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Mini review

Potential role of metabolomics in the improvement of research on traditional African medicine

Emmanuel Quansah[a,b,*], Thomas K. Karikari[c,d,**]

[a] Pharmacology, School of Health and Life Sciences, De Montfort University, Leicester LE1 9BH, UK
[b] Department of Molecular Biology and Biotechnology, School of Biological Science, University of Cape Coast, Cape Coast, Ghana
[c] Neuroscience, School of Life Sciences, University of Warwick, Coventry CV4 7AL, UK
[d] Midlands Integrative Biosciences Training Partnership, University of Warwick, Coventry CV4 7AL, UK

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ABSTRACT

The global market for herbal medicine is growing steadily. The usage of herbal medicine is particularly common in many parts of Africa; the World Health Organization estimates that approximately 80% of Africans rely on traditional African medicines (TAMs) for treating various diseases. TAMs hold promise in preventive treatment, early disease intervention and personalized medicine. However, clinical integration of TAMs is restricted due to limited information concerning their characterization. Presently, many studies on TAMs utilize a reductionist approach, making it extremely difficult to understand the holistic modifying effects that these therapeutic agents may have on biological systems. Fortunately, emerging technologies such as metabolomics platforms adopt a 'top-down' strategy that permits a holistic evaluation of the components, metabolic pathways and biomarkers modified by TAMs, which can aid in addressing common concerns over safety and toxicity, while also ensuring that quality control standards are met. Metabolomics approaches may also be beneficial for advancing our understanding of the efficacy and mechanism of action of TAMs, and may contribute to the advancement of research and drug discovery, early diagnosis, preventive treatment and TAMs-driven personalized medicine in Africa. This review also considers the main challenges that may hinder the adoption and integration of metabolomics approaches in research on TAMs in Africa and suggests possible solutions.

Contents

Abbreviations: ESI, electrospray ionization; LC–MS, Liquid Chromatography–Mass Spectrometer; NMR, nuclear magnetic resonance; OPLS-DA, orthogonal projection to latent structures discriminant analysis; PCA, principal component analysis; PLS-DA, projection to latent structures discriminant analysis; TAM, traditional african medicine; WHO, World Health Organization.

* Corresponding author at: Department of Molecular Biology and Biotechnology, School of Biological Science, University of Cape Coast, Ghana.
** Corresponding author at: Neuroscience, School of Life Sciences, University of Warwick, Coventry CV4 7AL, UK.
E-mail addresses: quansahmanuel@yahoo.com (E. Quansah), T.K.Karikari@warwick.ac.uk (T.K. Karikari).

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1. Introduction

Several plant species possess a variety of chemical constituents that are traditionally exploited in the management of diseases (Muthaura et al., 2015). Traditional medicines hold promise in early disease intervention, combination therapy and personalized medicine (Wang et al., 2011a,b). The global market for traditional medicine is projected to reach US $ 115 billion by 2020, with the sale of Chinese herbal medicine alone reaching US $ 83 billion in 2008 (Robinson and Zhang, 2011; WHO, 2013). The use of traditional medicine in disease management is particularly high in African communities. The World Health Organization (WHO) reported that about 80% of Africans use traditional medicine for primary health care (WHO, 2003) and that the ratio of traditional healers to population on the continent is 1:500, while the ratio of doctors to population is 1:40,000 (WHO, 2013). This reliance on traditional medicines is reportedly high among rural populations; this trend may have started due to a general lack of access to public healthcare facilities in such areas (Mothupi, 2014). In Ghana, Nigeria, Zambia and Mali, traditional African medicines (TAMs) constitute the first line of treatment for about 60% of children with high fever (resulting from malaria) that are treated at home (WHO, 2013). Moreover, about 75% of HIV/AIDS patients in South Africa use TAMs (WHO, 2003). The use of TAMs in these areas may be influenced by the general ease of access, perceived efficacy, and beliefs about their safety over generations (Langlois-Klassen et al., 2007). However, the use of TAM is similarly popular in urban areas where relatively good access to mainstream healthcare facilities exists (Bamidele et al., 2009; Njoroge and Kibunga, 2007), indicating a high consumer base for these products. Apart from using TAMs as the main treatment paradigmfor various diseases, consumers also use them to complement other medicines or as dietary supplements to improve their general health.

