The Application of Phytomedicine in Modern Drug Development

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Abstract

Background:
Phytomedicine or the use of herbal medicine with therapeutic properties has played a significant role throughout history. Although its usage greatly diminished during the dawn of the scientific era, there is a revival of interest in its potential by late 20th century, especially in the development of new drugs.
Methods:
A narrative review was conducted on the history of herbal medicine, its categorization, its current usage, the current methods in phytomedicine research, its challenges, and its future in modern medical practice. Results:
The history of herbal medicine can be traced back to thousand of years in both Western and Eastern tradition. Herbal medicine can be categorised into phytotherapy, over-the-counter herbal and traditional herbalism. There is an increase of interest in the pharmaceutical industry to develop new medications from plants. Phytomedicine research has employed high-throughput screening methods and the increasingly popular “reverse pharmacology” methods. Five major challenges for its progress was identified: (i) the reproducibility of biological activity of herbal extracts; (ii) its toxicity and adverse effects; (iii) its adulteration and contamination; (iv) herb–drug interactions issues; and (v) standardisation issues. Conclusions. The field of phytomedicine has a great prospect to be further developed hand-in-hand with modern medical disciplines.

LIST OF ABBREVIATIONS

INTRODUCTION

Phytomedicine or the use of herbal medicine with therapeutics properties has been around since the dawn of human civilisation. Sheng-Nongs Herbal Book, one of the earliest sources of folk knowledge on the use of herbs in China, dated back to 3000 B.C. and included knowledge of 365 plants, animals and minerals useful as medication[1]. A phytopharmaceutical preparation or herbal medicine is any manufactured medicine obtained exclusively from plants, either in the crude state or as pharmaceutical formulation[2]. Although the industrial revolution and the development of organic chemistry resulted in a preference for synthetic products, World Health Organisation (WHO) reports that between 70% and 95% of citizens in a majority of developing countries still rely on traditional medicine as their primary source of medication[3]. The role of herbal medicine started to decline after the 1960s as vast quantities of resources and money were used to promote synthetic medication. Besides this, advances in the human genome, increase knowledge of the structure and function of proteins and the notion that synthetic drugs are safer with fewer side effects (which does not necessarily be true) also contributed to the rise in the popularity of synthetic drugs. However, these advancements have several major constraints. The large number of possible new drug targets has already outgrown the number of existing compounds that could potentially serve as drug candidates and the field of chemistry has limitation when it comes to synthesising new drug structures.

In the last decade, herbal medicine has seen some form of revival, advancing at a greater pace in community acceptance of their therapeutics effects. This field is bringing forward new lead drug discoveries as well as safe and efficacious plant-based medicines. In turn, this leads to growing number of sales of commercialised medicinal herbs and most importantly, growing number of pharmaceutical companies that involve in the research and development of plants as a source for modern medicine. What chemists have been desperately seeking, Mother Nature has already plenty of stock. This review tries to expound on the importance of

herbal medicine in modern drug development by highlighting salient topics from the history of herbal medicine and examining its roles in modern drug development. In addition, this review discusses the challenges and future of herbal medicine in modern medical practice.

A SHORT HISTORY OF HERBAL MEDICINE

Traditional medical practice remains the largest healthcare system in the world. The Hindu Kush Himalayas (Afghanistan, Bangladesh, Bhutan, China, India, Nepal and Pakistan) host the four largest traditional medicinal systems in the world, comprising of Ayurvedic medicine, Chinese medicine, Tibetan medicine and Unani medicine[1]. Ayurveda remains one of the most ancient traditional medicine systems and is still widely practiced in India, Sri Lanka and other countries with 400 000 registered Ayurvedic practitioners in India alone. Atharvaveda (around 1200 B.C.), Charak Samhita and Sushrut Samhita (1000-500 B.C.) are the main literatures that give detailed description of over 700 herbs[4]. Currently, over 1000 plants form the Ayurvedic Pharmacopoeia. In China, herbal medicine continued it expansion from Sheng-Nongs Herbal Book (around 3000 B.C.) to the current updated inventory of medicinal plants used in Traditional Chinese Medicine (TCM) that includes 11 146 species of herbs/plants of which 492 species are cultivated and the remaining wild plants. Both the Ayurvedic and Chinese Traditional Medicine systems date back to ancient time, with an ever-expanding knowledge of plant properties and their medicinal qualities that were preserved in ancient texts. This body of knowledge has been constantly updated and passed down to newer generations in revised versions, while preserving its originality and values. Currently, only China has a frequently updated inventory of traditional medicines used, with India starting to initiate similar efforts. The Chinese government is one of the most active governments in the world in promoting the use of traditional medicine and integrating it with allopathic, conventional medicine.

