, it is subjected to phase 2 and phase 3 clinical trials that are tedious and may end up disapproved [17]. Obviously, this system is too risky as for the amount in hundreds of millions spent.

For instance, out of 529 molecules targeting cancer developed in 2002, only 389 molecules were allowed to proceed to phase 1 to phase 3 clinical trials; in cancer patients and disapproved. According to Forbes, financially sound conglomerates, such as Amgen and Astra Zeneca spent USD3.5 billion (RM14.1 billion) and USD11.5 billion (RM46.3 billion) respectively to develop a new drug; obviously not feasible to the tropical economies especially the third world countries.

As a consequence, the discovery of novel compounds has not progressed; whereby until the year 2015, 86% of the prescriptions were generic drugs or the variants of an existing drug [17]. Unless the drug discovery system is transformed, the efforts to deal with anti-microbial resistance (AMR) that has been claiming millions of lives worldwide will be hampered.

Dealing with anti-microbial resistance

The natural compounds from natural products are the most effective substitute for chemically synthesized antibiotic, in AMR, as they are efficacious in killing resistant microbes [16]. In addition, the development of resistance by aetiologies are slow or non-due to the complexity of multiple compounds within herbs [2], a polypharmacology system of medicine, naturally practices in herbal medicine. Lately, medical experts have to combine antibiotics to deal with resistant microbes such as in the treatment for tuberculosis and others [18]; to emulate the natural polypharmacology systems.

The excessive use of antibiotics in the poultry industry; has been blamed to cause the development of resistant microbes; by the World Health Organization (WHO). The transfer or resistant gene from one microbe to another has created a variety of or microbes developing resistance against wide range of antibiotics, a situation haunting the healthcare industry [13].

Statistics by the WHO shows at least 700,000 people die worldwide due to AMR and the figure is expected to escalate to 10 million a year by 2050 if no immediate remedial measures taken.

Zoonotic infection from livestocks farming has been a great threat whereby 2.5 billion illnesses with 2.7 million deaths reported by WHO were caused by 56 zoonoses. Approximately 13 zoonoses related to livestock and/or associated with wildlife responsible for the previously fatal avian flu and now with a greater fatality globally by the virulent mutant coronavirus or Covid 19. In another word, there has never been any zoonotic transfer between vegetables and humans; therefore, halting meat consumption is mandatory now [4,5].

Conclusion

In conclusion, unless the drug discovery system is reviewed and transformed; the global fatalities due to AMR and non-treat-

able diseases could not be handled efficiently. The funding system should be transformed to recover the treasure left behind by the Siddha system of medicine, to reveal the remaining diseases yet to be known to the modern medical experts; and the natural products used to treat them especially the dreadful disease; cancer.

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