Although TAMs are heavily relied on, their insufficient characterization at the molecular level limits their clinical use. The reporting and analysis of these traditional medicines, their interactions with other drugs, safety, side effects, tolerance, hypersensitivity, reactions due to overdose and toxic effects also need to be investigated and reported (Cordell, 2014). Moreover, the components, manufacturing standards, and the addition of synthetic drugs of low quality are of great concern, especially as some studies have reported a lack of quality in the production, trade and prescription of some traditional medicines (Abew et al., 2014; Cordell, 2014). However, identifying the components of traditional medicines in general and their formulation is quite challenging and time consuming due to the complexity and the large number of detectable metabolites (Guo et al., 2015). The methodologies used in traditional medicine research follow the path of reductive analysis, thus contributing to the difficulty in characterizing them, especially with regards to their holistic modifying effects on biological components (Wang et al., 2011a,b). Metabolomics offer an opportunity to develop a systematic/holistic analysis of the components, biomarkers and metabolic pathways modified by traditional medicines (Cao et al., 2015), which can clarify the mechanism of action of TAMs. Metabolomics (focused on the study of the set of metabolites present in a cell or tissue) or metabonomics (related to the investigation of the effect of human nutrition, drugs and diseases) adopt a 'top-down' strategy and reflects the function of organisms from terminal symptoms of metabolic networks and provides an holistic view of the alterations in metabolic pathways caused by interventions (Cao et al., 2015; Wang et al., 2011a,b). In recent times, metabolomics has increasingly been used in the study of Chinese and Western medicines (Cao et al., 2015). Based on this, we discuss how metabolomics approaches could be employed to advance research and clinical use of TAMs.

2. Research and therapeutic use of TAMs

Over the years, TAMs have been used in the management of several diseases, ranging from neurological disorders and inflammatory conditions to various forms of cancer (Akindele et al., 2015). While some of these medicines are used in the management of specific diseases, others seem to be potent against several diseases and may be used alone or in combination with other agents. A summary of the therapeutic importance of the commonly investigated TAMs is detailed below. *Sanseveiria liberica* Gerome and Labroy (family: dracaenaceae), which is commonly called "mother-in-law tongue" or "African bowstring" is an important perennial plant with thick woody rhizomes distributed widely in the tropical, subtropical and temperate zones (Chinasa et al., 2011). Extract preparations of this plant are used in the treatment of various diseases including inflammation (leaf juice), ear and eye infections, headache, fever, cold (fume from burning leaves must be inhaled), epilepsy, measles, venereal diseases, convulsion and diarrhea (Adeyemi et al., 2007; Bero et al., 2009; Chinasa et al., 2011). Recently, hydroethanolic extract of *S. liberica* has also been shown to exhibit significant dose-dependent antitumor activity in *in vivo* models of sarcoma and lymphoid leukemia (Akindele et al., 2015). In South Africa, *Burkea africana* Hook. (family: leguminosae), *Leucaenea lucocephala* (Lam) de Wit (family: fabaceae), and *Lippia javanica* (Burm. f.) Spreng. (family: verbenaceae) have been shown to possess anti-inflammatory, anticholinesterase and antioxidant activities (Dzoyem and Eloff, 2015). Also, acetone extracts of *Senna italica* Mill. subsp. arachoides (Burch.) Lock (family: fabaceae), *Catharanthus roseus* (L.) G.Don (family: apocynaceae), *Solanum panduriforme*, E.Mey. (family: solanaceae), and *Gomphocarpus fruticossus* (L.) Aiton f. subsp. Fruticosus (family: apocynaceae) have also shown potency (>70%) against *Neisseria gonorrhea* (Mulaudzi et al., 2015). In addition, *Ricinus communis* (family: euphorbiaceae) and *Zehneria scabra* (Linn. f.) Sond. (family: cucurbitacae), in Ethiopia, have been shown to have bactericidal activity against *Escheria coli* and methicillin resistant *Staphylococcus aureus* (Abew et al., 2014). *Dodonaea angustifolia* L. f. (family: sapindaceae) and *Rumex nepalensis* Spreng. (family: Polygonaceae) also demonstrated significant combinatory anti-proliferative/antioxidant effect, while *Verbascum sinaiticum* Benth. (family: scrophulariaceae) showed selective antiproliferative potential (Tauchen et al., 2015). Remarkably, a recent study has shown that acetate extracts of date palm pollen collected from Tunisian cultivars of Kerkennah and Tozeur showed effect against *Listeria monocytogenes* and *Staphylococcus aureus* respectively, suggesting that date palm pollen may be a potential inhibitor of some food-poisoning microbes (Daoud et al., n.d.). While these studies give an indication of a growing interest in TAM use, our current understanding of the mechanism of action, safety, and toxicity of these traditional medicines is still limited. Applying