Appearing later than its Oriental counterparts, the Western version of herbal medicine began at the cradle of Western civilisation in Ancient Greece around the fifth century B.C. with the influence of accumulated medical knowledge from Egypt, Persia and Babylon[5]. During the first century A.D., Dioscorides produced an influential herbal medicine text called De Materia Medica, which became a standard reference for Western practitioners for the next 1,500 years. Curiously, this book also included information on herbal remedies that had been used in Ayurvedic medicine for centuries. Around the same period, Galen of Pergamum formulated 130 antidotes and medicinal preparations (also known as galenicals) that may include up to 100 herbs and other substances. The complexity involved in preparing these intricate medicinal prescriptions gave rise to the Galenic system that saw physicians as the ultimate authority in health care. It was around this time that traditional herbalists, with their "simple" remedies, began to be ousted from the mainstream medical system in Medieval Europe. Nevertheless, the knowledge of traditional herbal medicine was preserved by Catholic monks throughout the Middle Ages, with its practitioners still existing outside the mainstream system. Around the eighth century A.D., Western herbal medicine began to be influenced by the herbal knowledge of Arab physicians who conducted extensive research on medicinal herbs found in Europe, Persia, India and the Far East. Later, with the discovery of the Americas in the fifteenth century A.D., a variety of the New World medicinal plants became available to Europeans. Among the ancient knowledge of herbal medicine that came from the New World, the significant ones came from the Mexican traditional medicine, which combined the knowledge of four indigenous groups – Maya, Nahua, Zapotec and Mixe as well as the Inca civilisation[6]. Medicinal plants continued to be the main source of products used for maintenance of health in Western conventional medicine until the nineteenth century when Friedrich Wohler accidentally synthesised urea in 1828[7]. This first organic synthesis in human history ushered the age of synthetic compound. For the next 100 years, synthetic drugs became the mainstay of Western conventional medicine, with phytomedicine pushed into the shadows.

CURRENT CATEGORIES OF HERBAL MEDICINE

The term "herbal medicine" is fraught with misconceptions that stems from the diversity of its approaches. According to Ernst[8], herbal medicine can be categorised into three general groupings, namely phytotherapy, over-the-counter (OTC) herbal medicine and traditional herbalism. Among these, phytotherapy is the one that adheres to scientific methodology and generates reasonably sound data[9]. Based on the principles of phytotherapy, a herb contains a number of pharmacologically active compounds that should be seen as a single unit. The whole extract can be standardised and clinically tested for a distinct clinical condition. This prominent feature differentiates phytotherapy from conventional pharmacotherapy, which generally favours the

more reductionist approach. Aside from this, phytotherapy strongly abides by the principles of pharmacotherapy that requires knowledge and skills for medical diagnosis and identification of suitable treatment[8]. OTC herbal medicine however lacked in scientific evidence[10], in terms of efficacy and safety[11]. In a similar note, traditional herbalism is rooted in beliefs that have been long abandoned by the rest of medicine[8]. Not beholden to the conventional disease categories, traditional herbalists would typically prescribe an individualised concoction of several plant extracts based on the characteristics of each individual patient[12]. A systematic review by Guo et al. [13] failed to find any convincing evidence that individualised herbal medicine is effective in any indications. They also warned that the lack of proper standardisation and the use of multi-herbs in a single prescription would massively increase the safety risk.

CURRENT USAGE, ISSUES AND ROLES

The majority population of the developing world relies on traditional herbal medicine as the primary source of treatment for illnesses[3]. The issue of compliance with traditional medicines varies according to local beliefs and socio-cultural status, and is less reliant on the efficacy of the traditional medicine. This may result in a disadvantage towards users of traditional medicines because patients may continue with treatment even though medicine is not efficacious and vice versa due to personal and population beliefs.'

