Ethiop. J. Biol. Sci. **21(2): 203–219, 2022**
 ISSN: 1819-8678

FEATURE ARTICLE: SCIENCE AND SOCIETY

PROSPECTS OF HERBAL MEDICINE TO ASSIST DRUG DEVELOPMENT IN THE 21ST CENTURY‡

Yalemtsehay Mekonnen[1]*

ABSTRACT: The use of herbal medicine is an integral part of many cultures all over the world. In recent years it has gained importance to be integrated along with modern medicine in many health systems. Herbal preparations are being sold in markets and becoming good sources of income to boost economies of producers. The issue of quality and safety is still a concern for consumers and health providers alike. Regulatory framework for ensuring safety and quality of production is critical for the benefit of all stakeholders but more for herbal users. There are good examples of some countries where they put in place regulatory measures to make sure that the herbal products are properly prescribed to end users and also the practitioners take responsibility. There are different perceptions and attitudes regarding the use of herbal medicine. There is limited knowledge regarding the possible side effects of herbal products. Many modern drugs have been synthesized from medicinal plants. Therefore, popularizing herbal products that still could serve as potential sources for drug development is very useful. On the other hand, wise use of the natural plant diversity should also be taken into consideration.

Key words/phrases: Healthcare system, Herbal preparations, Indigenous knowledge, Natural product, Traditional medicine.

INTRODUCTION

The 21st century could be considered as the beginning of the era of herbal medicine importance in combating diseases and ensuring public health. Many plant based and herbal preparations use are on the rise for many acute and chronic diseases in different parts of the world. Thus, there is a growing interest to exploit plants for drug development. Many governments are

‡This paper does not discuss the evolution of drug development from traditional natural products and the technological progress achieved to produce over the counter drugs today. It focuses mainly on how modern pharmaceuticals can benefit from incorporating traditional herbal knowledge and products in drug formulations, and reviews experiences of some countries in this line.

[1]Department of Zoological Sciences, College of Natural and Computational Sciences, Addis Ababa University, P.O. Box 1176, Addis Ababa, Ethiopia. E-mail: yalemtshay.mekonnen@aau.edu.et
*Author to whom all correspondence should be addressed

committed to validate traditional medicine (TM). For example, the rural Thai people relay mainly on TM taking care of their daily health needs. The Ministry of Public Health of Thailand established a Centre for Herbal Information. The Centre collected data and undertook scientific research to validate the different herbal products used in Thailand (Disayavanish and Disayavanish, 1998). The Foundation for Restoring Thai traditional medicine and the College of Ayurvedic Medicine have launched a programme and curricula to train personnel on TM, giving importance to the future of TM in Thai. In the recent years, the Ethiopian Food and Drug Authority (EFDA) has given special attention to the relevance of TM. It has developed TM Registration Directive in 2021. The directive focuses more on how TM is put into practice by those who want to promote TM products in health and disease related use.

Natural products have become the subject of interest for drug discovery (Brahmachari, 2006). It is now become a trend to seriously consider herbal medicine as an option and/ or as a combination to modern medicine in controlling and treating various diseases. In recent years, there are evidences that support the efficacy of herbal preparations on many diseases. Ritch (2005) reported the importance of *Ginko biloba* extract in being used for treatment of glaucoma. *G. biloba* has antioxidant effect, increases ocular blood flow, has platelet activating factor inhibitory activity, nitric oxide inhibition and general neuroprotective effect. One study conducted in placebo-controlled group demonstrated a commercial herbal preparation (STW 5) a combination of nine plant extracts, with the trade name Iberogas having a good result in the treatment of patients with functional dyspepsia and irritable bowel syndrome (Rosch *et al*., 2006).

Bell (2007) emphasized the importance of traditional Asian herbal mixtures in alleviating heart stroke prevention, treatment and rehabilitation. He further added the use of multivitamins, mineral supplements that could improve the health condition in patients with under-nutrition. Herbs and nutrients may boost the immune system and assist in treatment of stroke-related complications. It has to be taken into consideration that before utilizing supplements such as herbs and nutrients and introducing them into mainstream medical standards, a lot of research effort is required. In Japan, two herbal products called Saireito and Onpi-to are widely used for the treatment of chronic kidney disease (CKD) (Wang *et al*., 2008). It is observed that both herbal products are effective in delaying the progression or worsening of CKD.

Furthermore, Dai and co-workers (2009) have demonstrated the anitoxidant and anticancer effect of anthocyanin-containing blackberry extracts (ACEs) from selected cultivars. They optimized the extract by checking stability up to 90 days. They determined the cytotoxic effects of the ACEs on cell lines; HT-29, MCF-7, and HL-60. The extracts significantly enhanced production of hydrogen peroxide (H_2O_2), thereby enhancing cytotoxicity in all cell lines. The study suggested that anthocyanins and non-anthocyanin phenolics in ACEs act additively or synergistically in producing anticancer effects. It also gave important information for the development of ACEs derived from fruits as potential botanical drug products (Dai *et al*., 2009). The study of Dai and co-workers substantiated the fact that eating fruits like berries is also very good for keeping fit and being healthy. It is known that free radicals play important physiological functions. However, excess accumulation leads to oxidative stress. Phytochemicals which are rich sources of antioxidants are capable of reducing free radical reactions and prevent the body from oxidative damage (Sen *et al*., 2010).

