Biopiracy versus One-World Medicine – From Colonial Relicts to Global Collaborative Concepts

Thomas Efferth , Mita Banerjee , Mohammad Sanad Abu-Darwish , Sara Abdelfatah , Madeleine Böckers , Dipita Bhakta-Guha , Vanderlan Bolzani , Salah Daak , Ömür Lutfiye Demirezer , Mona Dawood , Monika Efferth , Hesham R. El-Seedi , Nicolas Fischer , Henry J. Greten , Sami Hamdoun , Chunlan Hong , Markus Horneber , Onat Kadioglu , Hassan E. Khalid , Sami A. Khalid , Victor Kuete , Nuha Mahmoud , José Marin , Armelle Mbaveng , Jacob Midiwo , Hiroshi Nakagawa , Janine Naß , Olipa Ngassapa , Dominic Ochwang'i , Leonida K. Omosa , Edna A. Ooko , Nadire Özenver , Paramasivan Poornima , Marta Rodriguez Romero , Mohamed E.M. Saeed , Ligia Salgueiro , Ean-Jeong Seo , Ge Yan , Zahir Yasin , Elfatih M. Saeed , Norbert W. Paul

PII: S0944-7113(18)30190-9
DOI: 10.1016/j.phymed.2018.06.007
Reference: PHYMED 52528

To appear in: *Phytomedicine*

Received date: 13 November 2017
Revised date: 10 May 2018
Accepted date: 7 June 2018

Please cite this article as: Thomas Efferth , Mita Banerjee , Mohammad Sanad Abu-Darwish , Sara Abdelfatah , Madeleine Böckers , Dipita Bhakta-Guha , Vanderlan Bolzani , Salah Daak , Ömür Lutfiye Demirezer , Mona Dawood , Monika Efferth , Hesham R. El-Seedi , Nicolas Fischer , Henry J. Greten , Sami Hamdoun , Chunlan Hong , Markus Horneber , Onat Kadioglu , Hassan E. Khalid , Sami A. Khalid , Victor Kuete , Nuha Mahmoud , José Marin , Armelle Mbaveng , Jacob Midiwo , Hiroshi Nakagawa , Janine Naß , Olipa Ngassapa , Dominic Ochwang'i , Leonida K. Omosa , Edna A. Ooko , Nadire Özenver , Paramasivan Poornima , Marta Rodriguez Romero , Mohamed E.M. Saeed , Ligia Salgueiro , Ean-Jeong Seo , Ge Yan , Zahir Yasin , Elfatih M. Saeed , Norbert W. Paul , Biopiracy versus One-World Medicine – From Colonial Relicts to Global Collaborative Concepts, *Phytomedicine* (2018), doi: 10.1016/j.phymed.2018.06.007

Biopiracy *versus* One-World Medicine –

From Colonial Relicts to Global Collaborative Concepts

Thomas Efferth[a,*], Mita Banerjee[b], Mohammad Sanad Abu-Darwish[a,c], Sara Abdelfatah[a], Madeleine Böckers[a], Dipita Bhakta-Guha[d], Vanderlan Bolzani[e], Salah Daak[f], Ömür Lutfiye Demirezer[g], Mona Dawood[a], Monika Efferth[a], Hesham R. El-Seedi[h], Nicolas Fischer[a], Henry J. Greten[i], Sami Hamdoun[a], Chunlan Hong[a], Markus Horneber[j], Onat Kadioglu[a], Hassan E. Khalid[k], Sami A. Khalid[l], Victor Kuete[m], Nuha Mahmoud[a], José Marin[n], Armelle Mbaveng[m], Jacob Midiwo[o], Hiroshi Nakagawa[p], Janine Naß[a], Olipa Ngassapa[q], Dominic Ochwang'i[r], Leonida K. Omosa[o], Edna A. Ooko[a], Nadire Özenver[a,g], Paramasivan Poornima[s], Marta Rodriguez Romero[n], Mohamed E.M. Saeed[a], Ligia Salgueiro[t], Ean-Jeong Seo[a], Ge Yan[a], Zahir Yasin[u], Elfatih M. Saeed[v], and Norbert W. Paul[w]

Affiliations:

[a] Department of Pharmaceutical Biology, Institute of Pharmacy and Biochemistry, Johannes Gutenberg University, Staudinger Weg 5, 55128 Mainz, Germany, Tel: 49-6131-3925751; E-mail: efferth@uni-mainz.de

[b] Department of English and Linguistics, American Studies, Center for Comparative Native and Indigenous Studies, Johannes Gutenberg University, Mainz, Germany

[c] Shoubak University College, Al-Balqa Applied University, Jordan

[d] School of Chemical and Biotechnology, SASTRA University, Thanjavur 613401, T.N., India

[e] Department of Organic Chemistry, Institute of Chemistry, São Paulo State University, Araraquara, Brazil

[f] Dr. Salah Wanesi Foundation for Cancer Research and Control. Khartoum, Sudan

[g] Hacettepe University, Faculty of Pharmacy, Department of Pharmacognosy, Ankara, Turkey.

[h] Chemistry Department, Faculty of Science, University of Malaya, Kuala Lumpur, Malaysia, and Division of Pharmacognosy, Department of Medicinal Chemistry, Uppsala University, Biomedical Center, Uppsala, Sweden

[i] Biomedical Sciences Institute Abel Salazar, University of Porto, Porto, Portugal and Heidelberg School of Chinese Medicine, Heidelberg, Germany

[j] Department of Internal Medicine, Division of Oncology and Hematology, Paracelsus Medical University, Klinikum Nürnberg, Germany

[k] Department of Pharmacognosy, University of Khartoum, Khartoum, Sudan

[l] Faculty of Pharmacy, University of Science and Technology, Omdurman, and Faculty of Pharmacy, University of Khartoum, Karthoum, Sudan

[m] Department of Biochemistry, Faculty of Science, University of Dschang, Dschang, Cameroon

[n] Department of Biochemistry and Molecular Biology, Experimental Hepatology and Drug Targeting (HEVEFARM), CIBERehd, IBSAL, University of Salamanca Campus Miguel de Unamuno, 37007 Salamanca, Spain.

[o] Department of Chemistry, University of Nairobi, Nairobi, Kenya

[p] Department of Applied Biological Chemistry, Graduate School of Bioscience and Biotechnology, Chubu University, Kasugai, Aichi, Japan

[q] Muhimbili University of Health and Allied Sciences, Dar es Salaam, Tanzania

[r] Department of Veterinary Anatomy and Physiology, University of Nairobi, Nairobi, Kenya

[s] Molecular and Cellular Pharmacology Laboratory, School of Science, Engineering and Technology, University of Abertay, Dundee, Scotland, United Kingdom

[t] Center of Neurosciences and Cell Biology and Faculty of Pharmacy, University of Coimbra, Coimbra, Portugal

[u] Tayba Cacner Center, Khartoum, Sudan

[v] Federal Government of Sudan, Khartoum, Sudan

[w] Institute for the History, Philosophy, and Ethics of Medicine, Johannes Gutenberg University Medical Center, Mainz, Germany

** Corresponding author:*

Department of Pharmaceutical Biology, Institute of Pharmacy and Biochemistry, Johannes Gutenberg University, Staudinger Weg 5, 55128 Mainz, Germany, Tel: 49-6131-3925751;

E-mail address: efferth@uni-mainz.de

Running title: From Biopiracy to One-World Medicine

Table of contents:

ABSTRACT

Background: Practices of biopiracy to use genetic resources and indigenous knowledge by Western companies without benefit-sharing of those, who generated the traditional knowledge, can be understood as form of neocolonialism.

Hypothesis: The *One-World Medicine* concept attempts to merge the best of traditional medicine from developing countries and conventional Western medicine for the sake of patients around the globe.

Study design: Based on literature searches in several databases, a concept paper has been written.

Legislative initiatives of the United Nations culminated in the Nagoya protocol aim to protect traditional knowledge and regulate benefit-sharing with indigenous communities. The European community adopted the Nagoya protocol, and the corresponding regulations will be implemented into national legislation among the member states. Despite pleasing progress, infrastructural problems of the health care systems in developing countries still remain. Current approaches to secure primary health care offer only fragmentary solutions at best. Conventional medicine from industrialized countries cannot be afforded by the impoverished population in the Third World. Confronted with exploding costs, even health systems in Western countries are endangered to burst. Complementary and alternative medicine (CAM) is popular among the general public in industrialized countries, although the efficacy is not sufficiently proven according to the standards of evidence-based medicine. CAM is often available without prescription as over-the-counter products with non-calculated risks concerning erroneous self-medication and safety/toxicity issues. The concept of integrative medicine attempts to combine holistic CAM approaches with evidence-based principles of conventional medicine.

Conclusion: To realize the concept of *One-World Medicine*, a number of standards have to be set to assure safety, efficacy and applicability of traditional medicine, *e.g.* sustainable production and quality control of herbal products, performance of placebo-controlled, double-blind, randomized clinical trials, phytovigilance, as well as education of health professionals and patients.

Keywords: Complementary and alternative medicine; Evidence-based medicine; Integrative medicine; Nagoya protocol; Quality control; Traditional medicine

Abbreviations:

AYUSH, Department of Ayurveda, Yoga and Naturopathy, Unani, Siddha and Homoeopathy; BCEA, Basic Conditions of Employment Act; CAM, Complementary and alternative medicine; CTMDR, Center for Traditional Medicine and Drug Research; GSP, Good Sourcing Practice; GAP, Good Agricultural Practice; GLP, Good Laboratory Practice; GMP, Good Manufacturing Practice; GCTP, Good Clinical trial Practice; KEMRI, Kenya Medical Research Institute; KNUST, Kwame Nkrumah University of Science and Technology; MCC, Medicines Control Council; NCCAM, National Center for Complementary and Alternative Medicine; NCCIH, National Center for Complementary and Integrative Health; NGO, non-governmental organization; NHIS, National Health Insurance Scheme; NNMDRA Nigeria Natural Medicine Development Agency; OTC, over the counter; THMP, traditional herbal medicinal product; TMMDA, Turkish Medicines and Medical Devises Agency; WHO, World Health Organization.

1 Introduction

This paper looks at the economic, legal and cultural underpinnings of biopiracy as both the historical and the contemporary practice. At the same time, it looks at current work in the life sciences, particularly in the field of pharmaceutical biology, in order to explore alternatives to biopiracy as a form of what Vandana Shiva has described as the *plunder of knowledge* (Shiva, 1997).

Biopiracy is a term to blame the use of biological resources and knowledge of indigenous communities without sharing the venues generated by the economic exploitation of these resources and knowledge, respectively. There are a number of infamous examples of piracy related to nutritional or medicinal plants, *e.g.* basmati rice, *Curcuma longa, Azadirachta indica, Harpagophytum procumbens, Commiphora mukul, Hoodia gordoni, Banisteriopsis caapi, Pelargonium reniforme* and *P. sidoides, Terminalia fernandiana* and others. World Health Organization (WHO) and the United Nations Educational, Scientific, and Cultural Organization (UNESCO) draw international attention on the protection of indigenous knowledge in the context of intellectual property rights. The Declaration on the Rights of Indigenous People (UNDRIP) was launched by the UN General Assembly in 2007. The International Convention on Biological Diversity (CBD) aimed to protect rights of indigenous people sustainable uses of bioresources and conservation biodiversity achieved modest success, however, this treaty was not signed by several countries. Another important step in this development was the Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from Their Utilization to the Convention on Biological Diversity. The Nagoya Protocol contained rules to protect traditional medicinal knowledge and to compensate indigenous people for knowledge that is already being patented or being used in an inappropriate manner in the past (Efferth et al., 2016). By creating incentives for the sustainable use of genetic resources, the Nagoya Protocol will not only foster research on genetic resources but will also contribute to the development of human well-being by utilization of biodiversity. The European Parliament accepted the protocol (EU, No 511/2014) on 16 April 2014. It entered into force on 12 October 2014. Main principles are (1) informed consent of the country of origin of the resource and (2) he mutually agreed terms between indigenous peoples and collaboration partner.

To bring forward the implementation of the protocol, the Access and Benefit-Sharing Clearing-House (ABS Clearing-House) has been established. The task is to facilitate legal

transparency and monitor utilization of genetic resources. Most EU member states signed the Nagoya Protocol and expressed their commitment to ratify it. The ratification of the Nagoya Protocol by the EU does not automatically lead to ratification by all member states. The EU legislation only applies, where relevant national legislation exists in the countries, in which the relevant genetic resources and traditional knowledge are obtained. At the national level of each country, specific administrative or institutional circumstances might be considered for its effective implementation.

Unless the ownership of indigenous knowledge is acknowledged, contemporary practices in the life sciences are still inclined regarding knowledge held by indigenous and local communities simply as *raw material* which, similarly to former colonialist models, are then used to manufacture goods produced in the West and with Western-based companies reaping the benefits from such industrial production (Efferth et al., 2016).