metabolomics approaches to the study of TAMs may be crucial for drug discovery and disease management.

3. Untargeted metabolomics for a comprehensive evaluation of TAMs

The rising popularity along with the increased toxicity of herbal products has resulted in a growing need for a deeper knowledge on these products. To improve our knowledge of these herbal products, metabolomics approaches may be crucial. The two main approaches in metabolomics are the targeted (biased) and untargeted (unbiased) metabolite profiling. While the targeted approach targets a specific subset of metabolites in a sample, the untargeted approach examines the complete metabolome (Commisso et al., 2013). Untargeted metabolomics has become a useful approach for carrying out comprehensive qualitative and quantitative evaluation of herbal products (Chauthe et al., 2012; Commisso et al., 2013; Heyman and Meyer, 2012). Analytical techniques employed in metabolomic studies include liquid chromatography-mass spectroscopy (LC–MS), gas chromatography–mass spectroscopy, capillary electrophoresis-mass spectroscopy, thin layer chromatography, Fourier transformed infrared spectroscopy and nuclear magnetic resonance (NMR) spectroscopy. Amongst these, the most popular analytical methods are those based on MS and NMR spectroscopy. Recent progress made in analytical chemistry regarding the detection and characterization of small molecule compounds such as MS and high-field NMR, along with modern multivariate statistics have resulted in highly efficient systems for comprehensive evaluation of metabolite data generated in metabolomic studies (Lindon et al., 2007). This review focuses more on the LC–MS and NMR techniques due to their rapid and robust characteristics, which are essential for evaluating TAMs.

3.1. Workflow of untargeted (LC–MS and NMR-based) metabolomics experiments

A flow chart of a typical NMR and LC–MS untargeted metabolomics experiment is shown in Fig. 1. The main stages include sample collection and preparation (extraction), data acquisition, data processing and analysis, and metabolite identification, which may allow biological interpretation. The sample collection and extraction stage is critical, as the collection of plant material needs to take into account several factors that can influence sample integrity including collection time, season, weather, soil, etc. (Heyman and Meyer, 2012). In addition, the extraction method and solvents used can influence the metabolite yield and the range of metabolites extracted. While a single solvent system has been used in extracting metabolites in some studies, using a combination of solvents (e.g. D_2O and CD_3OD or KH_2PO_4 combinations for NMR analysis) is preferred as it yields a much more diverse metabolites from plant samples (Kim et al., 2005; Van Der Kooy et al., 2009).