Herbal products can benefit in controlling osteoporosis which is manifested in women after the onset of menopause. The available anti-osteoporosis drugs usually have some adverse effects. Natural phytoestrogens are found to have similar chemical structure to 17 β-estradiol. Clinical and experimental studies have proved that phytoestrogenic substances, such as genistein, soy isoflavones and other phytomedicine have similar effects on postmenopausal osteoporosis with considerable development prospect (Zhang and Li, 2012; Poluzzi *et al*., 2014). If herbal products with natural phytoestrognes are consumed as supplemental food they might help in deterring the progression of osteoporosis.

Another approach promoted by some researchers is the integration of traditional medicine as complementary healthcare system (Vandebroek, 2013). The author found out that though there is literature that covers a broad range of information that is useful to healthcare; it is fragmented across different scientific disciplines. The conclusion from this finding is then that researchers devoting their time to medicinal plant research should have a more interdisciplinary approach to bring an impact to local communities most in need of such healthcare (Vandebroek, 2013). In Kenya as reported by Matheka and Demaio (2013), complementary and alternative medicine (CAM) is most frequently used and is recommended by family and friends. In addition, there are patients who do not have good access to modern health facilities and there is dissatisfaction with modern drug effects.

Among non-communicable diseases, type 2 diabetes (T2D) is becoming a public health problem all over the world (Janero, 2014). In experimental animal models the importance of phytomedicine in ameliorating T2D has been recognized in recent years. A more holistic approach that includes profiling of phytochemicals with functional biologicals, that includes genomics, transcriptomics, proteomics, metabolomics and chemical fingerprinting tools are necessary to address the effective treatment of T2D.

Many countries, mainly in the continent of Asia, are well known to have practiced traditional healing approach for a long period of time. Worth mentioning are China, India, Pakistan and others. These countries are pioneers of promoting homeopathic and alternative medicine in their health practices. The approach to using herbal preparation differs according to the knowledge, practice and culture of a given society. There is big trust by end-users due to the long history of the benefit of medicinal plants in different culture systems of treatment such as Allopathic, Homeopathic, Ayurvedic, Chinese system of treatment and the like. The developed nations have their own *Materia Medica*, compiling comprehensive information about various plants used for therapeutic purposes (Khan and Rauf, 2014). The international herbal trade market is revolving around China, India and Pakistan. As reported by Khan and Rauf (2014) the total global herbal market of plant-based drugs has been estimated as $ 25–30 billion annually. It appears that the modern medical setup is recognizing and moving to a system based on the combination of natural therapies for the effective treatment of many health disorders. Xiong *et al*. (2013) have explored the use of traditional Chinese medicine (TCM) in improving modern hypertensive drugs. It is believed that TCM is a good alternative to treat diabetes mellitus (DM). Some researchers (Pang *et al*., 2015) introduced a new approach to the use of TCM to treat DM. They suggest that doctors choose bitter and sour flavoured TCM to counteract sweet and also aim at main symptoms rather than common problems associated with DM. The right dose given to patients plays an important role in treating DM because it is associated with the clinical efficacy (Pang *et al*., 2015). However, rational use of TCM faces a series of obstacles due to the diversity of species and the gap in knowledge of the active components. In recent years, more and more applications of new technologies or methodologies for investigating the active components of TCM have provided additional information on active substances. Pharmacokinetics is one of the effective tools which can be used to investigate the many components of TCM. It is believed that *in vivo* models help understand the dynamic processes of

active components being absorbed, distributed, metabolized and excreted which offer guidance for clinical uses of TCM (Zhang *et al*., 2017).

The WHO report (2019) emphasizes that inclusion of traditional and complementary medicine can improve the universal health coverage that is one of the sustainable development goals which focuses on ensuring healthy lives for all.

ECONOMIC BENEFIT

Countries that are endowed with medicinal plants can benefit from mass production, packaging and sale to contribute to their national revenue. Herbal preparation is being recognized by countries that give it priority as one of the commodities to boost their economies. It is recorded that the expenditure by the Australian population on alternative therapies in 2000 was about $AUD 2.3 billion and in comparison the expenditure of the USA population was about $US 34 billion (MacLennan *et al*., 2002). In Australia this represented a 120% increase in the cost of alternative medicines since 1993. This example definitely demonstrates the increasing trend.

Gunjan and co-workers (2015) reviewed published literature and found that the global pharmaceutical market was worth US$ 550 billion and it was expected to exceed US$ 1,100 billion or more by the year 2015. Currently looking at the trend, the estimation could be even more. On the other hand, the global market for botanicals and plant-derived drugs is projected to about US$ 90.2 billion in 2020 growing at a compound annual growth rate (CAGR) of 6.1 to 7.5% for the period 2017–2022 (https://www.statista.com/statistics/939899/global-botanical-and-plant-derived-drugs-market-agr/,https://www.nuffoodsspectrum.in/news/39/1397/global-market-for-botanical-supplements-to-grow-to-90-2-billion-by-2020.html: accessed 21 July 2020).

In Africa, the situation is equally promising. Improved traditional phytomedicines (ITP) have found a good market in Mali (Diallo *et al*., 2010). The overall consumption of ITP in the district of Kadiolo, Mali showed 100 fold increases from 2001 to 2003 in the purchases as shown by the income generated in the local currency (Diallo *et al*., 2010). This shows that ITP is well appreciated by the prescribers and the consumers.