Moreover, it can be argued that some practices in the life sciences, which have amounted to biopiracy may have caused scholars from humanities to be suspicious of the life sciences and their ethical standards in our globalized world as a whole. Yet, it is crucial to recall that forms of biopiracy are closely connected to the commercial business of multinational corporations such as Monsanto, a company which, starting in the 1990s, proceeded to patent life-forms and indigenous knowledge from a variety of different areas in what has been called the *Global South*. The economic use and increasing *privatization* of knowledge thus has to be separated from the academic field of the life sciences. Thus, it is inherently short-sighted to criticize a given academic discipline for the economic uses to which it is put. At the same time, it is nonetheless essential to investigate the entanglement of particular methods in the life sciences with forms of biopiracy.

Finally, by bringing together cultural understandings of biopiracy with forms of contemporary practice in the life sciences, which have succeeded in steering clear of biopiracy by collaborating with local and indigenous communities, our paper is also meant to bridge the gap between the life sciences and the humanities with regard to biopiracy as a threat towards a globally shared, sustainable ownership of knowledge.

2 From colonialism to neocolonialism: Biopiracy

2.1 Cultural approaches to biopiracy

As a form of neocolonial exploitation of territories and people, biopiracy has been closely investigated by humanities. Its study has loomed large in fields such as postcolonial studies (Huggan and Tiffin, 2010), ecocriticism (Buell, 1995; Garrad, 2004), eco-feminism and material feminism (Kolodny, 1975; Shiva, 1997). Particularly in postcolonial studies, researchers have argued that the contemporary practice of biopiracy has to be seen in line with forms of neo-colonialism. At present, they argue that the exploitation of nature and Third-World territories by colonial powers has been replaced by similar forms of exploitation at the hands of multinational corporations driven by shareholder-value in a neoliberal economic arena.

Even more disturbingly, many critics argue that the *plunder of knowledge* is inextricably linked to the emergence of life sciences disciplines such as botany in the 19th century. Crucially, these approaches point to the entanglement between colonialism as a political and economic system on the one hand and the history of science on the other hand. These critics suggest that the emergence of empirical research and scientific disciplines such as botany was itself made possible and predicated upon colonial power structures and the related expropriation of natural resources (De Loughrey and Handley, 2011). At worst, the life sciences may become a hand-maiden of global corporations: life sciences research may discover the potency of indigenous and local forms of knowledge, which then provide the basis for the patenting of this knowledge by multinational companies, which continue to be based in the West. Scientific research may hence come to be appropriated by multinational companies in their quest for alternative and highly profitable forms of knowledge and find itself in an ethically undesirable moral complicity. This may be particularly true in the field of alternative and complementary medicine: as Western medicine increasingly acknowledges its limits, particularly in fields such as cancer research, the search for alternative medical knowledge increases. Yet, this search may in some contexts come to be inseparable from the financial benefits to be reaped from such newly-discovered knowledge.

2.2 The legal underpinnings of biopiracy

The charge of biopiracy is inextricably intertwined with notions of epistemology on the one hand and legal notions of intellectual property on the other hand. Epistemology denotes forms of

knowing, which are in their turn connected to forms and concepts of explanatory power, which often leads to concepts of ownership, *e.g*. in processes of patenting. Thus, historically, indigenous communities from across the globe – from Native Americans in the US to Maori in New Zealand and Aborigines in Australia – have held the notion that land cannot be owned. Their sense that neither land nor nature could be anyone's property, but needed to be cherished and sustained led to colonial practices of what legal scholar Lindsay Robertson has called *conquest by law*. Thus, the epistemologies of indigenous communities and settler communities were fundamentally at odds with one another, and they proved to be mutually exclusive. The act of conquest thus also implied that one epistemological framework assumed precedence over another. The Western notion of *land* as something which could be owned, something which could become property, overrode indigenous concepts of the land, which held such ownership to be impossible. The law, in turn, cemented Western concepts in a way that their assumed superiority was then reframed not only as intellectually or culturally superior, but as *legal*. Epistemology and law are – especially if routed in the tradition of Roman law - inseparable in this context.

What historically applied to differing epistemological notions of the land also held true for different definitions of *nature*. Here, too, local and indigenous communities held that nature could not be owned, nor could it consequently be patented. Local and indigenous knowledge of the medicinal power of plants, for instance, was recorded in documents which, in Western categories, could not be clearly classified. Thus, the Indian epic of the Bhagavad Gita recorded the use of turmeric and its anti-inflammatory medicinal properties; yet, the Bhagavad Gita was seen as a text which linked cultural, legal, social and medical forms of knowledge. As a hybrid text which was unclassifiable in the sense of Western systems of classification, the Bhagavad Gita hence held little value as a document with which Indian ownership of knowledge with regard to spices such as turmeric could be *proved*. It was this incompatibility of epistemologies and of traditions of knowledge transfer, which could serve as proof of ownership and of intellectual property rights which made the court decisions of the 1980s possible, which found in favor of the defendant (*e.g.* Monsanto) and against the plaintiff (*e.g.* the government of India).

It is equally significant, however, that more recent court cases reversed this legislation. What is significant here is that there may also have been a shift in the acknowledgment of non-Western epistemologies as forms of knowledge in their own right. Crucially, the beginning of the 21st century can thus not only be seen as an *age of apology* (Gibney et al., 2008), in which a number of Western governments apologized for the wrongs they had inflicted on their indigenous

populations in Australia, Canada or New Zealand, but also as the reversal of patent cases, which were now acknowledged to be severe infringements of the rights of indigenous communities. It is interesting to look at these court cases in some more detail for the following reasons. First, they illustrate, in the language of the court, the practices leading to the patenting of the medicinal power of plants by Western corporations or Western scientists working for pharmaceutical companies. Second, they address the relationship between bioprospecting and biopiracy. Third, they point to forms of political, legal, economic and epistemological resistance by non-governmental organization, governments and intellectuals in the so-called *Global South*.

The communities, which have been affected by cases of biopiracy, thus range from India and Madagascar to Africa and South-America. Significantly, most of the patents on traditionally used medical plants of indigenous communities were granted by Western corporations in the 1990s. Among the patent cases of the 1990s, the so-called *Maya ICBG controversy* was the first to draw attention to the difference between bioprospecting – the discovery and subsequent commercialization of products on the basis of biological resources – and biopiracy. The Maya ICBG controversy took place in 1999/2000 and revolved around the ethnobiologist Brent Berlin, who headed the International Cooperative Biodiversity Group (ICBG). This group had originally set out to document the biodiversity of Chiapas (Mexico), and explore the ethnobotanical knowledge held by the Maya in this region. Bioprospecting hence involved not only a mere survey of the biodiversity, but also hinged on *surveying* the knowledge of this biodiversity held by an indigenous community. This surveying, moreover, was clearly meant to result in the commercialization of this knowledge, the profits of which would not include the Maya as the original owners of this medical knowledge.

Another case which has been highly significant for the current debate on biopiracy and the related notions of intellectual property rights (rights which were often denied to indigenous communities) is the controversy surrounding the neem tree, which can be found in both India and Nepal. A patent which centered on extracts of the neem tree as agents effective in fighting the fungal infections of plants was originally secured, in 1994, by the US department of agriculture in collaboration with WR Grace, a company based in Columbia, Maryland, featuring a pharma and biopharma product line. This patent, however, was subsequently opposed by Indian physicist Vandana Shiva as well as different groups within the US, Europe and India, among them the EU Green Party and the International Federation of Organic Agriculture Movements (IFOAM). In order to understand some of the epistemological underpinnings of the debate around biopiracy, it

is important to note that these groups were eventually able to prove that the knowledge of the fungicidal quality of the neem tree had long been held by Indian traditional medicine. Once such prior knowledge could be used, the patent – based on an American *discovery* of the fungicidal qualities of the neem tree – no longer held water. WR Grace lost an appeal in 2005.

Another highly publicized case involved the attempted patenting of some hybrids of Basmati rice by the American corporation RiceTec in 2000. The damage resulting from the granting of this patent was immense in India: Indian farmers were deprived of the intellectual property and the knowledge they had held, over many generations, about the qualities and the farming of basmati rice. Indian companies which had hitherto exported basmati rice were threatened by bankruptcy; and American consumers thinking they had bought Indian rice were unaware of the fact that they had now in fact bought an American product. Through its intervention, the Indian government was able to invalidate some of the claims. The European commission subsequently set out to protect basmati rice, referring to regulations with regard to geographical indications. In order to prevent future cases, in which Indian traditional knowledge of plants could be patented by Western corporations, the Indian government drafted the *Protection of Plant Varieties and Farmers' Rights Act 53* in 2001, relating it to regulations aiming at the protection of biodiversity.

In some cases involving the patenting of indigenous knowledge by Western corporations, indigenous communities have fought for being allowed to share at least a small percentage of the profit which is then made through the commercialization of this knowledge. In South Africa, the hoodia plant found in the Kalahari Desert was discovered to be an appetite suppressant, a quality which had long been known to the San people in South Africa. When in 1996, Unilever proceeded to manufacture a product based on hoodia, in collaboration with the South African Council for Scientific and Industrial Research, it was originally agreed that the San would not be included in the profit. However, in 2003, the South African San Council was successful in securing a share of 6-8% of the profit made through the sale of hoodia-related products.

Yet, as of 2017, many attempts to counter forms of biopiracy have remained unsuccessful. For instance, the US-American company PureWorld Inc. holds a number of patents related to the use of Maca, whose medicinal power is documented to have been known by Peruvian indigenous communities since the sixteenth century. Consequently, the Peruvian government organization INDECOPI (National Institute for Defense against Competition and the Protection of Intellectual Property) has accused PureWorld of engaging in biopiracy. Yet, the patent has so far not been

revoked. Examples like these provoked a multitude of activities which resulted not only in legislative measures of affected nations but also global efforts to ban biopiracy such as the Nagoya protocol.

To be fair, it should be mentioned that biopiracy is not a general practice of pharmaceutical companies. On the other hand, the efforts of companies willing to commercialize herbal products based on indigenous knowledge according to the rules of fair benefit-sharing failed sometimes because of non-sufficient administrative infrastructures and individual attempts of corruption. The rare examples of biopiracy by multinational companies and corruptive elements in the Third World are, however, prominent and may have occasionally contributed to a poisoned atmosphere of mutual mistrust. Misleading developments like these illustrate once more the necessity to enforce the establishment of international regulations for the protection and fair use of indigenous knowledge on traditional medicines.

3 Towards a *One-World Medicine*

In this section, we will pinpoint aspects of contemporary life science research and relate to the question, how the knowledge of indigenous communities can be integrated in health care systems based on Western medicine. We argue that the term and concept of a *One-World Medicine* can be used as an ethically and socially acceptable alternative to forms of biopiracy. As a matter of fact, there are various medical concepts realized in the Western world, which differ from conventional medicine. These concepts deserve a closer look to decide, whether elements of them are valuable to be converted for the construction of a *One-World Medicine.*

3.1 Concept of complementary and alternative medicine

In industrialized countries, where conventional, science-driven medicine replaced traditional medicines several decades ago, there is a striking demand of the general public nowadays for the methods and practices of traditional medicine. Interestingly, all forms of non-conventional medicines often labeled as “complementary methods” of medicine or healing attract more the well-earning, settled people of middle class societies (Greten, 2005). The demand for *green medicine* with *gentle* natural remedies seems to be associated to an increasing reluctance towards synthetic chemical drugs and technomedicine.

While the interest in green medicines is tremendous, it is actually not quite clear, what it is. All kinds of non-conventional medicines can be summed up as *complementary and alternative medicine* (CAM). They can be categorized as (1) natural products (herbs, vitamins, minerals, probiotics) and (2) mind and body practices (acupuncture, music and massage, yoga, tai chi, qi gong, chiropractic and osteopathic techniques, meditation, movement techniques, relaxation techniques, and many other techniques), which augment conventional medical treatments. This vast collection of disparate and unrelated therapies are applied not only to prevent and treat diseases and ailments, but also to enhance quality of life (Ernst and Hung, 2011).

As a matter of fact, the current lack of regulations leaves consumers at the mercy of those, who promote unproved remedies. The general perception that herbal products were safe may lead to inappropriate use with unforeseeable consequences for consumers (Consolini and Ragone, 2010; Yusuff and Tayo, 2011). The term CAM implies two different approaches: Complementary medicine as the use of non-conventional treatments may be used together with conventional medicine, while alternative medicine is used instead of conventional medicine.

The popularity of CAM was recognized by some governments of industrialized countries, and research institutes investigating the scientific basis of CAM therapies have been founded. Selected examples are the National Center for Complementary and Alternative Medicine (NCCAM) in USA - later on re-established as National Center for Complementary and Integrative Health (NCCIH) and the National Institute of Complementary Medicine (NICM) at the University of Western Sydney, Australia.