Approximately 25% of drugs prescribed worldwide came from plants, with 121 such active compounds being in current use[2]. There are 252 drugs considered as basic and essential by the WHO, of which 11% are exclusively of plant origin, while the majority of synthetic drugs also have plant precursors. In 1997, world market for over-the-counter phytomedicinal products was USD 10 billion with an annual growth of 6.5%[14]. In 2003, growth was well over expectation with sales exceeding USD 65 billion, with USD 9 billion in Europe alone[4]. China and India have already a well-established herbal medicine industry, while Germany lead the developed countries with 54% of phytomedicinal products being sold as medical prescriptions that were covered by health insurance[15]. Plants can be used as therapeutic resources in several ways - herbal teas or other home remedies, crude extracts and extraction with purification to isolate an active compound. Among the examples of drugs obtained from plants are reserpine from Rauwolfia serpentina, digoxin from Digitalis spp., quinine and quinidine from Cinchona spp., vincristine and vinblastine from Cantharanthus roseus, atropine from Atropa belladonna and morphine and codeine from Papaver somniferum [2]. The use of Rauwolfia serpentine dates back to almost 3,000 years ago in India, with Ayurvedic medicine using it for the treatment of hypertension, insomnia and insanity[15]. It must be stressed that anti-tumour and anti-infectious drugs have a bigger plant-origin base, covering over an estimated 60% of these drugs[2].

As mentioned earlier, interest in herbal medicine as a path to drug development increased greatly in the early 1980s[7]. This could be due to the inefficiency of conventional medicine (e.g. cytotoxicity, side effects and ineffectiveness of synthetic drugs), abusive and incorrect use of synthetic drugs and most importantly, the high cost involved in conventional medicine and the fact that a large percentage of the world's population does not have access to conventional pharmacological treatment[2]. With the limitations of synthetic chemistry, there also arises the need to find new medicines to combat the emergence of multi-resistant pathogens[7], as well as to manage a whole range of chronic and difficult-to-treat diseases such as cancer, diabetes and AIDS. Natural products offer unmatched structural variety and their usefulness can be extended by probing biological pathways[4]. Large pharmaceutical companies now have specific departments dedicated to the study of new drugs from natural resources. Even though it was once thought that focusing on herbal medicine could provide a swifter and more economical approach to drug discovery[3], however the reality is actually a bit disheartening. Research and development of therapeutics materials from plant origin is an arduous task and involve high cost. Each new drug requires an investment of around USD 100-360 million and a minimum of 10 years of work, with only 1 in 10,000 tested compounds being considered promising[2]. However, this pales in comparison with a newly developed synthetic drug, where the development cost would reach USD 800 million[16], which is more than the gross national product of some countries. The cost effectiveness of modern drug development originating from phytomedicine is now increasingly being accepted with big pharmaceutical companies investing greatly[2].

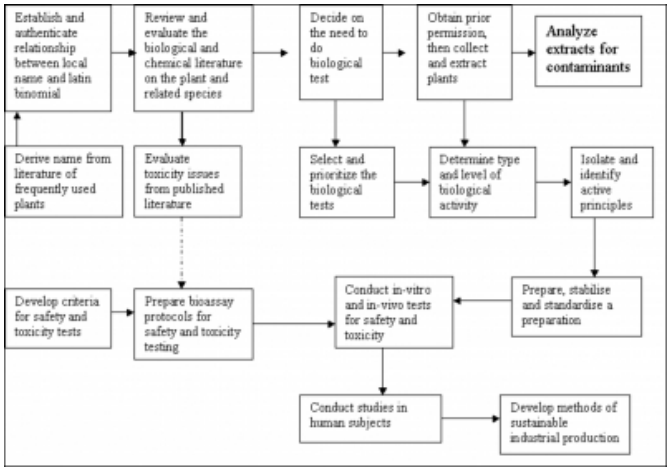
METHODS OF PHYTOMEDICINE RESEARCH

Modern natural drugs chemistry actually began with the work of Serturner, who first isolated morphine from opium poppy, Papaver somniferum. Natural compounds can be lead compounds, allowing the design and rational planning of new drugs, biomimetic synthesis development and the

discovery of new therapeutic properties not yet attributed to any known compounds[17]. Of the estimated 250 000 to 500 000 plant species, only a fraction (about 5000 species) have been studied for medical use[18]. Among the most important roles of herbal medicine in modern drug development is the identification of plants with useful therapeutics compounds. This is where the modern field of phytosciences comes in. This field attempts to verify health benefits of plants commonly used in traditional medicine and their mechanisms of action[7]. As an exact science, the researchers within this field aim to explore the side effects of plant-based compounds (phytocompounds), identify the bioactive elements, estimate the appropriate dosages, as well as describe the best methods of extraction and conservation of the compounds. Up until now, a few methods have been employed to identify the potential plants for drug development. The basic technique for the study of plants used in traditional medicine is summarised in the Figure 1.