In many developing countries, it is common to see small scale herbal shops sell herbal products in small stands, but only limited countries have large scale herbal markets. Delbanco and co-workers (2017), in a study of the

medicinal plants trade in two towns in Northern Kenya, found by interviewing vendors that per year, about 5,500 kg from thirty species of plants, was extracted having a retail price of US$ 25,900. This indicates the economic benefit to the communities in the area. In Ghana in a study made by Van Andel *et al*. (2012) found that about 244 medicinal plant products were sold in the local market. In 2010 alone an estimated 951tons of crude herbal medicine were sold at Ghana's herbal markets with a total value of around US$ 7.8 million (Van Andel *et al*., 2012). In Ethiopia, TM are sold in local markets by vendors. Most vendors get some income by selling popular TM. For example one study reported that 45 plant species were sold by vendors in Merkato, the large market in Addis Ababa (Kloos *et al*., 2014).

SAFETY AND EFFICACY

In recent years, developed countries have started using herbal medicine as complementary incorporating it with allopathic medicine. Regarding safety, there is misunderstanding how safe the herbal product is to be used for a particular disease. The issue of safety in the use of herbal medicine is of great concern to users, practitioners and regulators. Medicinal plants, if not used cautiously, can cause adverse reactions. It may not be fair to state that they are all healthy because there are many occasions where herbal products of diverse sources result in unwanted side effects (De Smet, 1991). The principle that the expected benefit of a drug must outweigh its potential risk is also true to traditional products as it does to synthetic drug preparations (De Smet, 1991).

It is believed that traditional drug therapies should be subjected to risk benefit analysis and also take into account the cultural context. Ernst (2005) believes that since herbal medicine has become a popular form of health care, it is better to test safety of herbal preparations using scientific methods. The public are misled by wrong perception that natural products are safe but this cannot be taken at face value. Herbal preparation can be risky. It is better to screen out and know the good from the harmful ones to health.

Quality plays a critical role in the process of translating the traditional or alternative medicines into modern evidence-based therapies (Rong *et al*., 2007). Isolation techniques such as High Performance Liquid Chromatography (HPLC) are widely applied to assess the chemical composition of herbal or botanical drug products. The most contemporary techniques of drug manufacturing should be applied to herbals, including the processes of high through put screening, extraction, purification,

separation, isolation, molecular characterization, lead compound modification.

The relevance of scientific methods in herbal preparations was used in China where the best-sold traditional Chinese medicine, Danshen Dropping Pill (DSDP0) was developed using chromatography fingerprinting (Fan *et al*., 2006). Xiong and co-workers (2013) have worked on the relevance of batch-to-batch quality consistency by combining chromatographic fingerprinting method and multivariate statistical analysis. They used Shenmai injection, a typical botanical drug product in China, to demonstrate the possible application and feasibility of this approach (Xiong *et al*., 2013).

Chromatography fingerprints or chemical profiles are currently used as the standard quality control protocol. In addition, as a complement to chemical profiles, a biological quality control assessment provides advantages. One such example to consider is from the work done by Rong and co-workers (2007). This study describes a genome-wide Biological Response Fingerprinting (BioReF) approach to a set of marker genes that define a signature pattern for a specific botanical formulation. These marker genes are chosen on the basis of the levels of the regulated expression and the involvement in the cellular signaling pathways. Thus, Real-Time Quantitative Reverse Transcription Polymerase Chain Reaction (qRT-PCR) technique is used to monitor the gene expression of multiple marker genes in an efficient and quantitative manner. This set of marker genes represents the biological responses of human cells to the chemical composition of the botanical drug that could serve as potential quality control of botanical or herbal drugs in terms of the consistency of biological activities. The authors (Rong *et al*., 2007) have furthermore demonstrated the BioReF approach with a well-documented Chinese Medicine formula, labelled as ISF-1, traditionally used for the management of post-stroke disorders. A set of nine marker genes were selected to assess the batch-to-batch consistency of the biological effects of ISF-1. This approach gives a potential comprehensive and cost-effective quality control measure of the biological activities of botanical drugs as the Chinese example showed.

An article published by Zhang and collaborators (2013) emphasizes the fact that assessing botanical drug products have high relevance. The authors assessed the value of quality by design (QbD) to improve the understanding of the manufacturing process of botanical drug products. They took as a sample the ethanol extraction of the dry root of *Salvia miltiorrhiza* Bunge to illustrate the use of QbD. The recovery of four Active Pharmaceutical

Ingredients (APIs) and the removal of saccharides were used to represent the performance of ethanol precipitation. It was observed that higher concentration leads to higher removal of saccharides, but results in lower recovery of APIs. The recovery of different APIs behaves in different ways with the rise of ethanol consumption. The results in this work help the understanding of the relationships between multiple factors such as process parameters and material attributes and the performance of ethanol precipitation. The authors concluded that this case study demonstrated that QbD is a powerful tool to develop manufactured process of botanical drug products (Zhang *et al*., 2013).