3.2 Concept of self-medication

Herbal medicines are frequently sold as over-the-counter (OTC) products (Agbabiaka et al., 2016). Such herbal products are classified as dietary supplements, but not as drugs. Therefore, manufacturers do not have to provide proof of efficacy or safety before selling these products. Their efficacy and safety is therefore doubtful. There are potential risks of self-medication, *e.g.* incorrect self-diagnosis, delays in seeking medical advice when needed, severe side effects, harmful herb-drug interactions, the risk of addiction and abuse etc. (Ruiz, 2010). There is still limited evidence on safety and efficacy of the estimated over 20,000 herbal products available in the market. It is imperative that more stringent regulations and guidelines are required to guarantee safety and efficacy of such products (Bent and Ko, 2004). Scientific evidence is needed to determine pharmacological activity, stability, and bioavailability of these products.

Laws pertaining to the labeling of dietary supplements prohibit specific claims for treatment or prevention of diseases. These products are nevertheless widely applied as CAM therapies (Glisson and Walker, 2010). In fact, dietary supplements are frequently taken by patients at their own discretion without knowledge of their physicians. Patients may underestimate the risks of self-medication and may anticipate physicians' disapproval to use OTC products. For physicians, it is imperative to ask patients about their use of CAM products. However, even if physicians are aware of it, they frequently feel poorly trained to judge on safety and efficiency of herbal preparations (Vora and Mansoor, 2005). The problem becomes even aggravated, if cross-reactions of herbal preparations with each other, with the diet of a patient, or with conventional medications are at stake. Physicians from conventional medicine therefore tend to generally prohibit patients the intake of CAM products – a situation which does merely increase confidence of patients and further favors the concealment of intake of CAM products by patients. This may cause vicious cycles, which have to be disrupted.

3.3 Concept of integrative medicine

Paradoxically, about 90% of the current conventional drugs are not active in approximately 40% of patients (No authors, 2012). Furthermore, it has long been recognized and still is a major problem to control and avoid adverse drug reactions of conventional drugs, leading to a situation, in which thousands of patients still die due to the improper use of therapeutic substances (Lazarou et al., 1998; Rolfes et al., 2017). Surprisingly, the principles of evidence-based medicine have seemingly not been applied for all conventional drugs. The lack of efficacy of numerous conventional drugs in all patients led to the current concept of *personalized or precision medicine*. The vision is to develop individualized treatment options for each single patient to reach higher treatment efficacy and with less side effects (Paul and Roses, 2003). Personalized medicine is, however, not a new concept of conventional medicine, but practiced in all traditional medicines for ages. This is another clue that both systems, traditional and conventional medicines should reflect on their specific advantages and disadvantages and that merging of systems may be beneficial for the patients.

The main idea of integrative medicine is to combine CAM with evidence-based conventional medicine (Snyderman and Well, 2002; May, 2011). While conventional medicine as discipline of modern life science in general follows reductionistic principles, integrative medicine

considers the patients in his/her entirety. According to this perception, diseases are caused by much more than reductionistic erroneous biochemical reactions or DNA mutations. Here, a holistic principle stands in the foreground. The body-mind-soul balance of the patient plays an important role. Therefore, integrative medicine focuses not only on direct disease treatment, but also on the wellness and lifestyle of patients. Ideally, integrative medicine is more than the addition of conventional and non-conventional approaches. Their right combination generates synergistic healing powers in the patient. Health is more than the absence of disease. In this context, the patient-physician relationship gains specific relevance.

Though the concept of integrative medicine is practiced at many places worldwide, an impressive example of a leading consortium for integrative medicine represents the Consortium of Academic Health Centers for Integrative Medicine with more than 60 US hospitals, including the John Hopkins School of Medicine, the Duke University of Medicine, the Georgetown University School of Medicine, the Mayo Clinic and many others.

Since 2012, the Swiss basic health insurance partly reimburse expenses from listed drugs belonging to CAM (*i.e.* phytotherapy, traditional Chinese medicine, neural therapy, anthroposophy, homeopathy), if done by a certified physician. Recipes not acknowledged by the basic insurance and therapies from non-medical practitioners may be reimbursed by supplementary and optional health insurances (Klein et al., 2015). The CAM medication is cheaper, but the consultation times are longer compared to conventional medicine. Hence, the overall costs are similar for both in Switzerland (Busato et al., 2006). CAM is accepted by over 90% of patients as treatment option and about half of the population prefers hospitals offering services both from conventional medicine and CAM. The vast majority of the population (85%) agrees that expenses for CAM are reimbursed by the basic health insurance (Wolf et al., 2006). About half of the patients have used CAM because of fewer side effects and lack of satisfaction with conventional medicine (Quattropani et al., 2003). Interestingly, women in the age range of 25-64 years and people with higher educational levels prefer CAM services (Esch et al., 2008; Klein et al., 2007).

Although the German government included naturopathy and homeopathy into the Germany Medical Licence Act in 1988, they have not been integrated in the academic teaching and practice as of yet (Albrecht, 2013). This is astonishing, since herbal medicine and naturopathy is even more popular in Germany than in Switzerland and also Austria (Brinkhaus et

al., 2011). Similar to Switzerland, German CAM users are more frequently women, have higher education levels, are more physically active and rarely over-weight (Schwarz et al., 2008). A negative aspect is certainly that more than half of the patients do not inform their general practitioners about their use of CAM (Schnabel et al., 2014). Hence, unintended herbal-drug interactions may occur without sufficient recognition by the physician.

3.4 Concept of traditional medicine

Since prehistoric times, all human societies and communities gathered knowledge on how to deal with diseases and ailments. Herbal practices may be categorized into (Elumalai and Eswariah, 2012):

1) Shamanic practices: The practitioner disposes of magical capabilities and uses plants as tools to interact with supernatural powers spirits and to cure patients. In this context, it is only of secondary relevance, whether or not the used plants reveal indeed pharmacological activity in a scientific sense.
2) Energetic practices: Herbs contain energetic power that restore the misbalanced energy in diseased subjects. This concept of herbal usage is practiced in TCM, Ayurveda and Unani etc.
3) Functional dynamic practices: Herbs reveal functional activities that provoke physiological consequences, although the underlying principles are not necessarily physically or chemical defined agents.
4) Rational phytotherapeutic practices: Herbs exert medical activity because of their defined chemical constituents and pharmacological modes of action. Phytochemical cooperative by synergistic interactions in plants or herbal mixtures.

Traditional medicine represents one of the most important cultural achievements of mankind during history before the rise of modern medicine. The World Health Organization (WHO) defines: "Traditional medicine is the sum total of the knowledge, skills, and practices based on the theories, beliefs, and experiences indigenous to different cultures, whether explicable or not, used in the maintenance of health as well as in the prevention, diagnosis, improvement or treatment of physical and mental illness" (WHO, 2000). To this end, traditional medicines comprises of all forms of formalized and documented practices and remedies in a community or society as well as all forms of informal practices, orally handed down from generation to

generation. There is a wide range of traditional practices, including herbal mixtures, processed herbal materials (essential oils, fresh juices, gums and resins etc.) and herbal extracts (fluid or dry extracts, tinctures, decoctions and infusions, oils etc.). Traditional Chinese medicine is largely based on the balance of powers in the body, *e.g.* the five elements, *yin* and *yang* etc. (Efferth et al., 2013). In addition to herbal medicine, Asian forms of traditional medicine can also comprise of reflex therapies such as acupuncture, manual therapies, dietetics, spiritual therapies and others.

In Africa, animism is far distributed, *i.e.* the belief that all living and non-living subjects in nature bear supernatural spirits, which maintain health. Therefore, traditional healing attempts to restore the spiritual balance of patients. Plants are not believed to exert curative effective because of their pharmacological activity, but because of the healer's capability to influence the spiritual relationship between the patient and his environment (Anyinam, 1987). Herbalists in Arab countries prefer medicinal plants that are well documented in the Arab-Muslim tradition (Khalid et al., 2012). Some national herbal pharmacopoeia (such as the Moroccoan) contain numerous of these plants (Bellakhdr, 1997). Herbal medicines also represent valuable assets to conventional medicine in Middle and South America (Berman et al, 1999; Hunt et al., 2000).

Remarkably, even in Western medicine many long established drugs were initially derived from medicinal herbs, *e.g.* opium, aspirin, digitalis, quinine and many others. WHO provided data that about one quarter of all modern drugs are plant-based (WHO, 2007). Even more striking, the usage of 80% of plant-based bioactive compounds in conventional medicine today correlate to their traditional ethnopharmacological use of the corresponding medicinal plants (WHO, 2013). This relationship emphasizes the potential relevance of medicinal herbs for modern medicine (Newman and Cragg, 2012; Cragg et al., 2014).

Therefore, it does not come as a surprise that the importance of natural resources for modern drug development process has also been appreciated by the Nobel Assembly of the Karolinska University in Stockholm, Sweden. The Nobel Prize in Physiology and Medicine 2015 was given to three scientists for their breakthrough inventions in the field of natural product-based drug development, especially in the field of communicable tropical diseases (Efferth et al., 2015). The so-called neglected tropical diseases especially worth mentioning are widely distributed in tropical and subtropical areas, where prevention and cure for these diseases are not sufficiently available. Here, phytotherapy and natural products bear high therapeutic potentials for their treatment.

Evidence-based medicine is thought to be a gold standard in conventional medicine, though it can be critically noted that this is not true for all western drugs. Nevertheless, it is common sense that the principles of evidence-based medicine should also be applied for traditional medicines. According to WHO, the "inappropriate use of traditional medicines or practices can have negative or dangerous effects" and "further research is needed to ascertain the efficacy and safety" of traditional practices and herbal preparation.[35] As a matter of course, phytotherapeutic remedies should meet stringent criteria of quality control, elucidation of modes of action, as well as clinical safety and efficacy.

There are three major requirements for herbal medicines to be defined as conditions to integrate traditional medicines into conventional medicine. They can be understood as pre-conditions to generate convincing approaches for *One-World Medicine*, *i.e.* (1) the traditional knowledge of healers and shamans is increasingly getting lost. This knowledge has to be preserved, (2) standardization and quality control of herbal products and (3) clinical proof of safety and efficacy in patients.

3.5 Concept for developing countries and beyond: *One-World Medicine*

WHO repeatedly reported during the past years that up to 80% of human beings in developing countries rely on traditional herbal medicines for primary health care (WHO, 2007; 2013). Patients with less income, less education and patients from rural areas are more likely to use traditional medicine (Oyebode et al., 2016). Not only that Western medicine is frequently not affordable and that traditional medicine is available at low prices for primary health care in developing countries. In many rural areas, hospitals are only reachable over far distances and the patients are frequently confronted with long waiting queues with common waiting times of 6-12 hours. Therefore, many patients rather rely on the reputation of healers and their traditional practices. Traditional medicine represents a remarkable reservoir for the drug development process (Zaenker and Entschladen, 2009).

This puts the responsibility on scientists and physicians alike to explore the scientific basis for a safe and efficient use of traditional practices. On the other hand, it is estimated that the vast majority of the estimated 30,000-70,000 medicinal plants worldwide have not yet been scientifically investigated (Verpoorte et al., 2005). The research-driven modernization of traditional medicines represents a primary goal to make them globally available, affordable and

safe. Based on the concept of integrative medicine, a comparable concept can be envisioned for the global use of traditional medicine embedded in and amalgamated with conventional medicine. The synopsis of medical knowledge from all around the world allows generating novel treatment options, which may be more suitable to the needs of the majority of the population on earth without access to expensive therapies which are exclusively reachable for rich minorities in the industrialized countries. Such a *One-World Medicine* might be able to link together the best of both worlds – conventional medicine from the developed in the North and scientifically proven efficient, safe and more affordable traditional medicines from the under-developed South (Efferth, 2010). The ultimate goal is to provide safe and efficient medical care to under-served populations in developing countries.

The health care systems of Third World countries frequently cannot afford the high costs for medical treatment for their populations. Sufficient health care is too often a privilege for rich elites not only in industrialized, but also in developing countries. Hence, the population is frequently left alone with their heritage of traditional medicine brought down from their ancestors. As a consequence, the majority of the world population without sufficient access to modern drugs relies on natural medicines. While there is no doubt about the considerable potential of traditional medicines, they have been largely used without stringent medical and scientific control to ensure safety and efficacy and without the rigorous rules necessary to register drugs nowadays in a comparable manner to conventional western drugs. This desperate situation illustrates the urgent need for evidence-based approaches for traditional medicines. Therefore, the establishment of rationale phytotherapies seems to be a major plausible option for the future (Efferth, 2012; Efferth and Koch, 2011; Efferth and Greten, 2012a; 2012b; Efferth et al., 2007).