Figure 1

Figure 1: Flow chart of the basic technique for the study of plants used in traditional medicine (adapted from G.A Cordell & Colvard)[16].



One of the methods of selecting potential plants for drug development is to decide on a well-defined pharmacological activity and perform a randomised search for this activity among plant extracts, resulting in active species to be considered for further study. At one point of time, the concept of high-throughput screening (HTS) became the paradigm of lead discovery of novel bioactive phytocompounds[19]. HTS allows a researcher to efficiently conduct hundreds of experiments simultaneously via a combination of modern robotics and other specialised laboratory hardware. It applies a forceful method to collect a large amount of experimental observations about the reaction of phytocompounds towards the exposure of various chemical compounds in a relatively short time. However, results of HTS in producing synthetic anti-cancer drug have been less than promising[20]. The National Cancer Institute (NCI) in the USA has tested more than 50 000 plant samples for anti-HIV activity and 33,000 samples for anti-tumour activity[2]. It should be reminded that these plants were not screened for other pharmacological activities. Through HTS, several plant products have been identified for the production of new anti-cancer drugs, which include the vinca alkaloids, the taxanes and camptothecins derived from Cantharantus roseus, Taxus brevifolia and Camptotheca acuminata respectively. Flavopiridol, derived from the plant Amoora rohituka and Dysoxylum binectariferum is currently the most exciting discovery as it represents the first anti-cancer agent targeting cell cycle progression[20]. Even though the discoveries mentioned above are commendable, one cannot help but wonder about the practicality of the HTS approach in identifying beneficial natural phytocompounds. In many cases, the deficiency of the supplies of varied plant extracts and their immense chemical diversities were not appropriate to feed the HTS. This setback caused the emergence of the science of combinatorial chemistry that produces high-throughput chemical synthesis of phytocompound analogs in the late 1980s and early 1990s[21]. This new technology initiated a decreasing interest in natural compound screening, which in turn, lead towards the complete abandonment of such programs by many companies. Combinatorial chemistry emerged as the preferred option for HTS resources, but unfortunately, this technique has not produced many high-quality drug candidates. Currently, the integration of combinatorial chemistry with a natural product lead is considered as the correct strategy to discover novel analogs[22]. Some synthetic phytocompounds have been found to be more potent than natural products, have superior drug-like properties as well as exhibit new biological activities not seen in the original molecule[21]. As an example, compound acquisition through chemosystemics is currently progressing at a rapid rate. Chemosystemics involves using phytochemical composition as a clue to evaluate related species for structurally comparable substance with better therapeutic index resulting in the synthesis of new analogs. Docetaxel, a derivative from Taxus baccata was developed using this method in order to resolve the initial development problems with paclitaxel[20].

The most common method of plant-based drug identification and selection remains with careful observation of the use of herbal medicine in the folk medicine of various cultures, which includes analysing traditional ethnobotanical

documentation and inventories[2]. This is sometimes referred as the "reverse pharmacology path" because clinical experiences, observation and available data from human use are utilised as the starting-point, instead of being the end-point, in conventional drug research. The information gathered can be extremely useful for the study of individual phytocompounds, with the determination of best extraction method by observing the traditional preparation procedure of individual plants, as well as the identification of pharmacological activity by observing the traditional formulation used, its route of administration and doses[2]. Examples of the application of the reverse pharmacology include the anti-malarial drug quinine, which had its origin in the royal households of the South American Incas. Another is tubocurarine, a muscle relaxant originating from curare in the plant species Strychnos guianensis and Chondrodendron tomentosum, which was initially used as arrowhead poison by the Amazonian Indians[23]. It remains a mystery how they were able to identify these few plant species out of over 50,000 species in the Amazons for this specific purpose. Even with HTS, it would be a huge task to screen all 50,000 species to identify curare. It is this 'knowledge in advance' that makes reverse pharmacology so enticing. Currently, Ayurveda, Chinese Traditional Medicine and the South American Traditional Medicine systems are being intensely researched using this method of identification and selection. The knowledge and experience from these traditional medical systems can significantly reduce the cost and time spend on studying the herbal compounds' bioactivity and toxicity since the effectiveness of these medicines has been continuously tested for thousands of years on human. These traditional systems can also provide clues as to which plants that may become prime candidates for further screening and chemical analysis for modern drug development. Some examples of these potential candidates come from Mexican traditional medicines, comprising of common plants such as Eucalyptus globules labill, Punica granatum, Artemisa mexicana and Bocconia arborea that have been used for a variety of illnesses, including wound treatment[24]. It was found that all these plants show antimicrobial activity against Staph. aureus, E. coli, P. aeruginosa and C. albicans. It should be emphasised here that this reverse pharmacology strategy is not only useful for new drug development, but also for improving current drugs. A good example would be the improvement of current anti-malarial medications via further research on the combination of plant species used by the Aguaruna native of Peruvian Amazon that show a synergistic effect against quinine resistant Plasmodium falciparum [25].