Data from prospective, controlled, randomized double-blind clinical trials are essential to relay on the effectiveness of natural products (Sertel, 2011). In the Western countries patients who experienced failure or adverse reactions with conventional Western medicine often switch to natural and holistic methods. For those patients in other parts of the world where Western medicine is unaffordable, they revert to herbal preparations (Sertel, 2011). Other studies also strengthen the importance of safety since herbal medicine is in high demand and has received great attention and popularity (Oga *et al*., 2016). Users of traditional medicine perceive that such products are effective and of relatively low cost in comparison to modern drugs. The popular belief that herbal medicines are safe is mostly exaggeration and unsubstantiated. Contrary to popular belief that "herbal medicines are totally safe," it is much better to be cautious since they are capable of causing significant toxic effects and altered pharmaceutical outcomes when co-administered with conventional medicines. There is a need to standardize and better regulate herbal medicines in order to ensure their safety and efficacy when used alone or in combination with conventional drugs.

QUALITY CONTROL AND REGULATION

The issue of addressing quality of herbal products has great relevance to protect the health of consumers. Quality has to be linked to proper regulatory framework and process. A survey conducted by US Federal Drug Authority (FDA, 2000) to assess the number of botanical drug products submitted for approval for use from 1990 up to 1998 found that there was a trend of increase in number. The therapeutic categories in the order of importance were dermatological, antiviral, oncological, neuropharmacological, endocrine, metabolic and cardio-renal products (Wu *et al*., 2000). The survey indicated the growing public interest in botanical supplements. Regulatory legislation may urge herbal manufacturers to

follow accepted standard, like good manufacturing practice (GMP) (Kroll, 2001). In 2016 the USA FDA published a revised Botanical Drug Development Guidance for Industry (Charles *et al*., 2020) to provide scientific guideline for botanical drug development.

The European Parliament agreed on a directive regarding traditional herbal medicinal products. The directive removes the constraints that have made it difficult granting marketing authorizations of herbal substances and preparations as traditional medicinal products. It included definition of herbal medicine, list of herbal substances, registration procedures, preparations and establishment of the Herbal Medicinal Products Committee (Silano *et al*., 2004). Regulatory bodies in Europe have considered proposing harmonized guidelines for the pharmaceutical registration of traditional herbal products (Minghett *et al*., 2016).

Kawahara (2011) published the information regarding the establishment of the Western Pacific Regional (e.g. China, Japan, Korea, and Vietnam) Forum for the Harmonization of Herbal (FHH) Medicines. The general objective of FHH is promoting public health through developing standards and technical guidelines to improve efficacy, quality and safety of herbal medicines (Kawahara, 2011).

The first step in the harmonization of nomenclature and standardization was comparing the descriptions of herbal medicines as they appear in the pharmacopoeias or monograph standards of member countries. They set up expert working groups to expedite the harmonization. Such an approach is very instrumental in assuring quality and safety of herbal medicines that are of use in the member countries and it is also exemplary for other regions to follow suit.

One good example that can be cited is what the Nigerian Government did back in 2002. They gave importance and recognized the fast rate of globalization of herbal products and adopted guidelines for the practice of traditional medicine (Osuide, 2002). The regulatory authority, the National Agency for Food and Drug Administration and Control (NAFDAC), drafted the 'Guidelines for the Registration and Control of Herbal Medicinal Products and Related Substances in Nigeria' to take care of the health of consumers (Osuide, 2002). The Herbal medicinal products manufactured on a large scale, whether locally manufactured or imported, must be registered and their advertisement messages and scripts approved by NAFDAC prior to their marketing. Post-registration evaluation or monitoring is also mandatory for both large-scale herbal medicinal products and homeopathic

products. In 2021 the Ethiopian Food and Drug Authority (EFDA) developed a directive to control and monitor TM related activities. However, whether the directive is put into practice is yet to be seen. In one published article they reported that in the survey they made, despite the mandate the EFDA has on herbal medicine regulation, they did not get any evidence that EFDA exercised its mandate. On the other hand some traditional healers are licensed by regional health bureaus (Henok Demeke *et al*., 2022).

It is thus evident that herbal medicine or botanical drug products have to be produced following standard procedures that should not compromise quality. There is no compromise on the issue of safety while efficacy and affordability are also of high importance. In some countries botanical medicine is a narrow subdivision of allopathic medicine and it may not be of good service to benefit patients to the maximum. It is suggested that botanical medicine practitioners should be recognized and given credential so that they can handle the practice skillfully (Yarnell *et al*., 2002). In this regard/connection we can look at the experience of the USA system. In the USA prior to approval of botanical products there was a wide range of scientific studies conducted. Studies include acute and chronic toxicity study, mutagenicity study and carcinogenicity and clinical trials (Wu *et al*., 2004). In recent years, new technologies of "omics" methods (proteomics, metabolonomics, etc.) are being applied to assess the toxicity (genotoxicity, nephrotoxicity and teratogenicity) of herbal medicines (Ouedraogo *et al*., 2012). From the regulation and quality control point of view, the integration of conventional methods for toxicity assessments with new "omics" (e.g. proteomics, metabolomics) technologies could be useful.