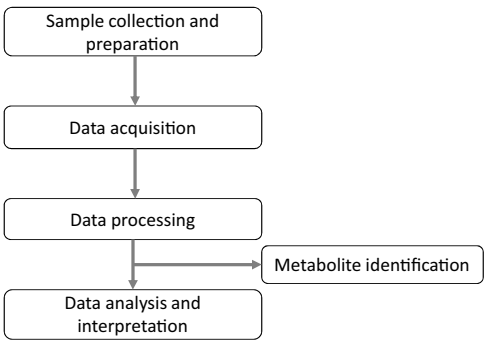

Fig. 1. Typical untargeted metabolomics workflow.

Several studies have recently considered the major data processing challenges that may arise from untargeted metabolomics, and ways of overcoming them (Boccard et al., 2010; Eliasson et al., 2012; Gil et al., 2016; Nicholson and Lindon, 2008). Data processing tools such as ACD Labs (http://www.acdlabs.com/), MetaboAnalyst (http://www.metaboanalyst.ca/) and SIMCA (http://umetrics.com/products/simca) for NMR and XCMS (https://metlin.scripps.edu/xcms/), MZmine (http://mzmine.sourceforge.net/), and MetAlign (http://www.metalign.wur.nl) for LC–MS, have been designed to extract useful information from batches of crude spectroscopic and chromatographic data, permitting the rapid processing of multiple variables or data points, making untargeted metabolomics quite useful (Commisso et al., 2013).

3.2. Data analysis and metabolite identification in untargeted metabolomics

The data acquired using LC–MS or NMR may be analyzed using one of the two major routes, based on the aim of the study (Boccard et al., 2010; Heyman and Meyer, 2012). In targeted metabolomics where a small number of specific metabolites are profiled, quantitative methods may be used to analyze the metabolites of interest and statistical significance tested via univariate and other classical statistical methods. However, in untargeted metabolomics, which aims to provide a more global/holistic picture of the investigated sample, a large number of known and unknown metabolites are obtained, which are all quantified and analyzed simultaneously (Schultz et al., 2013). Statistical significance of such large data sets from untargeted metabolomics are tested using multivariate statistical methods, as the use of univariate and other classical statistical methods becomes less feasible. While both targeted and untargeted metabolomics approaches detect patterns in metabolites, only untargeted metabolomics permits the detection of synergistic effects between variables, which cannot be detected at the individual level. Commonly used multivariate statistical techniques are based on projection methods, which combine examined variables into the so-called latent variables for solving the problem being investigated (Westerhuis et al., 2010). The unsupervised technique, principal component analysis (PCA) is used for exploratory data analysis and it summarizes the information in a given data set using a small number of orthogonal latent variables. However, the supervised techniques such as projection to latent structures discriminant analysis (PLS-DA) or orthogonal projection to latent structures discriminant analysis (OPLS-DA) are preferred to extract hidden information that classifies and explain system behavior (Westerhuis et al., 2010).

Metabolite identification represent another significant challenge in untargeted metabolomics, especially as plants often transform secondary metabolites via glycosylation and esterification to produce species dependent metabolic profiles. While these diverse molecules could be beneficial in terms of their pharmacological properties, they are rather difficult to identify with accuracy (Commisso et al., 2013). However, several metabolite feature databases have been assembled including MS2T (http://prime.psc.riken.jp/lcms/ms2tview/ms2tview.html), METLIN (https://metlin.scripps.edu/), HMDB (http://www.hmdb.ca/;), Birmingham Metabolite Library (http://www.bml-nmr.org/;), Campus Chemical Instrument Center (http://www.bml-nmr.org/;), and MASSBANK (http://www.massbank.jp/index.html) (Bingol et al., 2014; Horai et al., 2010; Matsuda et al., 2009). NMR parameters can be particularly sensitive to temperature, concentration, pH, and ionic conditions (Weljie et al., 2006), therefore for a better metabolite identification, the spectra of samples being examined may need to