We would now examine one example of herbal medicine detailing its role in modern drug development with the reverse pharmacology approach. Qian Ceng Ta, a Chinese herbal medicine that is prepared from the moss Huperzia serrata, has been in used in China for centuries to treat fever and inflammation[26]. H. serrata contains alkaloid huperzine A, which is currently prescribed in China for senile dementia. In studies using hippocampal and cerebellar cell cultures, huperzine A decreases neuronal cell death caused by high concentration of glutamate, which is relevant for reducing neuronal cell injury from strokes, epilepsy and brain disorders[27]. It is postulated that huperzine A increases acetylcholine, noradrenaline and dopamine levels in the brain[28]. X-ray crystallography studies revealed that huperzine A is more potent than tacrine as an acethylcholinesterase inhibitor and has a longer half-life[29]. Huperzine A appears to be an attractive candidate for treating Alzheimer's disease. This is just a simple example where the incorporation of herbal medicine into modern methods of drug development might potentially yield impressive results. There are many other well-established drugs developed from the modern methods in herbal medicine research and each of them is currently used with impressive therapeutics results.

CHALLENGES

Ahmad et al. [30]identified at least five major limitations in the development of herbal medicine: (i) the reproducibility of biological activity of herbal extracts; (ii) its toxicity and adverse effects; (iii) its adulteration and contamination; (iv) herb–drug interactions issues; and (v) standardisation issues. We shall now briefly examine each of these limitations.

REPRODUCIBILITY OF BIOLOGICAL ACTIVITY OF HERBAL MEDICINE

One of the most problematic issues faced by the field of phytomedicine is the high failure rate to reproduce the biological activity of individual herbal extracts after the success of initial screening process. Over 40% of plant extracts found actually lack this reproducibility[31]. This failure in re-sampled and re-extracted batches points towards the variation of biochemical profiles of plants harvested at different times and locations, as well the existence of unique variation in the same type of plant. The different methods of extraction and detection of biological activities in laboratories may also contribute to this lack of reproducibility. Wide variations in chemical composition of

herbal medicine require careful chemical analysis to ensure consistency. Conflicting reports of efficacy could be due to this difference in consistency. Additionally, the synergistic interactions between the varieties of phytocompounds in each individual extract may also influence its activity and efficacy. The desired pharmacological effect may not be caused by a single phytocompound but by a combination of phytocompounds resulting in pharmacodynamic synergism. This is seen in Panax ginseng where the whole plant is more active than the isolated compounds[2]. Nonetheless, sometimes in our pursuit to isolate an active compound from a particular plant, we might inadvertently exclude phytocompounds with relevant pharmacological activities.

TOXICITY AND ADVERSE EFFECTS OF HERBAL MEDICINE

There is a predominant myth in society that medicinal herbs or plants are much safer than conventional pharmaceuticals due to its "natural" origin. This cannot be further than the truth! Like all other medicines, there is a specific dosage threshold for each herbal medicine to be efficacious as well as to be toxic. There have been reports in the literature [32, 33] that many herbal medicine preparations are potentially toxic and some are even carcinogenic. For example, aristolochic acid derived from Aristolochia spp. is associated with the development of nephropathy and urothelial cancer[34]. The toxic effect of herbal medicines may be due to (i) existence of phytotoxins in some unadulterated herbal medicines; (ii) mistakes in botanical identification; (iii) unsuitable combinations of plants; and (iv) usage of plants that interfere with conventional pharmacotherapy[2, 32, 35, 36].