ATTITUDE AND PERCEPTION

The use of medicinal products is perceived differently by different people of a given society. Some of the reasons why such varied perceptions exist could be cultural differences and failure of such products to be effective to some and working for others. MacLennan and co-workers (2002) conducted a survey of the use and cost of alternative medicine in South Australia. They interviewed 2,027 persons over the age of 15 years. The parameters used for the assessment were; types of alternative medicine and therapists, rate of use, costs and beliefs of users and nonusers. The results indicated that the use of at least one non-medically prescribed alternative medicine was about 52%. The users were more females and they practised self-prescription. Though most thought that alternative medicine was safe still they believed

that they should be of similar standards to prescribed drugs (MacLennan *et al*., 2002). A study conducted in Trinidad on the acceptance of herbal remedies by physicians showed that of the 192 physicians interviewed, 60.4% believed that herbal remedies were beneficial to health (Clement *et al*., 2005) and 78 physicians (40.6%) admitted being satisfied with the outcome of the herbs they used in the past. They also acknowledged that 52 physicians (27.1%) recommended use of herbs to their patients with limited herb-drug interaction of about 15.1%. The authors concluded that based on the study educational intervention is required to narrow the gap between acceptance and knowledge so that the physicians can communicate with their patients. They also recommended integration of herbal medicine courses in medical schools and also availing reputable pharmacopoeias for referencing (Clement *et al*., 2005).

The other issue regarding the attitude or perception that medicinal plant users have is lack of trust or in telling the truth to health providers or their physicians. The lack of trust or not being transparent raises the concern of serious interactions that occur between prescribed, over the counter drugs and herbal medicines. This is substantiated by the report of Vickers and associates (2006) who studied women in Cheshire, UK. They did a qualitative, cross-sectional study, with purposive sampling. In depth semi-structured interviews were conducted with female herbal medicine users greater than 18 years of age. The results revealed that the large majority did not inform their doctors of their use of herbal medicines, the reason being either they were not asked by their physicians or fear of negative response. The study showed that the women had limited knowledge about herb-drug interactions. This study leads to the recommendation of the need for increased access of reliable information on herbal medicines in the health care system. Above all the doctors' openness and communication regarding herbal medicine is critical (Vickers *et al*., 2006).

One study done in Nigeria (Oreagba *et al*., 2011) focused on recording the general knowledge of the benefits and safety of herbal medicines among urban residents in Lagos, Nigeria. Participants (n=388) were interviewed with a structured open- and close-ended questionnaire. The data gathered comprised the demography and types of herbal medicines used by the respondents; the sources, their particular use, benefits and adverse effects if any of the herbal medicines they used posed health problems. The results showed that a total of 12 crude or refined herbal medicines either alone or in combination with other herbal medicines were used by 66.8% of the respondents. 'Agbojedi-jedi' (35%) was the most frequently used herbal

medicine preparation, followed by 'agbo-iba' and Oroki herbal mixture, 27.5%, 9%, respectively. The influence of family and friends was remarkable accounting for 78.4% of the respondents who used herbal medicine preparations. About half of the subjects considered herbal medicines to be safe. Mild to moderate adverse effects were experienced by 20.8%. What is interesting to find was that the respondents were ignorant of the possible toxicities of herbal medicines. The authors concluded from the above study that it is necessary to evaluate the efficacy, quality and safety of herbal medicines and their products through randomized clinical trial studies. They emphasized that public awareness programmes about safe use of herbal medicines could be a good intervention by concerned bodies as a means of minimizing the potential adverse effects (Oreagba *et al*., 2011).

In Ethiopia, a study done on the knowledge, attitude and practice of TM in a small town in Western Ethiopia found out that among the 302 participants interviewed, about 23.83% believed that CAM is more effective than modern medicine. About 168 (55.7%) of them were knowledgeable of herbal medicine use (Negash Belachew *et al*., 2017). In another hospital-based cross-sectional study of 387 Type 2 diabetes mellitus patients who visited University of Gondar Comprehensive Hospital, 62% were herbal medicine users (Mekuria Abebe *et al*., 2018). Most of them (87%) did not consult their physicians about their use of the herbal products. Therefore, the study showed that the patients may be at risk of using the herbal medicines independently. Unless follow up study is done, it is not easy to know the benefit or harm induced by herbal medicine.

Another study looked at how herbal medicine users perceive the integration of herbal medicine in the health care system in the UK (Little, 2012). Nineteen adult clients of medical herbalists were interviewed about their experiences. The patients responded that they perceived that dealing with the cause of the illness, the collaboration of the practitioner with the patient and providing genuine evidence were relevant in achieving effectiveness in herbal medicine practices (Little, 2012). The author stated that, if a responsive health care system is to be in place and maintained, health care professionals should address the need of the patients and their preferences.

It is observed that herbal product use is on the rise across the world, especially among pregnant women. John and Shantakumari (2015) reviewed the situation in the Middle East to explore the pattern of use, motivation and attitude towards use of herbal medicine by pregnant women. Based on the literature published up to December 2012, there was a trend in a rise of

herbal medicine use by pregnant women (22.3–82.3%). The most common herbs used against gastrointestinal complaints, cold and flu were green tea, ginger, aniseed, peppermint, chamomile, sage, thyme and fenugreek. Most women were advised by family and friends to use herbal medicines and believed they were more effective and had fewer side effects than modern medicine. The pregnant women were reluctant to inform their health providers of the use of herbal medicine during their pregnancy. In another survey, Kennedy *et al*. (2016) did a cross-sectional study on the use of herbal medicine for different health ailments by pregnant women between Oct. 2011 and Feb. 2012 in Europe, North America and Australia. The study aimed at evaluating and classifying the herbal medicines used according to their safety in pregnancy and also investigated the risk factors associated with the use of contraindicated herbal medicines during pregnancy. The results showed that among the 2,673 subjects 29.3% reported the use of herbal medicines in pregnancy. The researchers were able to identify 126 specific herbal medicines used by 89% (2,379 women). Herbal medicines that were classified as contraindicated in pregnancy were 27 out of the 126 and these were used by 476 women (20.0 %). Those who used the herbals classified as safe were 47.4% (n=1128). There were 60 herbal medicines that were classified as requiring caution and were used by 31.6% (n=751). What was interesting in the finding of the study was that contraindicated herbal medicines were recommended more by healthcare practitioners (HCPs) than an informal source. This indicates an urgent need for education of HCPs.