Facilitating global interconnectedness certainly poses tremendous challenges, but it also represents an encouraging vision to empower impoverished indigenous communities to achieve long-term improvements in primary health care. The goal is to provide high quality and at the same time affordable healthcare to people in the regions, where they live. The care the people are receiving should be audited by partners and reviewed by medical advisory boards. The establishment of medical centers specifically designed to provide quality healthcare to poor people may serve as a model in this respect (OneWorldHealth, 2016).

If herbal medicines meet rigorous quality control in production and evidence-based standards, they would not only provide safe and efficient drugs to the Third World, but also reduce costs for the health systems in industrialized countries. Faced with ever-increasing costs

for medications, *One-World Medicine* also bears considerable potentials for future health care in the Western world in times of bursting in health systems (Efferth, 2010).

In most countries of Africa, Middle East and South America, herbal medicine is not yet officially acknowledged by the governmental health care systems. Health insurances do not cover the costs even for registered herbal drugs. They are accounted as food supplements and are widely used outside the official health systems. WHO has defined guidelines for the institutionalized integration of traditional medicine into the official health system. These guidelines include:

1. Political recognition by government
2. Development of legal and regular frameworks
3. Scientific research on traditional medicine
4. Protection of intellectual property on traditional medicine
5. Dissemination of information and education on traditional medicine of the general public
6. Creating economic opportunities for traditional medicine (WHO, 1978).

The Division of Traditional Medicine, a collaborating center of WHO and recognized by the Organization of African Unity, has started activities for the identification of natural areas to grow medicinal plants (Keita, 1993). The WHO Regional Committee for Africa released a resolution (AFR/RC50/R3) to support the integration of traditional medicines, if safety, efficacy and quality is evident (WHO, 2001). Other resolutions followed, *e.g.* the Abuja Declaration and the declaration of the organization of African Unity in 2001 (Abuja Declaration, 2001) and others.

While traditional medicine was sometimes banned in the past by the governments (*i.e.* the Apartheid regime in South Africa had forbidden herbal practices by the Witchcraft Suppression Act of 1957 and the Witchcraft Suppression Amendment Act of 1970), traditional medicine reached a more official status with more formal regulations in the past few years.

However, in some African countries such as Botswana and Mozambique, the traditional healthcare systems enjoy official status and in these countries a more formal trade exists. Botswana, Namibia, Mozambique, Zimbabwe and Malawi import medicinal plants form South Africa (Economic Commission for Africa, 2008).

In South Africa, the expenses for services of traditional health practitioners are not covered by the official Basic Conditions of Employment Act (BCEA) (Mbatha, 2012). The trade of crude medicinal plants is not regulated. However, once a health-related claim is made for a

finished product, it has to go through the full drug evaluation procedure in the Medicines Control Council (MCC) before marketing (Sharad et al., 2011).

Under the present health care reform of the Federal Government of Nigeria, traditional medicine is recognized as important segment of the primary health care system. The Federal Government of Nigeria has established the Nigeria Natural Medicine Development Agency (NNMDA) to promote Nigerian traditional medicine products and practices and to integrate traditional medicine into the mainstream of modern health care system. The Nigerian Ministry of Health encouraged the University of Ibadan to perform research on medicinal herbs to foster standardization and regulation of traditional medicine (Ekeopara and Ugoha, 2017).

Ethiopia supports the sustainable use of plant resources. This is part of broader political strategies including environmental protection, development of natural resources and diversification of domestic and export commodities (Srivastava et al., 1996).

In Ghana, the National Health Insurance Scheme (NHIS) from 2003 does not cover traditional medicine services (Barimah, 2013). Although prescription and dispense even of certified herbal products is not supported, the integration of standard Western medicine and herbal medicine is recommended (Bodeker, 2001).

In the meantime, more than 30 African countries implemented national policies on traditional medicine into the official health systems and more than 20 countries developed legal frameworks for traditional medicine practices (Kasilo et al., 2010). It remains to be seen, to what extent these national policies and regulatory frameworks will be translated to medical routine in everyday life.

Governmental support for the integration of herbal medicines into the official health care systems represents only a part of the aspects that have to be considered (Ochwang'i and Oduma, 2017). Physicians trained and educated in Western medicine also have to accept practices from herbal medicines (Bodeker, 2001; Awodele et al., 2012; Puoane et al., 2012). These integration processes may be slow and troublesome but worth attempting (Bodeker, 2001; Lee, 2016). On the other hand, many traditional medicine practitioners would like to have some kind of formal education both in Western medicine and herbal medicine, which provides excellent chances for concepts of integrative one-world medicine (Bruce, 2002).

Japan may represent a showcase example for the concept of *one-world medicine*. Japanese traditional medicine known as Kampo medicine is integrated into the official health care system. Conventional medicine and Kampo are subject to the same strict regulations (Maegawa et al., 2014; Hakamatsuka, 2017). The National Health Insurance Reimbursement System contains 148 Kampo recipes that are prescribed by physicians. The medicinal plants and extracts are described in the Japanese Pharmacopeia, and strict quality standards are set by law. Physicians easily use both Western and Kampo medicines in their daily practice. According to recent investigations, more than 80% of the Japanese physicians prescribe Kampo formulae and 73-84% of patients take Kampo drugs (Moschik et al., 2012; Hottenbacher et al., 2013). Kampo is preferentially used for chronic ailments than acute diseases, *e.g.* common cold, gastrointestinal complaints, stress and anxiety etc. (Hottenbacher et al., 2013).

In China and Taiwan, the costs for services of traditional Chinese medicine are partly covered by health insurances. The costs for academic medicine are higher than for practices of Chinese medicine (herbal remedies, acupuncture etc.) (Liao et al., 2012). More than 60% of patients use Chinese medicine (Chen et al., 2007). While self-treatment of chronic diseases seems to be most attractive for patients, most cancer patients also use Chinese medicine in addition to Western medicine (Liao et al., 2013; Wu et al., 2015). Socio-demographic studies showed that herbal medicines, which are cheaper than conventional drugs, are popular among under-insured patients (Chung et al., 2013). The further integration of Chinese medicine into the national health care systems became a national policy in China to save expenses. The national "essential drug list" contains more than 200 formulated herbal drug and 1100 herbal preparations. The financial budget for Chinese medicine doubled from 2011 to 2014 to 4.66 billion USD, which may be taken as a strong indicator for the willingness to integrate Chinese medicine into the official health care system (Dang et al., 2016).

Brazil, with its 8.5 million km^2 of land area and a coastline around 8,500 km long, is a highly privileged country as to the variety and number of species that are home to six major terrestrial biomes: Amazon, Caatinga (an genuine Brazilian extremely environment), Cerrado (a type of savanna), Atlantic Forest, Pantanal and Pampa, besides the three marine ecosystems, twelve major hydrographic regions (MAA, 2011), and the mangroves that constitute a intermediate biome between terrestrial and marine environments. This biological wealth can be translated into a great diversity of molecular models produced by thousands of organisms that compose the

Brazilian biodiversity. This "natural molecular factory" still been completely unexplored, consequently, is a potential source of new bioproducts, such as pharmaceuticals, cosmetics, agrochemicals. With great chemo-biological wealth, Brazil was one of the 192 countries signatories of the Convention on Biological Diversity (CBD), during the Rio de Janeiro United Nations Conference, which held on 5 June 1992, in Rio de Janeiro, Brazil. This meeting was stated for the signature at the Earth Summit, and inputted into force on 29 December 1993. Representatives of all nations had committed themselves to the conservation of biological diversity, its sustainable use, and the just distribution of the benefits of economic uses. Approved by the National Congress, the CBD was the starting point for the creation of Law Decree No. 2519 of March 1998. With the publication of this Decree, Brazil formally assumed that the Biodiversity Law would be put into practice and implemented. However, the lack of a legal framework made it quite difficult to be implemented. Thus, this legal problem became an obstacle for the country to sign the Nagoya Protocol, which came into operation in October 2014. This new pact, an outgrowth of the Convention on Biological Diversity, ratified by 50 countries, was intended to implement the measures defined by the Convention. In order to protect biodiversity and curb biopiracy, Brazil has stepped forward, being one of the first countries to establish a Regulatory Law for Access to Genetic Resources based on the CBD.

The President of Brazil, with the justification of prohibiting bio-piracy, issued the Provisional Measure - MP 2186-16 (MP 2052/2000) and it has become public in August 2001. This MP has gained force of law, at the moment in which it was edited the Constitutional Amendment 32 of 11 of September of 2001. The MP 2186-16 was decreed by law in May 2015, when Law No. 13,123 of 20 May 2015, also known as the Biodiversity Law, was approved by the President of Brazil, Dilma Rousseff. The stated intention of the Biodiversity Act was to avoid bio-piracy and ensure the sharing of benefits in a "fair" and "equitable" with indigenous peoples on the innovations arising from our biodiversity. The regulation was published, after intense negotiations with the scientists, private sector, ministries and communities involved, but still remain doubts as will be implemented.

3.6 Conditions to realize *One-World Medicine*

3.6.1 Preservation of traditional medicinal knowledge

Although certain traditional medicines are increasingly booming worldwide (*e.g.* traditional Chinese medicine, Ayurveda), traditional knowledge on other natural medicines is endangered, because the knowledge of shamans and traditional healers is getting lost, since their oral traditions handed down for thousands of years is getting more and more extinguished nowadays. With progressing economic development in tropical and subtropical countries, the offspring of traditional healers and shamans may be less motivated to take over the same profession as their parents. Although shamans are highly respected persons in their communities, many young people seek their fortune in urban cities rather than spending a life as shamans in rural environments. Sometimes there is considerable reluctance of herbalists to talk about their traditional medical knowledge, because they argue that their knowledge could be stolen by pharmaceutical companies. Though such threats may be justified, this attitude might foster the loss of knowledge for further generations. Hence, the death of each traditional healer represents an irretrievable loss of age-old medical knowledge.

An approach to prevent the loss of traditional knowledge is the systematic performance of ethnobotanical and ethnopharmacological field studies to collect all kind of information on herbal medicines, their preparation and traditional uses for diseases, adverse side effects *etc*.). These data can be compiled and made available by the establishment of electronic databases as recently demonstrated (Johnson, 2002; Babu et al., 2006; Latheef et al., 2008).

Traditional medicines are also threatened by the destruction of rainforests and other biological biotopes, which irreversibly leads to a loss of plant resources and also destroys the living spaces of indigenous tribes with their knowledge on herbal medicine and traditional practices. Further reasons that may negatively impact the use of traditional medicinal herbs include environmental pollution, the anthropogenic invasion of foreign species into biotopes, and more recently consequences of climate change, which all may contribute to the displacement of indigenous species (Newman, 1994; Forest et al., 2007; Cavaliere, 2009).

3.6.2 Sustainable production medicinal plants and phytochemicals

A considerable problem, if medicinal herbs are used not only in small local communities but at larger scales, is overharvesting of plants growing in the wild. This may not only lead to

extinguishing plant species and progressing destruction of biodiversity, but also to bottlenecks in sustainable supplies of plant material for national and international markets (Li et al., 2007).

A promising concept to reduce another societal problem in Africa, *i.e.* ivory-poaching of elephants and rhinoceroses, is to establish protected reserves and to provide jobs to the indigenous population by their employment as rangers and sometimes even establishing novel gendered identities at the same time like in a bespoke all female anti-poaching unit, *Black Mambas* (http://www.blackmambas.org/, accessed on June 20th, 2017). It can be envisioned that comparable concepts might also be applicable to herbal medicine. The controlled cultivation of medicinal plants in plantations and greenhouses provides numerous advantages: (1) jobs for indigenous people, (2) protection of medicinal plants from being extinguished by over-harvesting in the wild, (3) better quality of herbal material due to standardized cultivation and harvesting conditions, (4) sustainable production to maintain supply sufficient amounts of herbs for primary health care in developing countries etc.

Specific guidelines for good field collection practices for medicinal plants have been developed (Fong, 2002). Education and training of local people may facilitate and support plant conservation (Busia, 2005; Frenkel et al., 2005). If indigenous people understand that uncontrolled harvest of medicinal herbs from the wild foster the ultimate extinction of plant species and, therefore, shorten their economical basis, strategies for sustainable cultivation of herbs may be easier realized.

Avoiding wild collections by culturing medicinal plants in fields and greenhouses may have more advantages (Delabays et al., 2001). Cultivation conditions (temperature, humidity, soil etc.) are well-known to influence the yield of the desired chemical constituents in plants. Hence, the optimization of the specific cultivation conditions in greenhouses may result in higher yields of natural product contents in medicinal plants.

Modern techniques adapted from classical agriculture and horticulture can also be applied for the cultivation of medicinal plants such as the breeding of high-yield cultivars at optimized culture conditions. Naturally occurring individual variations of plants can be exploited due the specific selection of strains with higher amounts of the phytochemicals of interest. One may take advantage of classical breeding techniques to cross high yield clones and to generate synthetic variants of medicinal plant species. Another option may be the cultivation of genetically modified, transgenic plants, which reveal substantially higher amounts of natural products compared to their wild-type counterparts (Muntendam et al., 2009). From an economical,

ecological and ethical point of view, however, the conservation of the genome information of traditional breeds and wild-types will be another task, which needs to be accomplished, if we want to preserve genetic diversity.