be acquired under conditions similar to those acquired in the databases. For a set of similar samples in a study, it may be necessary for identified metabolites to be verified using a series of multidimensional NMR experiments, which maps the carbon skeleton. Such multidimensional NMR experiments may include HSQC, HMQC, HMBC, TOCSY or a combination of either HSQC or HMQC and TOCSY (HSQC/HMQC-TOCSY) (Carvalho et al., 1998; Powers, 2009). In addition, functional groups could be determined by making use of derivatizing reagents (chemically selective probes), which target specific functional groups. When an enriched atom (^{15}N or ^{13}C) is introduced at a specific position in the chemically selective probe, the isotope-editing feature of NMR could be utilized to detect only those metabolites with the functional groups of interest (Bousamra et al., 2014). Chemically selective probes have, for example, been designed to select for functional groups such as ketones and aldehydes (Bousamra et al., 2014), carboxylates and thiols (Gori et al., 2014).

3.3. Challenges associated with untargeted metabolomics and emerging measures to overcome them

Untargeted metabolomics approaches such as LC–MS and NMR allowfor a rapid, high-throughput and automated assessment of crude extracts and the quantitative detection of several different metabolites (Kim et al., 2010), while also providing structural information including stereochemical details (Seger and Sturm, 2007). Over the last few decades, these metabolomics approaches have been used to successfully determine the small molecule basis of several biological processes such as those linked with disease pathogenesis (Wang et al., 2011a,b), plant physiology (Leiss et al., 2009), microbial biochemistry (Vinayavekhin and Saghatelian, 2009), and mode of action of drugs (Allen et al., 2004). However, some important methodological concerns remain to be addressed. For instance, although NMR gives unique structural information regarding metabolites, it suffers from limitations in chemical resolution and sensitivity (Schultz et al., 2013). Given that the intensity and sensitivity of magnetic resonance signals depend on the strength of the magnetic field, the NMR technique is continually being improved to include more powerful magnets (Pourmodheji et al., 2016; Powers, 2009). In particular, recent advances in the next generation of high-throughput NMR spectrometers using complementary metal oxide semiconductors, consisting of a series of high-sensitivity micro-coils integrated with interfacing radio-frequency circuits on the same chip, promises to enhance the sensitivity of the technique while also ensuring that a large number of experiments can be run simultaneously in one unit (Pourmodheji et al., 2016). In addition, NMR evaluation of plant extracts has the challenge of extensive resonance overlap, which could obstruct the quantification and identification of metabolites. To overcome this challenge, several NMR studies use an enrichment or fractionation step (Simmler et al., 2014).

In comparison, the LC–MS method provides a good sensitivity and selectivity, allowing for the detection and quantification of less concentrated (trace) metabolites (Sumner et al., 2003). LC–MS is well suited for analyzing non-volatile, thermally sensitive, and non-polar compounds which otherwise would require derivatization prior to other MS approaches. The overall aim of metabolomics approaches is to determine as many metabolites as possible responsive to a given condition or a set of conditions (Fan and Lane, 2016). This indicates that the metabolomics approaches provide an opportunity to observe several altered metabolites which may be known (and are present in databases) or unknown (Schultz et al., 2013). Importantly, due to sheer diversity of plant metabolites, most databases do not provide complete coverage of metabolites. However, if the correct structures of the metabolites are not present in a database, their accurate identification may be challenging. This notwithstanding, when coupled to a high resolution MS, such as an Orbitrap (Kamleh et al., 2008) or time of flight (Lu et al., 2008) instrument, high mass accuracy can be obtained for metabolite identification (Schultz et al., 2013). Although the high mass accuracy significantly decreases the potential molecular formulas corresponding to an individual metabolic peak, problems do arise with this approach as there may be several molecular formulas appropriate for the accurate mass data and several potential isomers for each given molecular formula (Schultz et al., 2013). Therefore, a fragmentation mechanism is usually required to provide some structural information. Matching the fragmentation and accurate mass data with standard MS/MS spectra in the METLIN (https://metlin.scripps.edu/) database, for instance, may give a more convincing metabolite identification than using accurate mass data alone (Schultz et al., 2013). In addition, accurate fragmentation patterns and mass determination may be obtained by a combination of standard MS/MS with electrospray ionization (ESI), which may allow *de novo* metabolite structure determination. For instance, ESI–MS/MS has been used with reverse-phased high performance liquid chromatography to isolate and identify proanthocyaninidins in Saskatoon berries (*Amelanchier alnifolia*) (Hellström et al., 2007). Moreover, the LC–MS approach has been used to detect and accurately identify a wide array of semi-polar phytochemical compounds. For example, it has been used to examine the anti-inflammatory activity of lipophilic stinging nettle extracts (Johnson et al., 2013) and lipophilic leaf extracts of *Staphylea* L. species (Lacikova et al., 2009). In identifying unknown spectral features in NMR studies, multidimensional NMR would be essential and it would be important to include heteronuclear NMR methods based on ^{15}N or ^{31}P nuclei, rather than ^{13}C (Fan and Lane, 2016). While the combination of chemical shift information and heteronuclear scalar coupling may be sufficient in identifying a given compound by comparison with databases or comparison with a compiled list of chemical shifts with different functional groups, the functional groups of such compounds may not be clear unless one carries out additional experiments. Such additional experiments could take the form of pH titrations to confirm the presence or otherwise of carboxyl or amino functional groups (Fan and Lane, 2016).