CONCLUSION

It is known that medicinal plants are the source of biologically active compounds. They provide lead compounds for drug discovery. Hundreds of natural products from plants and natural product-derived drugs have been put into preclinical and clinical trials. The ones that were effective are available in the market (Mark *et al*., 2012). Standardization and regulation at all level is critical for the approval of such plant-derived drugs. Herbal medicines are generally not carefully studied with similar rigour as standard allopathic medicines (Cock, 2005). In many instances there is lack of regulation on manufacturing and standard guidelines as a consequence the products sold on the market are of poor quality thus compromising safety and efficacy. In addition, there is a lack of understanding among many medical practitioners of both traditional and allopathic medicine systems of how drugs from the two systems can be safely used together.

Some authors believe that there may not be a need to develop drugs from new molecular entities. Their suggestion is to focus on an alternative way of drug discovery from traditional herbal formulations; they call this reverse pharmacology approach (Patwardhan and Mashelkar, 2009). They suggest that traditional medicine and Ayurveda can offer a strategy for new drug candidates. Based on safe, long term human use data, the general data requirements for botanicals are far less, compared to the requirements of conventional drugs. Prospective and retrospective studies on herb-drug interactions may be handled by academic institutes, researchers and clinicians. There is a need to initiate and stimulate research on both safety issues and standardization.

The benefit of wisely using and conserving plant biodiversity cannot be overemphasized. It is one very important commodity to boost economies of entities that put safe, affordable and efficacious herbal product on world market.

REFERENCES

Bell, I.R. (2007). Adjunctive care with nutritional, herbal, and homeopathic complementary and alternative medicine modalities in stroke treatment and rehabilitation. *Top. Stroke Rehabil*. **14**(4): 30–39.

Brahmachari, G. (2006). Prospects of natural products research in the 21st century: a sketch. In: **Chemistry of Natural Products: Recent Trends and Developments,** pp. 1–22 (Brahmachari, G., ed.). Research Signpost.

Charles, W., Su-Lin, L., Cassandra, T., Jing, Li., Yen-Ming, C., Rajiv, A., Robert, T., Douglas, T., and Katherine, T. (2020). Scientific and regulatory approach to botanical drug development: A U.S. FDA perspective. *J. Nat. Prod*. **83**(2): 552–562.

Clement, Y.N., Williams, A.F., Khan, K., Bernard, T., Bhola, S., Fortune, M., Medupe, O., Nagee, K., and Seaforth, C.E. (2005). A gap between acceptance and knowledge of herbal remedies by physicians: the need for educational intervention. *BMC Complement. Altern. Med*. **5**: 20.

Cock, I.E. (2005). The safe usage of herbal medicines: counter-indications, cross-reactivity and toxicity. *Pharmacogn. Comm.* **5**(1): 2–38.

Dai, J., Gupte, A., Gates, L., and Mumper, R.J. (2009). A comprehensive study of anthocyanin-containing extracts from selected blackberry cultivars: Extraction methods, stability, anticancer properties and mechanisms. *Food Chem. Toxicol*. **47**(4): 837–847.

Delbanco, A.S., Neild, B., and Aida, C.S. (2017). Medicinal plant trade in northern Kenya: Economic importance, uses, and origin. *Econ. Bot.* **71**(1): 13–31.

De Smet, P.A. (1991). Is there any danger in using traditional remedies? *J. Ethnopharmacol.* **32**(1–3): 43–50.

Diallo, D., Diakite, C., Diawara, A., Konate, N., Teme, S., and Giani, S. (2010). Study of the consumption of the improved traditional phytomedicines in the health district of Kadiolo (Region of Sikasso, Mali). *Le Mali Med.* **25**(1): 5–13

Disayavanish, C. and Disayavanish, P. (1998). Introduction of the treatment method of Thai traditional medicine: its validity and future perspectives. *Psychiatry Clin. Neurosci* **52** Suppl.: S334–7

Ernst, E. (2005). The efficacy of herbal medicine: An overview. *Fundam. Clin. Pharmacol*. **19**(4): 405–409.

Fan, X.H., Cheng, Yi-Yu., Ye, Z.L., Lin, R.C., and Qian, Z.Z. (2006). Multiple chromatographic fingerprinting and its application to the quality control of herbal medicines. *Anal. Chim. Acta*. **555**(2): 217–224.

Gunjan, M., Naing, T.W., Saini, R.S., Bin Ahmad, A., Naidu, J.R., and Kumar, I. (2015). Marketing trends and future prospects of herbal medicine in the treatment of various diseases. *World J. Pharm. Res*. **4**(9): 132–155.