ADULTERATION AND CONTAMINATION OF HERBAL MEDICINE

Herbal medicine may become adulterated and contaminated in countries that are lax in their purity control regulation. This may cause significant medical problems, especially in children[37,38]. For example, a review found 13 reports of heavy metal poisoning among children who consumed herbal medicine in Singapore, Hong Kong, the USA, the UK and the UAE from 1975 to 2002[38]. A recent cross-sectional study among 13,504 adults in the USA showed that women using herbal supplements (including Ayurvedic or traditional Chinese medicine herbs, St. John's Wort, and "other" herbs) had blood lead levels that were 10% higher than women non-users, although these increased levels were not seen among men[39].

HERB–DRUG INTERACTIONS ISSUES

Not surprisingly, the pharmacokinetic profile of administered conventional pharmaceuticals can be changed by the usage of herbal medicine[40]. These interactions may potentiate or antagonize the absorption and metabolism of drugs, as well as cause adverse effects like allergy[41]. However, it is worthy of note that herbal medicine has the lowest level (7.6%) of reported adverse effects compared to other modes of complementary and alternative medicine[42].

HERBAL MEDICINE STANDARDISATION ISSUES

Herbal medicine rarely meet the standard of standardisation, which is partially due to the scarcity of scientific information about the acting pharmacological principles of the extracted phytocompounds and the fact that the plants are not cultivated under controlled condition[30]. The significant variability in content and quality of commercialised herbal products is the result of variability in the content and concentration of phytocompounds within the extract as well as the different extraction and processing techniques employed by different producers[36].

Aside from the limitations discussed above, among the problems faced from plant-based drug development is the issue of eco-sustainability. Taxol, an anti-tumour agent, is isolated from the bark of Taxus brevofolia and Taxus bacata [43]. In order to produce 2.5kg of taxol, 27,000 tons of bark is required, equivalent to 12,000 trees. We can imagine that if there was no alternative to the natural phytocompound extraction method, then the mass production of taxol would cause the extinction of these unique tree species. Hopefully, the problem of low yield will be outdated with the advancement in combinatorial organic chemistry, with the creation of semi-synthetic analogues and better method of extraction and purification that will result in higher yield.

THE FUTURE OF HERBAL MEDICINE

What does the future hold in store for herbal medicine? Socio-cultural and economical problems, lack of well-planned and integrated strategies, as well as poor access to scientific information must be dealt with in order to fully utilise the available resources for the modern concept of drug development. It is important to encourage more ethnobotanical studies among indigenous people before their way of life or they themselves disappear[25]. Besides this, the problem of patents, intellectual property and rights of the native population where the phytomedicine knowledge originated should be addressed adequately. This native

population is often found to be in need of better care, but they do not usually benefit from sharing their knowledge to the rest of the so-called "modern world". It is curious to note that drug companies generate more than USD 100 million each year from the sale of drugs from natural compounds, without returning profits to the countries where the compounds were found[44]. Protecting and compensating local groups for their indigenous knowledge as well as providing access to modern medicine should be seen as a reasonable expectation from the conventional pharmaceutical or herbal medicine companies that stand to benefit greatly from this "collaboration". Meanwhile, it is unfortunate that current herbal medicine companies are still mainly small businesses and as a result, products sold are of inferior quality and frequently mixed with contaminants and sometimes toxin. Professional links must be forged between these businesses, the government, large pharmaceutical companies, academic institution and the local community to continue the expansion and development of herbal medicine in the right direction. This will promote the rational and responsible exploitation of biodiversity as a source of chemical compounds that can be used for developing new drugs. For example, the International Cooperative Biodiversity Group (ICBG) program, which is currently based in Peru, has been established to form interdisciplinary collaboration between universities, research institutions, government and pharmaceutical companies[25]. In China, Yunnan Institute of Tropical Botany (YITB) has collaborated with Yamanouchi Pharmaceutical of Japan, resulting in the development of seven patents from 1988 to 1991[1]. Similar programs should be encouraged worldwide.

Besides this, the improvement of drugs found in nature is now possible by organic chemistry, gene amplification and recombinant procedures, high-throughput screening, gene chip technology, or chemosystemics[25]. Through these methods, now there are new local anaesthetics derived from cocaine without its original dangerous effects [45] and there is also chloroquine that is less toxic than quinine[4].