Seed, germplasm and DNA banks are important means for the conservation of endangered plant species. An example is China's first national seed bank for wild plants at the Kunming Institute of Botany, which contains some 30,000 seeds (http://www.bgci.org/resources/news/0716/).

The slow growth of medicinal plants may limit their commercialization. Solutions to this problem may represent the total chemical synthesis, the semi-synthesis from isolated precursors, or the systematic derivatization of natural lead compounds to obtain generate pharmacologically improved drugs (Kowole et al., 2008; Szpilman and Carreira, 2010). This, however, cannot be regarded as traditional medicine anymore, but as classical pharmacological drug development inspired by drugs from nature. Furthermore, total synthesis can be time-and cost-consuming and, therefore, not applicable for industrial large-scale production (Schmid and Hofheinz, 1983).

It is not out of reach for some developing countries also to consider biotechnological techniques to enhance and accumulate natural products (Efferth, 2011; Gandhi et al., 2015). Hairy root cultures of medicinal plants are easy to maintain and produce large amounts of natural products (Mehrotra et al., 2015). The same is true for suspension or callus cultures derived from medicinal plants (Georgiev et al., 2009; Ogita, 2015). With the help of molecular biology, entire biosynthetic pathways for natural products can be expressed in biotechnologically applicable microorganisms, *i.e. Escherichia coli* or *Saccharomyces cerevisiae* etc. (Julsing et al., 2006). A famous example for the success of this technology is the production of the antimalarial drug artemisinin from the Chinese medicinal plant, *Artemisia annua* L. (Zeng et al., 2008).

3.6.3 Standardization and quality control of herbal products

Herbal recipes frequently consist of complex mixtures of different plant. The composition and amount of chemical constituents may vary even within one and the same species, depending on climate, soil composition, habitat altitude *etc.* Herbal products should therefore reach a similar degree of reproducibility as any other approved synthetic drug as well. To reach this goal, internationally accepted standards need to be established (Efferth, 2010). Three main levels of standards can be defined: (a) Quality control of herbal product materials, (b) preclinical evidence

of safety and efficacy, and (c) clinical evidence of safety and efficacy. It is however, not only about the standardized constitution of herbal mixtures, there is also a lot of concern about intentional adulterations or non-intentional contamination, which have to be taken as alarming signs to set high quality standards (Efferth and Kaina, 2011; Efferth and Greten, 2012c).

International standard setting has to consider several levels:

(1) The correct identification of medicinal plants is of utmost importance (de Jong et al., 2015), since wrongly identified plants may not only be without therapeutic effect, but even worse may contain poisonous ingredients. Botanical misidentification or mislabeling of herbal material might exert toxic reactions in human subjects (Booker et al., 2016; Osathanunkul et al., 2016).

(2) Standardization of production of herbal prescriptions by international quality guidelines such as Good Sourcing Practice (GSP) to guarantee authentication of medicinal plants, Good Agricultural Practice (GAP), Good Laboratory Practice (GLP), Good Manufacturing Practice (GMP), and Good Clinical Trial Practice (GCTP) (Zhang et al., 2010; Franz et al., 2011).

(3) Chemical analyses to detect and avoid contamination of herbs with mycotoxins, pesticides, heavy metals, other chemical toxins, and radioactivity taken up from the soil as well as organic solvents and microbial contamination due to unprofessional processing of harvested herbs (Posadzki et al., 2013).

(4) Chemical analyses to detect and avoid substitution or adulteration with other herbs or chemical drugs, which may deliberately occur for economic reasons. It is an illegal act to replace authentic herbs by faked ones, because it is cheaper, or to intentionally increase the activity of an herbal mixture by adding a synthetic chemical drug with well-known pharmacological activity (Efferth and Kaina, 2011; Posadzki et al., 2013).

International regulations for herbal products will improve the safe and efficient use of traditional medicines. The WHO introduced quality control regulations to set standards and specifications for herbal materials (WHO, 1998). European Union (EU) regulated the production and distribution herbal medicines according to the European Directive on Traditional Herbal Medicinal Products (Efferth and Greten, 2012d). In the United States, herbal remedies are still frequently traded as dietary supplements. Herbal products of this category do not underlie the strict regulations for safety or efficacy. They are widely available without prescription as OTC products on the own expense of the patients (Eichhorn et al., 2011), although the corresponding governmental authorities may withdraw them from the market, if there is evidence for toxicity.

In many countries in Africa and Middle East, there are non-sufficient regulations for trading herbal products. As an example, medicinal plant products were sold in *Akthar* shops, where no special training was required for the persons responsible. Since 1986, it has been made mandatory that each *Akthar* shop must be registered by the local branch of the Ministry of Health to obtain the official permission to sell herbs. Promotion of these products with health claims is not permitted. In 2010, a regulation to license for traditional herbal medicinal products (THMPs) was published by the Turkish Medicines and Medical Devises Agency (TMMDA) and these products are subjected to a marketing authorization procedure within the scope of which the product quality, safety and efficacy for the defined therapeutic or preventive indications are evaluated. A scientific commission for examining application of THMPs was established under TMMDA. On the other hand, the Turkish market currently offers an ever increasing number of dietary supplements, which are assessed and authorized by the Ministry of Food, Agriculture and Livestock. Registration is done based on the manufacturer's declaration. Manufacturers are prohibited to claim any medical indications. These products are not subject to any analysis and examination before going to market. Therefore, the quality, safety and efficacy have not been proven.

Several institutions have been established in African countries to standardize herbal drugs, perform clinical trials and care about regulatory affairs, *e.g.*

- Center for Scientific Research into Plant Medicine (Ghana). In Ghana, herbal medicine producers need a license by the national Food and Drug Administration. Only qualified ventors should be allowed to trade and sell herbal products (Aziato and Antwi, 2016).
- Center for Research on Pharmacopoeia and Traditional Medicine (Rwanda);
- "Village Chemist" for Development of Pharmacognosy, Obafemi Awolowo University, Ile-Ife (Nigeria);
- Swaziland Center for Research in Medicinal and Indigenous Food Plants, university of Swaziland, Swaziland;
- Department of Traditional Medicine, Bamako (Mali);
- Center for Traditional Medicine and Drug Research (CTMDR) in Kenya Medical Research Institute (KEMRI).

In India, the government established a National Medicinal Plants Board and the Ministry of Health and Family Welfare founded a department to deal with herbal medicine (Ministry of

AYUSH) (Elumalai and Ewariah, 2012). More than half a million traditional practitioners are licensed and registered by the Indian Medicine Practitioners Act.

3.6.4 Mode of action analyses and network pharmacology

It is not a trivial task to unravel the molecular modes of action of complex herbal mixtures, especially if one applies the one-drug-one mechanism concept which frequently used in classical pharmacology of synthetic drugs. The concept of mono-specific small molecules was and has been very fashionable since a couple of years, to increase the specificity of therapeutic drugs action and to decrease the non-specific toxic reactions to healthy normal tissues. Inspired by the theoretical idea to generate more specific and safer drugs, conventional pharmacologists sometimes called drugs from traditional medicine "dirty drugs". There are numerous examples of approved drugs, *e.g.* for cancer therapy following this concept. This concept showed, however, only modest clinical success, because mono-specific drugs are easily prone to resistance development. Frequently point mutations in the monospecific drug target are sufficient to make a drug inefficient (Volm and Efferth, 2015; Patel et al., 2017; Lim et al., 2018). Here, the multi-specific nature of medicinal plants and herbal mixtures provides a striking advantage. Because of a multitude of phytochemicals in plant extracts, numerous cellular targets are addressed, which makes the therapeutic effect much more efficient and robust against resistance development. Single mutations in singe target proteins will not hamper treatment success, because many different targets in the diseased cell are addressed. Therefore, multi-specific extracts of medicinal plants or herbal mixtures are more effective. It can be assumed that during evolution of life on earth, multi-specific approaches were more successful towards selection pressure than mono-specific approaches. From an evolutionary point of view, the "dirty drugs" are the better drugs, because they better cope with resistance phenomena.

The analysis of multi-specific modes of actions is much more complicated because of the complexity of numerous phytochemicals each addressing multiple target proteins. The advent of the so called omics technologies (genomics, epigenomics, transcriptomics, proteomics, metabolomics, lipidomics, glycomics etc.) allow the measurement of highly complex alterations upon treatment with herbal mixtures (Kadioglu et al., 2016; Li et al., 2018; Lin et al., 2018). Bioinformatical techniques are necessary to unravel affected signaling pathways and mechanisms in a plethora of single data points that are generated by these "-omics" approaches". A new

discipline emerged termed "network pharmacology", which focusses on the elucidation of complex modes of action (Schmidt and Efferth, 2016; Poornima et al., 2016; Efferth et al., 2017; Ulrich-Merzenich et al., 2017; Wagner and Efferth, 2017; Guo et al., 2018). It can be expected that many relevant advancements will be made in the understanding of the therapeutic effects of medicinal herbs and herbal mixtures.

3.6.5 Herb-drug interactions

An issue that should be adequately addressed is the interaction of some commonly used herbs with synthetic drugs from conventional medicine (Kober et al., 2008; Meng and Liu, 2014; Zuo et al., 2015; Liu et al., 2015; Choi et al., 2016). Due to the influence of herbal preparations with the metabolizing enzyme machinery in the liver, drug-herb interactions may lead to unexpected (increased or decreased) concentrations of therapeutic drugs (Woo et al., 2015; Dai et al., 2017; Lu et al., 2017). Between 50% and 63% of these interactions occurred between prescribed drugs and OTC herbal products (Glisson and Walker, 2010). The majority of cases showed mild pharmacokinetic interactions. However, the consequences of these interactions are not well understood as yet in the clinical setting.

3.6.6 Clinical trials

Scientific evidence on the clinical safety and efficacy of herbal preparations is still not sufficient. Numerous case reports on considerable use of herbal products are indicative for their effectiveness. The only option for the integration of traditional medicines into conventional medicine is to perform sound clinical trials (Zeng et al., 2015; Sahebkar et al., 2016; Schwinghackl et al., 2016; Tomé-Carneiro and Visioli, 2016). Herbal products should fulfill the criteria of evidence-based medicine just like synthetic chemical drugs too, in order to gain full recognition in conventional medicine. Therefore, placebo-controlled, double-blind and randomized clinical trials are required.

Quality control is of utmost importance, actually everywhere in medicine, not only in traditional medicine in general or specifically phytotherapy. There have been considerable efforts during the past years to improve the quality of herbal preparations (Efferth, 2011; Efferth and Greten, 2012c; 2012d; Booker et al., 2016; Singh et al., 2017; Liao et al., 2018). Other forms of traditional medicine such as acupuncture, massage, tuina massage, tai chi chuan etc. may not be

as easy accessible to quality control measures as phytotherapy. The relatedness of scientific methods to investigate natural products and synthetic drugs facilitate to generate high quality standards in both fields. However, even if the preclinical scientific understanding of these non-pharmacological techniques of traditional medicine might be more difficult, the clinical efficacy can be monitored in a comparable way as other techniques of conventional medicine too. It is crucial to perform clinical phase I-III trials to demonstrate the clinical efficacy of non-pharmacological forms of traditional medicine. Clinical trials will not only unravel the clinical efficacy of these methods themselves, but also the skills of those health professionals, who perform them (*e.g.*, acupuncturists, masseur etc.). There have been several examples in the literature of randomized double blind clinical trials that have been performed according to the state of the art (Maimer et al., 2013; Sousa et al., 2015; Mayer-Hamme et al., 2018). Scholars working in non-pharmacological fields of traditional medicine should be encouraged to perform clinical trials and if adequate performance faces difficulties, novel adequate methods for clinical trials should be developed. This represents an important area of research that has to be developed in the yards to come.

3.6.7 Phytovigilance

As precise prescribing guidelines for self-prescribed herbal products are missing, the introduction of *phytovigilance* guidelines is justified to minimize the risk of herb-induced toxicity. Once evidence-based traditional medicines enter the market after the performance of clinical trials, pharmacovigilance studies should monitor adverse effects (Shaw et al., 2012; Zhang et al., 2012). Self-medication-induced morbidity can largely be avoided by proper documentation of the intake of herbal medicines in the patients' personal medical. The relevance of this issue has been previously illustrated (Jaski et al., 2000). The authors surveyed primary care internists and family practitioners from the American Medical Association Physician Masterfile regarding their patients' use of prescription drugs, OTC products, nutritional supplements, and herbal treatments. Almost all among the 655 responders reported reviewing prescription medications prior to prescribing a new therapy (99.8%), but only 86% reported simultaneous OTC product use of their patients. Less than half of the physicians reported the use of nutritional supplements or herbal products among their patients before prescribing a new therapy. These alarming results demonstrated that the use of non-prescription substances is not routinely documented in primary

care practice. Physicians should routinely ask patients about their use of dietary supplements and OTC products prior to starting treatment with prescribed drugs. There are still scant guidelines to assess safe self-administration of conventional and herbal medication (Mitty and Flores, 2007).