Henok Demeke, Gemmechu Hasen, Teshome Sosengo, Jafer Siraj, Tatiparthi, R., and Sultan Suleman (2022). Evaluation of policy governing herbal medicines regulation and its implementation in Ethiopia. *J. Multidiscip. Healthcare*. **15**: 1383–1394.

Janero, D.R. (2014). Relieving the cardiometabolic disease burden: a perspective on phytometabolite functional and chemical annotation for diabetes management. *Expert Opin. Pharmacother*. **15**(1): 5–10.

John, L.J. and Shantakumari N. (2015). Herbal medicines use during pregnancy: A review from the Middle East. *Oman Med. J*. **30**(4): 229–36.

Kawahara, N.Y. (2011). Recent progress of international harmonization of crude drugs and medicinal plants--activity of FHH (The Western Pacific Regional Forum for the Harmonization of Herbal Medicines). *J. Pharm. Soc. Japan.* **131**(3): 383–93.

Kennedy, D.A., Lupattelli, A., Koren, G., and Nordeng, H. (2016). Safety classification of herbal medicines used in pregnancy in a multinational study. *BMC Complement. Altern. Med*. **16**: 102/1-102/9

Khan, H. and Rauf, A. (2014). Medicinal plants: economic perspective and recent developments. *World Appl. Sci. J*. **31**(11): 1925–1929.

Kloos, H., Temesgen Menberu, Ashenif Tadele, Tebaber Chanie, Yared Debebe, Abiy Abebe, Kidist Zealiyas, Getnet Tadele, Mebruka Mohammed, and Asfaw Debella. (2014). Traditional medicines sold by vendors in Merkato, Addis Ababa: Aspects of their utilization, trade, and changes between 1973 and 2014. *Ethiop. J. Health Dev*. **28**(2): 136–152.

Kroll, D.J. (2001). Concerns and needs for research in herbal supplement pharmacotherapy and safety. *J. Herb. Pharmacother*. **1**(2): 3–23.

Little, C.V. (2012). Patient expectations of 'effectiveness' in health care: an example from medical herbalism. *J. Clin. Nurs*. **21**(5–6): 718–727.

MacLennan, A.H., Wilson, D.H., and Taylor, A.W. (2002). The escalating cost and prevalence of alternative medicine. *Prev. Med*. **35**(2): 166–73.

Mark, S.B., Avril, A., Robertson, B., and Matthew, A.C. (2012). Natural product and natural product derived drugs in clinical trials. *Nat. Prod. Rep.* **31**(11): 1612–61.

Matheka, D.M. and Demaio, A.R. (2013). Complementary and alternative medicine use among diabetic patients in Africa: a Kenyan perspective. *Pan Afr. Med. J*. **15**: 110.

Mekuria Abebe, Sewunet Admasu, Henok Getachew, Dawit Simegnew, Adeladlew Kassie, Eskedar Lemlemu, and Daniel Asfaw (2018). Prevalence and correlates of herbal medicine use among type 2 diabetic patients in Teaching Hospital in Ethiopia: a cross-sectional study. *BMC Complement. Altern. Med*. **18**: 85.

Minghetti, P., Franze, S., Zaccara, V., Raso, F., and Morazzoni, P. (2016). Innovation in

phytotherapy: Is a new regulation the feasible perspective in Europe? *Planta Med*. **82**(7): 591–595.

Negash Belachew, Tarekegne Tadesse, and Addisu Alemayehu (2017). Knowledge, attitude, and practice of complementary and alternative medicine among residents of Wayu Town, Western Ethiopia. *Evid-Based Complement. Alternat. Med*. **22**(4): 929–935.

Oga, E.F., Sekine, S., Shitara, Y., and Horie, T. (2016). Pharmacokinetic herb-drug interactions: Insight into mechanisms and consequences. *Eur. J. Drug Metab. Pharmacokinet*. **41**(2): 93–108.

Oreagba, I.A., Oshikoya, K.A., and Amachree, M. (2011). Herbal medicine use among urban residents in Lagos, Nigeria. *BMC Complement. Altern. Med*. **11**: 117.

Osuide, G.E. (2002). Regulation of herbal medicines in Nigeria: the role of the National Agency for Food and Drug Administration and Control (NAFDAC). *Adv. Phytomedicine.* **14**(10)*:* 1243–1248

Ouedraogo, M., Baudoux, T., Stevigny, C., Nortier, J., Colet, J.M., Efferth, T., Qu, F., Zhou, J., Chan, K., Shaw, D., Pelkonen, O., and Duez, P. (2012). Review of current and "omics" methods for assessing the toxicity (genotoxicity, teratogenicity and nephrotoxicity) of herbal medicines and mushrooms. *J. Ethnopharmacol*. **140**(3): 492–512.

Pang, B., Zhao, T.Y., He, L.S., Guo, J., Chen, H.D., Tong, X.L., Zhou, Q., and Zhao, L.H. (2015). Innovative thoughts on treating diabetes from the perspective of traditional Chinese medicine. *Evid-Based Complement. Alternat. Med.*: 905432

Patwardhan, B. and Mashelkar R.A. (2009). Traditional medicine-inspired approaches to drug discovery: can Ayurveda show the way forward? *Drug Discov. Today*. **14**(1–16): 804–811.