CONCLUSION

The golden field of herbal medicine must be explored and harvested to the fullest in order for the mainstream medical field to progress further. The great new discoveries promised by the budding field of modern phytomedicine are just too tempting to be resisted by those who respect the dynamic of scientific progress. Be it in the jungle or in a dusty monastery, some traditional herbal knowledge can be seen as a gift from the past to those in the future, who should refine this knowledge using the state-of-the-art methods. Indeed, the future of phytomedicine in modern drug development looks very promising, as long as scientists keep a curious and objective mind, without prejudice towards the concept of "herbal medicine".

References

1. Sheng-Ji P: Ethnobotanical approaches of traditional medicine studies: some experience from Asia. Pharmaceutical Biology; 2001; 39 (l) : 74-79.
2. Rates SMK: Plants as source of drugs. Toxicon; 2001; 39 (5) : 603-613.
3. Robinson MR & Zhang X : The world medicines situation 2011 (Traditional medicines: global situation, issues and challenges). Geneva: World Health Organization ; 2011.
4. Patwardhan B, Vaidya ADB, Chorghade M : Ayurveda and natural products drug discovery. Current Science ; 2004; 86 (6) : 789-799.
5. Longe JL, Blanchfield DS, Fundukian L, Watts E : The Gale encyclopaedia of alternative medicine, Detroit: Thomson Gale, 2005.
6. Heinrich M : Ethnobotany and its role in drug development. Phytotherapy Research; 2000; 14 (7) : 479-488.
7. Mendonca-Filho FF: Bioactive phytocompounds: new approaches in the phytosciences," in Modern phytomedicine, I. Ahmad, et al., Eds., ed Weinheim: Wiley-VCH; 2006; 1-24.
8. Ernst E: Herbal medicine: buy one, get two free. Postgraduate Medical Journal; 2007; 83 (984) : 615-616.
9. Schulz V, Hansel R & Tyler VE: Rational phytotherapy: a physician's guide to herbal medicine. Berlin: Springer-Verlag ; 2001.
10. Ernst E, Pittler MH, Wilder B, Boddy K: The desktop guide to complementary medicine. Edinburgh: Elsevier Mosby; 2006.
11. Marcus DM & Grollman AP : Botanical medicines – the need for new regulations. New England Journal of Medicine ; 2002; 347 (25) : 2073-2076.
12. Casey MG, Adams J, Sibbritt d : An examination of the prescription and dispensing of medicine by Western herbal therapists: a national survey in Australia. Complementary Therapies in Medicine ; 2007; 15(1) : 13-20.
13. Guo R, Canter PH, Ernst E : A systematic review of randomised clinical trials of individualised herbal medicine in any indication. Postgraduate Medical Journal ; 2007; 83(984) : 633-637.
14. Soldati F: The registration of medicinal plant products. What quality of documentation should be required? The industrial point of view," presented at the World Congress on Medicinal and Aromatic Plants for Human Welfare : 1997.
15. Misra R : Modern drug development from traditional medicinal plants using radioligand receptor-binding assays . Medicinal Research Reviews; 1998; 18(6) : 383-402. (Abstract)
16. Cordell GA & Colvard MD: Some thoughts on the future of ethnopharmacology. Journal of Ethnopharmacology ; 2005; 100(1-2) ; , no. 1-2, pp. 5-14, 2005.
17. Hamburger M & Hostettmann K : Bioactivity in plants: the link between phytochemistry and medicine. Phytochemistry ; 1991; 30(12) : 3864-3874.
18. Payne G, Bringi V, Prince C, Shuller M : The quest for commercial production of chemicals from plant cell culture: plant cell and tissue culture in liquid systems. Oxford: Oxford University Press, 1991.