3.6.8 Educational programs, databases and information centers

As a matter of fact, most traditional uses of medicinal plants have not been sufficiently recorded to be available for a broad audience. It is reasonable to fear the loss of knowledge on medicinal plants for several reasons, *e.g.* destruction of habitats, disinterest of younger generations in practices handed down by older generations. The conversion of oral knowledge from shamans and indigenous healers to written documents will not only prevent the distinction of herbalistic knowledge, but will also foster the development of rational and scientifically based concepts for education and training at universities.

There are several options to save knowledge on the use of traditional medicine for future generations. One such possibility is the generation of electronic database. An example is the Databank of Turkish Folk Medicine (Yesilada and Sezik, 2003). Furthermore, regional education centers may provide courses for further and continuing education of traditional practitioners such as the Bezmialem Center for Education, Research and Practice in Phytotherapy, which is the first phytotherapy center approved by the Council of Higher Education in Turkey. Finally, academic degrees from universities represent the most sophisticated from of formal education in traditional medicine. Indeed, several Bachelor programs have been established in the past years. An example is the B.Sc. Herbal Medicine degree program at the Kwame Nkrumah University of Science and technology (KNUST) in Ghana. This is a four-year program and graduates are licensed by the Traditional and Alternative Council of Ghana as herbal medicine practitioners (Aziato and Antwillo, 2016).

In the United Kingdom, the University of East London, the Middlesex University, the University of Central Lancashire, the University of Westminster, the University of Lincoln, and the Napier University in Edinburgh offer B.Sc. degree programs in herbal medicines (Elumalai and Eswariah, 2012).

At the patient side, self-administration of medication implies that the consumers are cognitively competent to manage their health care. However, this cannot always be guaranteed. Therefore, health care professionals (physicians, pharmacists, nurses, midwifes *etc.*) have the responsibility assessing the self-care ability of their patients (Glisson and Walker, 2010). To

fulfill this requirement, pharmaceutical databases are available with relevant information on drug action, adverse effects and toxicities as well as herb-drug interactions, *e.g.* the ABDA database of the German Institute for Medical Documentation and Information (http://www.dimdi.de/static/de/amg/abda/index.htm). With increasing popularity of complementary therapies, measures should be taken to provide reliable information to health professionals and patients alike (Tiran, 2006).

Information centers for consumers and general practitioners represent a promising tool to meet the demand among patients for counseling and providing evidence-based information on toxicity risks. An example is "MotherSafe", which has been established at the Royal Hospital for Women (Randwick NSW, Australia) to inform women on teratogenic exposures during pregnancy and lactation (Lim et al., 2009).

4 Conclusions and perspectives

The commercial misuse of indigenous knowledge on medicinal plants by some multinational companies culminated in efforts to ban biopiracy practices. While the Nagoya protocol was launched by the United Nations to regulate fair benefit-sharing at the legislative level, the momentum of this international development should be taken up by academia, where monetary and commercial aspects are not that much in the foreground. The valuable knowledge of traditional medicine represents and exquisite starting point for the realization of a *One-World Medicine*, whose concept is to integrate the best conceptual elements of conventional medicine CAM and traditional medicines to secure affordable primary health care for those patients in developing countries, who have no access to the expensive hi-tech medicine of the Western World. To have safe and efficient medications at hand, a number of measures have to be realized to improve traditional medicines, including

- Performance of pharmacological mode-of-action analyses to clarify molecular and cellular mechanisms. It is advisable to use novel state-of-the art methods and high-tech approaches to gain reputation also in the scientific community outside of medicinal herb research.
- Quality control of herbal products by controlled cultivation and harvesting of medicinal plants, standardization of herbal products by phytochemical analyses, and safety control to avoid toxic contaminations and adulterations.

- Conduction of placebo-controlled, randomized, and double-blind clinical trials to provide convincing evidence for the safety and efficacy of herbal products.
- Formal education of phytotherapists. Production and trade with herbal products should be licensed by the national governments.

The establishment of primary health care infrastructure represents a main goal of all governments all over the world. Therefore, *One-World Medicine* approaches should rather be initiated and realized by governmental authorities than by the industry. Appropriate control organs should monitor the implementation of the processes to avoid biopiracy, corruption and any other kind of misuse.

Acknowledgment

This work was supported by the German Research Association (*Deutsche Forschungsgemeinschaft,* Research Training Group "Life Science – Life Writing", DFG/GRK 2015/1).

Conflict of interest

The authors declare that there is no conflict of interest.

References

- Abuja Declaration of the African Summit of Heads of State and Government of April 2001 on research on traditional medicines used for the treatment of malaria, TB, HIV/Aids and other infectious diseases as a priority. http://www.un.org/ga/aids/pdf/abuja_declaration.pdf (accessed: June 17th, 2017).
- Agbabiaka, T., Wider, B., Watson, L.K., Goodman, C., 2016. Concurrent use of prescription drugs and herbal medicinal products in older adults: a systematic review protocol. Syst. Rev., 5, 65.
- Albrecht, H., 2013. [The situation of complementary medicine in Germany]. [Article in German] Forsch. Komplementmed, 20, 73-77.
- Anyinam, C., 1987. Availability, accessibility, acceptability and adaptability: four attributes of African ethnomedicine. Soc. Sci. Med., 25, 803-811.
- Awodele, O., Agbajea, E.O., Abiolaa, O.O., Awodeleb, D.F., Dolapoc, D.C., 2012. Doctors' attitudes towards the use of herbal medicine in Lagos, Nigeria. J. Herbal Med., 2, 16-22.
- Aziato L., Antwi, H.O., 2016. Facilitators and barriers of herbal medicine use in Accra, Ghana: an inductive exploratory study. BMC Complement. Alternat. Med., 16, 142.
- Babu, P.A., Suneetha, G., Boddepalli, R., Lakshmi, V.V., Rani, T.S., Rambabu, Y., Srinivas, K., 2006. A database of 389 medicinal plants for diabetes. Bioinformation, 1, 130-131.
- Barimah, K.B., 2013. Traditional healers as service providers in Ghana's National Health Insurance Scheme: the wrong way forward? Glob. Public Health, 8, 202-208.
- Bellakhdr, J., 1997. La Pharmacopee Marocaine Traditionnelle: Medecine Arabe Ancienne et Saviors Populaires. Ibis Press, Paris. 764 p.
- Bent, S., Ko, R., 2004. Commonly used herbal medicines in the United States: a review. Am. J. Med. 116, 478-485.
- Berman, B.M., Swyers, J.P., Kuczmarczyk, J., 1999. Complementary and alternative medicine: herbal therapies for diabetes. J. Assoc. Acad. Mino. Phys., 10, 10-14.
- Bodeker, G., 2001. Lessons on integration from the developing world's experience. Br. Med. J. 322, 164-167.
- Booker, A., Jalil, B., Frommenwiler, D., Reich, E., Zhai, L., Kulic, Z., Heinrich, M., 2016. The authenticity and quality of *Rhodiola rosea* products. Phytomedicine, 23, 754-762.
- Brinkhaus, B., Witt, C.M., Jena, S., Bockelbrink, A., Ortiz, M., Willich, S.N., 2011. Integration of complementary and alternative medicine into medical schools in Austria, Germany and Switzerland - results of a cross-sectional study. Wien. Med. Wochenschr., 161, 32-43.
- Bruce, J.C., 2002. Marrying modern herbal practices and technology with traditional practices: issues for the African continent. Int. Nur. Rev., 49, 161-167.
- Buell, L., 1995. The Environmental Imagination: Thoreau, Nature Writing and the Formation of American Culture. Cambridge: Harvard UP.
- Busato, A., Eichenberger, R., Künzi, B., 2006. Extent and structure of health insurance expenditures for complementary and alternative medicine in Swiss primary care. BMC Health Serv. Res., 6, 132.
- Busia, K., 2005. Medical provision in Africa - past and present. Phytother. Res., 19, 919-923.
- Cavaliere, C., 2009. The effects of climate change on medicinal and aromatic plants. HerbalGram, 81, 44-57.
- Chen, F.P., Chen, T.J., Kung, Y.Y., Chen, Y.C., Chou, L.F., Chen, F.J., Hwang, S.J., 2007. Use frequency of traditional Chinese medicine in Taiwan. BMC Health Serv. Res., 7, 26.
- Choi, J.G., Eom, S.M., Kim, J., Kim, S.H., Huh, E., Kim, H., Lee, Y., Lee, H., Oh, M.S., 2016. A Comprehensive review of recent studies on herb-drug interaction: A focus on pharmacodynamic interaction. J. Altern. Complement. Med., 22, 262-279.

- Chung, V.C., Ma, P.H., Wang, H.H., Wang, J.J., Hong, L.C., Wei, X., Wong, S.Y., Tang, J.L., Griffiths, S.M., 2013. Integrating traditional Chinese medicine services in community health centers: insights into utilization patterns in the Pearl River region of China. Evid. Based Complement. Alternat. Med., 2013, 426360.
- Consolini, A.E., Ragone, M.I., 2010. Patterns of self-medication with medicinal plants and related adverse events--a South American survey. Curr. Drug Saf., 5, 333-341.
- Cragg, G.M., Grothaus, P.G., Newman, D.J., 2014. New horizons for old drugs and drug leads. J. Nat. Prod. 77, 703-723.
- Dai, G., Jiang, Z., Bai, Y., Zhang, Q., Zhu, L., Bai, X., Ju, W., Pan, R., 2017. Pharmacokinetic herb-drug interaction of *Xuesaitong* dispersible tablet and aspirin after oral administration in blood stasis model rats. Phytomedicine, 26, 62-68.
- Dang, H., Wang, Q., Wang, H., Yan, M., Liu, X., 2016. The integration of Chinese Materia Medica into the Chinese health care delivery system, an update. Phytother. Res., 30, 292-297.
- de Jong, Y., Kouwenberg, J., Boumans, L., Hussey, C., Hyam, R., Nicolson, N., Kirk, P., Paton, A., Michel, E., Guiry, M.D., Boegh, P.S., Pedersen, H.A.E., Enghoff, H., von Raab-Straube, E., Guntsch, A,, Geoffroy, M., et al., 2015. PESI - a taxonomic backbone for Europe. Biodivers. Data J., 3, e5848.
- De Loughrey, E., Handley, G., 2011. Postcolonial Ecologies: Literatures of the Environment Oxford: Oxford UP.
- Delabays, N., Simonnet, X., Gaudin, M., 2001. The genetics of artemisinin content in *Artemisia annua* L. and the breeding of high yielding cultivars. Curr. Med. Chem., 8, 1795-1801.
- Economic Commission for Africa, 2008. Economic and Social Conditions in Southern Africa in 2007. http://repository.uneca.org/bitstream/handle/10855/3574/Bib.%2028555_I.pdf?sequence=1 (Accessed: June 17th, 2017)
- Efferth, T., 2010. Personalized cancer medicine: from molecular diagnostics to targeted therapy with natural products. Planta Med., 76, 1143-1154.
- Efferth, T., 2011. Perspectives for globalized natural medicines in the 21st century. Chin. J. Nat. Med., 9, 1-6.
- Efferth, T., 2012. Stem cells, cancer stem-like cells, and natural products. Planta Med., 78, 935 - 942.
- Efferth, T., Greten, H.J., 2012a. Medicinal and aromatic plant research in the 21st century. Med. Aromat. Plants 1, e110.
- Efferth, T., Greten, H.J., 2012b. Autophagy by natural products in cancer cells. Biochem. Anal. Biochem., 1, 8.
- Efferth, T., Greten, H.J., 2012c. Quality control for medicinal plants. Med. Aromat. Plants (Los Angeles), 1, 7.
- Efferth, T., Greten, H.J., 2012d. The European directive on traditional herbal medicinal products: friend or foe for plant-based therapies? Zhong Xi Yi Jie He Xue Bao, 10, 357-361.
- Efferth, T., Kaina, B., 2011. Toxicities by herbal medicines with emphasis to traditional Chinese medicine. Curr. Drug Metab., 12, 989-996.
- Efferth, T., Koch, E., 2011. Complex interactions between phytochemicals. The multi-target therapeutic concept of phytotherapy. Curr. Drug Targets, 12, 122-132.
- Efferth, T., Banerjee, M., Paul, N.W., Abdelfatah, S., Arend, J., Elhassan, G., Hamdoun, S., Hamm, R., Hong, C., Kadioglu, O., Nass, J., Ochwangi, D., Ooko, E., Ozenver, N., Saeed, M.E., Schneider, M., et al., 2016. Biopiracy of natural products and good bioprospecting practice. Phytomedicine, 23, 166-173.