Poluzzi, E., Carlo, P., Emanuel, R., Angela. R., Maurizio, R., and Fabrizio, De P. (2014). Phytoestrogens in postmenopause: The state of the art from a chemical, pharmacological and regulatory perspective. *Curr. Med. Chem*. **21**(4): 417–436.

Ritch, R. (2005). Complementary therapy for the treatment of glaucoma: a perspective. *Ophthalmol. Clin. North Am*. **18**(4): 597–609.

Rong, J., Tilton, R., Shen, J., Ng, K.M., Liu, C., Tam, P.K.H., Lau, A.S.Y., and Cheng, Y.C. (2007). Genome-wide biological response fingerprinting (BioReF) of the Chinese botanical formulation ISF-1 enables the selection of multiple marker genes as a potential metric for quality control. *J. Ethnopharmacol.* **113**(1): 35–44.

Rosch, W., Liebregts, T., Gundermann, K.J., Vinson, B., and Holtmann, G. (2006). Phytotherapy for functional dyspepsia: a review of the clinical evidence for the herbal preparation STW 5. *Phytomedicine.* **13** (Suppl. 5): 114–121.

Sen, S., Chakraborty, R., Sridhar, C., Reddy, Y.S.R., and De, B. (2010). Free radicals, antioxidants, diseases and phytomedicines: current status and future prospect. *Int. J. Pharm. Sci. Rev. Res*. **3**(1): 91–100.

Sertel, S. (2011). Phytomedicine in otorhinolaryngology - evidence-based medicine with medicinal plants. *HNO* **59**(12): 1198–1202.

Silano, M., De Vincenzi, M., De, V.A., and Silano, V. (2004). The new European legislation on traditional herbal medicines: main features and perspectives. *Fitoterapia*. **75**(2): 107–16.

Van Andel, T., Britt, M., and Van Onselen, S. (2012). Ghana's herbal market. *J. Ethnopharmacol.* **140**(2): 368–378.

Vandebroek, I. (2013). Intercultural health and ethnobotany: How to improve healthcare for

underserved and minority communities? *J. Ethnopharmacol.* **148**(3): 746–754.

Vickers, K.A., Jolly, K.B., and Greenfield, S.M. (2006). Herbal medicine: women's views, knowledge and interaction with doctors: a qualitative study. *BMC Complement. Altern. Med*. **6**: 40

Wang J., Wan, Y.G., Sun, W., Zhang, H.L., Chen, P., and Yao, J. (2008). [Progress in Japanese herbal medicine in treatment of chronic kidney disease]. *Zhongguo Zhong Yao Za Zhi.* **33**(11):1348–52.

WHO (World Health Organization) (2019). **WHO Global Report on Traditional and Complementary Medicine 2019.** World Health Organization.

Wu, K.M., DeGeorge, J.G., Atrakchi, A., Barry, E., Bigger, A., Chen, C., Du, Tao., Freed, L., Geyer, H., Goheer, A., Jacobs, A., Jean, D., Rhee, H., Osterberg, R., Schmidt, W., and Farrelly, J.G. (2000). Regulatory science: a special update from the United States Food and Drug Administration preclinical issues and status of investigation of botanical drug products in the United States. *Toxicol. Lett.* **111**(3): 199–202.

Wu, K.M., Farrelly, J., Birnkrant, D., Chen, S., Dou, J., Atrakchi, A., Bigger, A., Chen, C., Chen, Z., Freed, L., Ghantous, H., Goheer, A., Hausner, E., Osterberg, R., Rhee, H., and Zhang, Ke. (2004). Regulatory toxicology perspectives on the development of botanical drug products in the United States. *Am. J. Ther*. **11**(3): 213–217.

Xiong, H., Yu, L.X., and Qu, H. (2013). Batch-to-batch quality consistency evaluation of botanical drug products using multivariate statistical analysis of the chromatographic fingerprint. *AAPS Pharm. Sci. Tech*. **14**(2): 802–810.

Xiong, X., Yang, X., Liu, W., Chu, F., Wang, P., and Wang, J. (2013). Trends in the treatment of hypertension from the perspective of traditional Chinese medicine. *Evid-Based Complement. Alternat. Med.*: eCAM 2013:275279

Yarnell, E., Abascal, K., Greenfield, R.H., Romm, A., and Sudberg, S. (2002). Credentialing of practitioners of botanical medicine. *Am. J. Med. Qual*. **17**(1): 15–20.

Zhang, J.M. and Li, W.L. (2012). Advances in studies on phytoestrogens in the prevention and treatment of postmenopausal osteoporosis. *Drugs Clinic*. **27**(1): 65–69.

Zhang, L., Binjun, Yan, X.G., Lawrence, X.Y., and Haibin, Q. (2013). Application of quality by design to the process development of botanical drug products: A case study. *AAPS Pharm. Sci. Tech*. **14**(1): 277–286.

Zhang, K., Yan, G., Zhang, A., Sun, H., and Wang, X. (2017). Recent advances in pharmacokinetics approach for herbal medicine. *RSC Advances*. **7**(46): 28876–28888.

https://www.statista.com/statistics/939899/global-botanical-and-plant-derived-drugs-market-cagr/ accessed 21 July 2020).

https://www.nuffoodsspectrum.in/news/39/1397/global-market-for-botanical-supplements-to-grow-to-90-2-billion-by-2020.html: accessed 21 July 2020).