19. Ganesan A : Recent developments in combinatorial organic synthesis. Drug Discovery Today ; 2002; 7(1) : 47-55.
20. Mans DR, Rocha AB, Schwartsmann G : Anti-cancer drug discovery and development in Brazil: targeted plant collection as a rational strategy to acquire candidate anti-cancer compounds. The Oncologist; 2000; 5(3) : 185-198
21. Breinbauer R, Vetter IR, Waldmann H : From protein domains to drug candidates-natural products as guiding principles in the design and synthesis of compound libraries. Angewandte Chemie (International Edition in English); 2002; 41(16) : 2879-2890.
22. Hall DG, Manku S, Wang F : Solution- and solid-phase strategies for the design, synthesis, and screening of libraries based on natural product templates: a comprehensive survey. Journal of Combinatorial Chemistry ; 2001; 3(2) : 125-150.
23. Verpoorte R, Choi YH, Kim HK : Ethnopharmacology and system biology: a perfect holistic match. Journal of Ethnopharmacology, 2005.
24. Navarro V, Villareal L, Rojas G, Lozoya X : Antimicrobial evaluation of some plants used in Mexican traditional medicine for the treatment of infectious diseases. Journal of Ethnopharmacology; 1996; 53(3) : 143-147.
25. Lewis WH : Pharmaceutical discoveries based on ethnomedicinal plants: 1985 to 2000 and beyond. Economic Botany; 2003; 57(1) : 126-134.
26. Chang J : Medicinal herbs: drugs or dietary supplements?. Biochemical Pharmacology; 2000; 59(3) : 211-219.
27. Ved HS, Koenig ML, Dave JR : Huperzine A, a potential therapeutic agent for dementia, reduces neuronal cell death caused by glutamate. Neuroreport ; 1997; 8(4) : 963-968.
28. Zhu XD & Giacobini E : Second generation cholinesterase inhibitors: effect of (L)-huperzine-A on cortical biogenic amines. Journal of Neuroscience Research; 1995; 41(6) : 828-835.
29. Ashani Y, Grunwald J, Kronman C, Velan CB, Shafferman A : Role of tyrosine 337 in the binding of huperzine A to the active site of human acetylcholinesterase. Molecular Pharmacology ; 1994; 45(3) : 555-560.
30. Ahmad I, Aqil F, Ahmad F, Owais M : Herbal medicine: prospect and constraints," in Modern phytomedicine, I. Ahmad, et al., Eds., ed Weinheim: Wiley-VCH; 2006 : 59-78.
31. Cordell GA : Biodiversity and drug discovery-- a symbiotic relationship. Phytochemistry; 2000; 55(6) : 463-480.
32. Wojcikowski K, Johnson DW, Gobe G : Medicinal herbal extracts – renal friend or foe? Part one: the toxicities of medicinal herbs. Nephrologyvol. 9, no. 5, pp. 313–318, 2004.
33. Akinboro A & Bakare AA : Cytotoxic and genotoxic effects of aqueous extracts of five medicinal plants on Allium cepa Linn. Journal of Ethnopharmacology; 2007; 112(3) : 470-475.
34. Arlt VM, Stiborova M, Schmeiser HH : Aristolochic acid as a probable human cancer hazard in herbal remedies: a review. Mutagenesis ; 2002; 17(4) : 265-277.
35. Stewart MJ & Steenkamp V: Toxicology of African herbal remedies. Southern African Ethnobotany; 2000; 1: 32-33.
36. Goldman P : Herbal medicines today and the roots of modern pharmacology. Annals of Internal Medicine; 2001; 135(8) : 594-600.
37. Saper RB, Kales SN, Paquin J, Burns MJ, Eisenberg DM, Davis RB, Phillips RS. Heavy metal content of Ayurvedic herbal medicine products. JAMA; 2004; 292(23) : 2868-2873.
38. Ernst E & Coon JT: Heavy metals in traditional Chinese medicines: a systematic review. Clinical Pharmacology and Therapeutics; 2001; 70(6) : 497-504.
39. Buettner C, Mukamal KJ, Gardiner P, Davis RB, Phillips RS, Mittleman M : Herbal supplement use and blood lead levels of United States adults. Journal of General Internal Medicine; 2009; 24(11) : 1175–82.
40. Fugh-Berman A : Herb-drug interactions. Lancet; 2000; 355(9198) : 134-138.
41. Chan K : Some aspects of toxic contaminants in herbal medicines. Chemosphere; 2003; 52(9) : 1361-1371.
42. Li W : Botanical drugs: a future for herbal medicines. The Journal of Contemporary Health Law and Policy; 2002; 19(1) : 117-149.
43. Goodman J & Walsh V : The story of taxol: nature and politics in the pursuit of an anti-cancer drug. Cambridge: Cambridge University Press, 2001.
44. Onaga L, "Cashing in on nature's pharmacy: bioprospecting and protection of biodiversity could go hand in hand. EMBO Reports; 2001; 2 (4) : 263-265.
45. Calatayud J & Gonzalez A : History of the development and evolution of local anaesthesia since the coca leaf. Anaesthesiology ; 2003; 98(6) : 1503-1508.

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