- Efferth, T., Banjerjee, M., Hornung, A., 2013. Therapeutic intervention of post-traumatic stress disorder by Chinese medicine - Perspectives for Transdisciplinary cooperation between life sciences and humanities. Med. Studies, DOI 10.1007/s12376-013-0085-4.
- Efferth, T., Fu, Y.J., Zu, Y.G., Schwarz, G., Konkimalla, V.S., Wink, M., 2007a. Molecular target-guided tumor therapy with natural products derived from traditional Chinese medicine. Curr. Med. Chem., 14, 2024-2032.
- Efferth, T., Li, P.C., Konkimalla, V.S., Kaina, B., 2007. From traditional Chinese medicine to rational cancer therapy. Trends Mol. Med., 13, 353-361.
- Efferth, T., Zacchino, S., Georgiev, M.I., Liu, L., Wagner, H., Panossian, A., 2015. Nobel Prize for artemisinin brings phytotherapy into the spotlight. Phytomedicine, 22, A1-3.
- Eichhorn, T., Greten, H.J., Efferth, T., 2011. Self-medication with nutritional supplements and herbal over-the counter products. Nat. Prod. Bioprospect. 1, 62-70.
- Efferth, T., Saeed, M.E.M., Mirghani, E., Alim, A., Yassin, Z., Saeed, E., Khalid, H.E., Daak, S., 2017. Integration of phytochemicals and phytotherapy into cancer precision medicine. Oncotarget, 8, 50284-50304.
- Ekeopara, C.A., Ugoha, A., 2017. The contributions of African traditional medicine to Nigeria's health care delivcery system. IOSR - J. Hum. Soc. Sci., 22, 32-43. http://www.iosrjournals.org/iosr-jhss/papers/Vol.%2022%20Issue5/Version-4/F2205043243.pdf (Accessed online: June 17th, 2017).
- Elumalai, A., Eswariah, M.C., 2012. Herbalism - a review. Int. J. Phytother., 2, 96-105.
- Ernst, E., Hung, S.K., 2011. Great expectations: what do patients using complementary and alternative medicine hope for? Patient, 4, 89-101.
- Esch, B.M., Marian, F., Busato, A., Heusser, P., 2008. Patient satisfaction with primary care: an observational study comparing anthroposophic and conventional care. Health Qual. Life Outcomes, 6, 74.
- Franz, C., Chizzola, R., Novak, J., Sponza, S., 2011. Botanical species being used for manufacturing plant food supplements (PFS) and related products in the EU member states and selected third countries. Food Funct., 2, 720-730.
- Fong, H.H., 2002. Integration of herbal medicine into modern medical practices: issues and prospects. Integr. Cancer Ther., 1, 287-293; discussion 293.
- Forest, F., Grenyer, R., Rouget, M., Davies, T.J., Cowling, R,M., Faith, D.P., Balmford, A., Manning, J.C., Proches, S., van der Bank, M., Reeves, G., Hedderson, T.A., Savolainen, V., 2007. Preserving the evolutionary potential of floras in biodiversity hotspots. Nature, 445, 757-760.
- Frenkel, M., Ben-Arye, E., Baldwin, C.D., Sierpina, V., 2005. Approach to communicating with patients about the use of nutritional supplements in cancer care. South Med. J., 98, 289-294.
- Garrard, G., 2004. Ecocriticism: The New Critical Idiom. New York: Routledge.
- Gandhi, S.G., Mahajan, V., Bedi, Y.S., 2015. Changing trends in biotechnology of secondary metabolism in medicinal and aromatic plants. Planta, 241, 303-317.
- Georgiev, M.I., Weber, J., Maciuk, A., 2009. Bioprocessing of plant cell cultures for mass production of targeted compounds. Appl. Microbiol. Biotechnol., 83, 809-823.
- Gibney, M., Howard-Hassmann, R., Coicaud, J.-M., Steiner, N., 2008. The Age of Apology: Facing up the Past. Philadelphia: University of Pennsylvania Press.
- Glisson, J.K., Walker, L.A., 2010. How physicians should evaluate dietary supplements. Am. J. Med., 123, 577-582.
- Greten, H.J., 2005. Erhebung im Daomed Network. In: Gesundheitswirtschaftskongress.
- Hakamatsuka, T., 2017. Marketing approval of ethical Kampo medicines. Yakugaku Zasshi, 137, 163-165.

- Guo, R., Zhang, X., Su, J., Xu, H., Zhang, Y., Zhang, F., Li, D., Zhang, Y., Xiao, X., Ma, S., Yang, H., 2018. Identifying potential quality markers of Xin-Su-Ning capsules acting on arrhythmia by integrating UHPLC-LTQ-Orbitrap, ADME prediction and network target analysis. Phytomedicine [Epub ahead of print]
- Hottenbacher, L., Weißhuhn, T.E., Watanabe, K., Seki, T., Ostermann, J., Witt, C.M., 2013. Opinions on Kampo and reasons for using it--results from a cross-sectional survey in three Japanese clinics. BMC Complement. Altern. Med., 13, 108.
- Huggan, G., Tiffin, H., 2010. Postcolonial Ecocriticism: Literature, Animals, Environment (New York: Routledge).
- Hunt, L.M., Arar, N.H., Akana, L.L., 2000. Herbs, prayer and insulin. Use of medicinal and alternative treatments by a group of Mexican American diabetes patients. J. Fam. Pract., 49, 216-223.
- Jaski, M.E., Schwartzberg, J.G., Guttman, R.A., Noorani, M., 2000. Medication review and documentation in physician office practice. Eff. Clin. Pract., 3, 31-34.
- Johnson, O., 2002. Venezuelan project establishes indigenous plant database. Br. Med. J., 325, 183.
- Julsing, M.K., Koulman, A., Woerdenbag, H.J., Quax, W.J., Kayser, O., 2006. Combinatorial biosynthesis of medicinal plant secondary metabolites. Biomol. Eng., 23, 265-279.
- Kadioglu, O., Jacob, S., Bohnert, S., Naß ,J,. Saeed, M.E., Khalid, H., Merfort, I., Thines, E., Pommerening, T., Efferth, T.. 2016. Evaluating ancient Egyptian prescriptions today: Anti-inflammatory activity of *Ziziphus spina-christi*. Phytomedicine, 23, 293-306.
- Kasilo, O.M.J., Trapsida, J.M., Mwikisa, C.N., Lusamba-Dikassa, P.S., 2010. An overview of the traditional medicine situation in the African region. Afr. Health Monitor, 14, 7-15.
- Keita, J.D., 1993. Non-wood forest products in Africa: an overview. Paper prepared for the Regional Expert Consultation on Non-wood forest products for English-speaking African Countries, Arusha, Tanzania, Council Commonwealth Science Council, 12 pp.
- Khalid, H., Abdalla, W.E., Abdelgadir, H., Opatz, T., Efferth, T., 2012. Gems from traditional north-African medicine: medicinal and aromatic plants from Sudan. Nat. Prod. Bioprospect., 2, 92-103.
- Klein, S.D., Torchetti, L., Frei-Erb, M., Wolf, U., 2015. Usage of complementary medicine in Switzerland: Results of the Swiss Health Survey 2012 and development since 2007. PLoS One, 10, e0141985.
- Klein, S.D., Frei-Erb, M., Wolf, U., 2007. Usage of complementary medicine across Switzerland: results of the Swiss Health Survey 2007. Swiss Med. Wkly., 142, w13666.
- Kober, M., Pohl, K., Efferth, T., 2008. Molecular mechanisms underlying St. John's wort drug interactions. Curr. Drug Metab., 9, 1027-1037.
- Kolewe, M.E., Gaurav, V., Roberts, S.C., 2008. Pharmaceutically active natural product synthesis and supply via plant cell culture technology. Mol. Pharm., 5, 243-256.
- Kolodny, A., 1975. The Lay of the Land: Metaphors os Experience and History in American Life and Letters. Chapel Hill: University of North Carolina Press.
- Latheef, S.A., Prasad, B., Bavaji, M., Subramanyam, G., 2008. A database on endemic plants at Tirumala hills in India. Bioinformation, 2, 260-262.
- Lazarou, J., Pomeranz, B.H., Corey, P.N., 1998. Incidence of adverse drug reactions in hospitalized patients: A meta-analysis of prospective studies. J. Am. Med. Assoc., 279, 1200-1205.
- Lee, R.P., 2016. Comparative studies of health care systems. Soc. Sci. Med., 16, 629-642.
- Li, K., Li, J., Su, J., Xiao, X., Peng, X., Liu, F., Li, D., Zhang, Y., Chong, T., Xu, H., Liu, C., Yang, H., 2018. Identification of quality markers of Yuanhu Zhitong tablets based on integrative pharmacology and data mining. Phytomedicine [Epub ahead of print]

- Li, X.Q., Yang, J.N., Su, Y.H., 2007. [Does the utilization of traditional Chinese herbs threaten the biodiversity?]. Zhong Xi Yi Jie He Xue Bao, 5, 363-367.
- Liao, M., Shang, H., Li, Y., Li, T., Wang, M., Zheng, Y., Hou, W., Liu, C., 2018. An integrated approach to uncover quality marker underlying the effects of Alisma orientale on lipid metabolism, using chemical analysis and network pharmacology. Phytomedicine [Epub ahead of print]
- Liao, Y.H., Lin, C.C., Li, T.C., Lin, J.G., 2012. Utilization pattern of traditional Chinese medicine for liver cancer patients in Taiwan. BMC Complement. Altern. Med., 12, 146.
- Liao, Y.H., Lin, J.G., Lin, C.C., Li, T.C., 2013. Distributions of usage and the costs of conventional medicine and traditional Chinese medicine for lung cancer patients in taiwan. Evid. Based Complement. Alternat. Med., 2013, 984876.
- Lim, J.M., Sullivan, E., Kennedy, D., 2009. MotherSafe: review of three years of counselling by an Australian Teratology Information Service. Aust. N. Z. J. Obstet. Gynaecol., 49, 168-172.
- Lim, S.M., Syn, N.L., Cho, B.C., Soo, R.A., 2018. Acquired resistance to EGFR targeted therapy in non-small cell lung cancer: Mechanisms and therapeutic strategies. Cancer Treat. Rev., 65, 1-10.
- Lin, Y., Kazlova, V., Ramakrishnan, S., Murray, M.A., Fast, D., Chandra, A., Gellenbeck, K.W., 2016. Bone health nutraceuticals alter microarray mRNA gene expression: A randomized, parallel, open-label clinical study. Phytomedicine 23, 18-26.
- Liu, M.Z., Zhang, Y.L., Zeng, M.Z., He, F.Z., Luo, Z.Y., Luo, J.Q., Wen, J.G., Chen, X.P., Zhou, H.H., Zhang, W., 2015. Pharmacogenomics and herb-drug interactions: merge of future and tradition. Evid. Based Complement. Alternat. Med., 2015, 321091.
- Lu, J., Zhang, Y., Sun, M., Liu, M., Wang, X., 2017. Comprehensive assessment of Cucurbitacin E related hepatotoxicity and drug-drug interactions involving CYP3A and P-glycoprotein. Phytomedicine, 26, 1-10.
- Maegawa, H., Nakamura, T., Saito, K., 2014. Regulation of traditional herbal medicinal products in Japan. J. Ethnopharmacol., 158 Pt B, 511-515.
- Maimer, A., Remppis, A., Sack, F.U., Ringes-Lichtenberg, S., Greten, T., Brazkiewicz, F., Schröder, S., Goncalves, M., Efferth, T., Greten, H.J., 2013. Objectifying acupuncture effects by lung function and numeric rating scale in patients undergoing heart surgery. Evid.-Based Complement. Alternat. Med., 2013:219817.
- May, J., 2011. What is integrative health? Br. Med. J., 343, d4372.
- Mbatha, N., Street, R.A., Ngcobo, M., Gqaleni, N., 2012. Sick certificates issued by South African traditional health practitioners: current legislation, challenges and the way forward. S. Afr. Med. J. 102, 129-131.
- Mehrotra, S., Srivastava, V., Ur Rahman, L., Kukreja, A.K., 2015. Hairy root biotechnology--indicative timeline to understand missing links and future outlook. Protoplasma, 252, 1189-1201.
- Meng, Q, Liu, K., 2014. Pharmacokinetic interactions between herbal medicines and prescribed drugs: focus on drug metabolic enzymes and transporters. Curr. Drug Metab., 15, 791-807.
- Meyer-Hamme, G., Friedemann, T., Greten, H.J., Plaetke, R., Gerloff, C., Schroeder, S., 2018. ACUDIN - ACUpuncture and laser acupuncture for treatment of diabetic peripheral neuropathy: a randomized, placebo-controlled, partially double-blinded trial. BMC Neurol. 18, 40.
- Ministério do Meio Ambiente (MAA), 2011. Portal Brasileiro sobre Biodiversidade – PortalBio/MMA: www.mma.gov.br/portalbio.
- Mitty, E., Flores, S., 2007. Assisted living nursing practice: medication management: Part 1. Assessing the resident for self-medication ability. Geriatr. Nurs., 28, 83-89.
- Moschik, E.C., Mercado, C., Yoshino, T., Matsuura, K., Watanabe, K., 2012. Usage and attitudes of physicians in Japan concerning traditional Japanese medicine (kampo medicine): a descriptive

evaluation of a representative questionnaire-based survey. Evid. Based Complement. Alternat. Med., 2012, 139818.

- Muntendam, R., Melillo, E., Ryden, A., Kayser, O., 2009. Perspectives and limits of engineering the isoprenoid metabolism in heterologous hosts. Appl. Microbiol. Biotechnol., 84, 1003-1019.
- Newman, E.B., 1994. Earth's vanishing medicine cabinet: rain forest destruction and its impact on the pharmaceutical industry. Am. J. Law Med., 20, 479-501.
- Newman, D.J., Cragg, G.M., 2012. Natural products as sources of new drugs over the 30 years from 1981 to 2010. J. Nat. Prod., 75, 11-35.
- No authors, 2012. What happened to personalized medicine? Nat. Biotechnol., 30, 1.
- Paul, N.W., Roses, A.D., 2003. Pharmacogenetics and Pharmacogenomics: Recent developments, their clinical relevance and some ethical, social, and legal implications. J. Mol. Med., 81, 135-140.
- Ochwang'i, D.O., Oduma, J.A., 2017. Chapter 6 – Overview of governmental support across Africa toward the development and growth of herbal medicine. In: Medicinal spices and vegetables from Africa therapeutic potential against metabolic, inflammatory, infectious and systemic diseases. Kuete, V., Eds. Elsevier: London, San Diego, Cambridge, Oxford, pp. 153–169.
- Ogita, S., 2015. Plant cell, tissue and organ culture: the most flexible foundations for plant metabolic engineering applications. Nat. Prod. Commun., 10, 815-820.
- OneWorldHealth, 2016. OneWorldHealth. http://www.OneWorldHealth.com (accessed: June 17th, 2017)
- Osathanunkul, M., Suwannapoom, C., Osathanunkul, K., Madesis, P., de Boer, H., 2016. Evaluation of DNA barcoding coupled high resolution melting for discrimination of closely related species in phytopharmaceuticals. Phytomedicine, 23, 156-165.
- Oyebode, O., Kandala, N.B., Chilton, P.J., Lilford, R.J., 2016. Use of traditional medicine in middle-income countries: a WHO-SAGE study. Health Policy Plan, 31, 984-991.
- Patel, A.B., O'Hare, T., Deininger, M.W., 2017. Mechanisms of resistance to ABL kinase inhibition in chronic myeloid leukemia and the development of next generation ABL kinase inhibitors. Hematol. Oncol. Clin. North Am., 31, 589-612.
- Poornima, P., Kumar, J.D., Zhao, Q., Blunder, M., Efferth, T., 2016. Network pharmacology of cancer: From understanding of complex interactomes to the design of multi-target specific therapeutics from nature. Pharmacol. Res. 111, 290-302.
- Posadzki, P., Watson, L., Ernst, E., 2013. Contamination and adulteration of herbal medicinal products (HMPs): an overview of systematic reviews. Eur. J. Clin. Pharmacol., 69, 295-307.
- Puoane, T.R., Hughes, G.D., Uwimana, J., Johnson, Q., Folk, W.R., 2012. Why HIV positive patients on antiretroviral treatment and/or cotrimoxazole prophylaxis use traditional medicine: perceptions of health workers, traditional healers and patients: a study in two provinces of South Africa. Afr. J. Tradit. Complement. Altern. Med., 9, 495-502.
- Quattropani, C., Ausfeld, B., Straumann, A., Heer, P., Seibold, F., 2003. Complementary alternative medicine in patients with inflammatory bowel disease: use and attitudes. Scand. J. Gastroenterol., 38, 277-282.
- Rolfes, L., Van Hunsel, F., Van Der Linden, L., Taxis, K., van Puijenbroek, E., 2017. The quality of clinical information in adverse drug reaction reports by patients and healthcare professionals: A retrospective comparative analysis. Drug Saf. 40, 607-614.
- Ruiz, M.E., 2010. Risks of self-medication practices. Curr. Drug Saf., 5, 315-323.
- Sahebkar, A., Gurban, C., Serban, A., Andrica, F., Serban, M.C., 2016. Effects of supplementation with pomegranate juice on plasma C-reactive protein concentrations: A systematic review and meta-analysis of randomized controlled trials. Phytomedicine, 23, 1095-1102.
- Schmid, G., Hofheinz, W., 1983. Total synthesis of *qinghaosu*. J. Am. Chem. Soc., 105, 624-625.

- Schmidt, F., Efferth, T., 2016. Tumor heterogeneity, single-cell sequencing, and drug resistance. Pharmaceuticals (Basel), 9, pii:E33.
- Schnabel, K., Binting, S., Witt, C.M., Teut, M., 2014. Use of complementary and alternative medicine by older adults - a cross-sectional survey. BMC Geriatr., 14, 38.
- Schwarz, S., Messerschmidt, H., Völzke, H., Hoffmann, W., Lucht, M., Dören, M., 2008. Use of complementary medicinal therapies in West Pomerania: a population-based study. Climacteric, 11, 124-134.
- Schwingshackl, L., Missbach, B., Hoffmann, G., 2016. An umbrella review of garlic intake and risk of cardiovascular disease. Phytomedicine, 23,1127-1133.
- Sharad, S., Manish, P., Mayank, B., Mitul, C., Sanjay, S., 2011. Regulatory status of traditional medicines in Africa regions. Int. J. Res. Avurveda Pharmacy 2011;2(1):103-110. http://www.ijrap.net/issue-three/103-110.pdf (Accessed online: June 17th, 2017).
- Shaw, D., Graeme, L., Pierre, D., Elizabeth, W., Kelvin, C., 2012. Pharmacovigilance of herbal medicine. J. Ethnopharmacol., 140, 513-518.
- Shiva, V., 1997. Biopiracy: The Plunder of Nature and Knowledge. New York: South End Press.
- Snyderman, R., Weil, A.T., 2002. Integrative medicine: bringing medicine back to its roots. Arch. Intern. Med., 162, 395-397.
- Singh, D.K., Cheema, H.S., Saxena, A., Jyotshana, Singh, S., Darokar, M.P., Bawankule, D.U., Shanker, K., Luqman, S., 2017. Fraxetin and ethyl acetate extract from *Lawsonia inermis* L. ameliorate oxidative stress in *P. berghei* infected mice by augmenting antioxidant defence system. Phytomedicine 36, 262-272.
- Sousa, C.M., Coimbra, D., Machado, J., Greten, H.J., 2015. Effects of self-administered exercises based on Tuina techniques on musculoskeletal disorders of professional orchestra musicians: a randomized controlled trial. J. Integr. Med., 13, 314-318.
- Srivastava, J., Lambert, J., Vietmayer, N., 1996. Medicinal plants. An expanding role in development. World Bank Technical Paper No. 320. Washington, D.C.)
- Szpilman, A.M., Carreira, E.M., 2010. Probing the biology of natural products: molecular editing by diverted total synthesis. Angew. Chem. Int. Ed. Engl., 49, 9592-9628.
- Tomé-Carneiro, J., Visioli, F., 2016. Polyphenol-based nutraceuticals for the prevention and treatment of cardiovascular disease: Review of human evidence. Phytomedicine, 23, 1145-1174.
- Tiran, D., 2006. Integrated healthcare: herbal remedies for menopausal symptoms. Br. J. Nurs. 15, 645-648.
- Ulrich-Merzenich, G., Hartbrod, F., Kelber, O., Müller, J., Koptina, A., Zeitler, H., 2017. Salicylate-based phytopharmaceuticals induce adaptive cytokine and chemokine network responses in human fibroblast cultures. Phytomedicine 34, 202-211.
- Verpoorte, R., Choi, Y.H., Kim, H.K., 2005. Ethnopharmacology and systems biology: a perfect holistic match. J. Ethnopharmacol., 100, 53-56.
- Volm, M., Efferth, T., 2015. Prediction of cancer drug resistance and implications for personalized medicine. Front. Oncol., 5, 282.
- Vora, C.K., Mansoor, G.A., 2005. Herbs and alternative therapies: relevance to hypertension and cardiovascular diseases. Curr. Hypertens. Rep., 7, 275-280.
- Wagner, H., Efferth, T., 2017. Introduction: Novel hybrid combinations containing synthetic or antibiotic drugs with plant-derived phenolic or terpenoid compounds. Phytomedicine, 37, 1-3.
- Wolf, U., Maxion-Bergemann, S., Bornhöft, G., Matthiessen, P.F., Wolf, M., 2006. Use of complementary medicine in Switzerland. Forsch. Komplementmed., 13 Suppl 2, 4-6.
- World Health Organization, 1978. Alma Ata Declaration Primary Health Care. Health for all series No. 1. http://www.who.int/publications/almaata_declaration_en.pdf (accessed: June 17th, 2017)

- World Health Organization, 1998. WHO quality control methods for herbal materials. https://de.scribd.com/document/151544729/WHO
- World Health Organization, 2000. General guidelines for methodologies on research and evaluation of traditional medicine. In: WHO, ed. http://appswhoint/iris/bitstream/10665/66783/1/WHO_EDM_TRM_20001pdf.
- World Health Organization, 2001. Promoting the role of Traditional Medicine in Health Systems: A Strategy for the African Region. WHO Regional Office for Africa, Temporary location, Harare, Zimbabwe. Document AFR/RC50/9 and resolution AFR/RC50/R3
- World Health Organization, 2007. The health of indigenous people. http://wwwwhoint/mediacentre/factsheets/fs326/en/.
- World Health Organization, 2013. WHO traditional medicine strategy: 2014– 2023. http://appswhoint/iris/bitstream/10665/92455/1/9789241506090_eng.pdf.
- Wu, M., Lu, P., Shi, L., Li, S., 2015. Traditional Chinese patent medicines for cancer treatment in China: a nationwide medical insurance data analysis. Oncotarget, 6, 38283-38295.
- Wu, C.F., Seo, E.J., Klauck, S.M., Efferth, T., 2016. Cryptotanshinone deregulates unfolded protein response and eukaryotic initiation factor signaling in acute lymphoblastic leukemia cells. Phytomedicine, 23, 174-180.
- Woo, H.J., Kim, H.Y., Choi, E.S., Cho, Y.H., Kim, Y., Lee, J.H., Jang, E., 2015. Drug-induced liver injury: A 2-year retrospective study of 1169 hospitalized patients in a single medical center. Phytomedicine, 22, 1201-1205.
- Yesilada, E., Sezik, E., 2003. Survey on the traditional medicine of Turkey: Semiquantitative evaluation of the results. In: Singh, V.K., Govil, J.N., Hashmi, S., Singh, G. (Eds.). Recent Progress in Medicinal Plants. Ethnomedicine and Pharmacognosy II. Studium Press, LLC, Houston, TX, 7, 389-412.
- Yusuff, K.B., Tayo, F., 2011. Frequency, types and severity of medication use-related problems among medical outpatients in Nigeria. Int. J. Clin. Pharm., 33, 558-564.
- Zaenker, K.S., Entschladen, F., 2009. Paving roads for new drugs in oncology. Recent Pat. Anticancer Drug Discov., 4, 137-145.
- Zeng, Q., Qiu, F., Yuan, L., 2008. Production of artemisinin by genetically-modified microbes. Biotechnol. Lett., 30, 581-592.
- Zeng, L., Zou, Y., Kong, L., Wang, N., Wang, Q., Wang, L., Cao, Y., Wang, K., Chen, Y., Mi, S., Zhao, W., Wu, H., Cheng, S., Xu, W., Liang, W., 2015. Can Chinese herbal medicine adjunctive therapy improve outcomes of senile vascular dementia? Systematic review with meta-analysis of clinical trials. Phytother. Res., 29, 1843-1857.
- Zhang, B., Peng, Y., Zhang, Z., Liu, H., Qi, Y., Liu, S., Xiao, P., 2010. GAP production of TCM herbs in China. Planta Med., 76, 1948-1955.
- Zhang, L., Yan, J., Liu, X., Ye, Z., Yang, X., Meyboom, R., Chan, K., Shaw, D., Duez, P., 2012. Pharmacovigilance practice and risk control of Traditional Chinese Medicine drugs in China: current status and future perspective. J. Ethnopharmacol., 140, 519-525.
- Zuo, Z., Huang, M., Kanfer, I., Chow, M.S., Cho, W.C., 2015. Herb-drug interactions: systematic review, mechanisms, and therapies. Evid. Based Complement. Alternat. Med., 2015, 239150.