In Africa, metabolomics and metabonomics approaches are currently being employed in research on diseases such as HIV/AIDS (Sitole et al., 2013), schistosomiasis (Balog et al., 2011), and tuberculosis (Mahapatra et al., 2014; Olivier and Loots, 2012), as well as in the study of antifungal agents (Tugizimana et al., 2014), soya-milk (Ogegbo et al., 2012) and anti-HIV chemical entities (Heyman et al., 2015). However, little attention has been paid to the application of metabolomics and metabonomics approaches in the study of TAMs.

4. Metabolomics for advancing TAMs-based research on preventive treatment and personalized medicine in Africa

Metabolomics in combination with pharmacology provide robust means for the discovery of novel active compounds and may as well be useful in proving the occurrence of synergy and prodrugs (Verpoorte et al., 2009). Given that metabolomics provides some of the most advanced approaches to molecular system readout and offers excellent technological platforms for discovering biomarkers associated with healthy and diseased states, it could play crucial roles in the design of individualized interventions and personalized health monitoring programs (Wang et al., 2011a,b). In practice, personalized medicine involves a customized medical care tailored towards each individual patient's unique condition. Thus implementing a systems approach would make significant contributions in disease

phenotyping and the development of novel therapeutics to address system-wide molecular perturbations resulting from disease processes (van der Greef et al., 2006). Currently, there is a growing interest in personalized medicine as well as preventive treatment options (Wang et al., 2011a,b). The concepts pertaining to personalized medicine and preventive treatment have three main foci: (a) disease control – stressing on regimen and disease prevention (b) early diagnosis, treatment and control of the evolution of disease, and (c) prognosis and prevention of disease recurrence (Wang et al., 2011a,b). Premedical intervention before disease is a key aspect of TAMs usage in tackling health challenges in Africa. Scientific interpretations of some successes of various preventive treatments involving traditional medicines in China and elsewhere suggest that disease prevention; especially those targeted towards individual conditions should surpass medical intervention in humans (Liang and Yin, 2010). Metabolomics holds the potential of enabling the identification of predictive biomarkers that can signal the onset of specific diseases and as well define TAMs that can be useful in early interventions. Indeed, some studies have already demonstrated that early-intervention metabolomic approaches may provide deeper insights into disease-preventive mechanisms in clinical trials (Bast, 2004; Martin et al., 2009; Winnike et al., 2010). At present, it is widely believed that elimination of cancer and related diseases will likely be dependent on both individualized treatment and earlier detection as well as prevention of malignancies (Bast, 2004). Metabolomics-based investigations of TAMs, on the one hand, and traditional medicines in general, may be crucial in combatting cancer and several other diseases confronting mankind. Already, evidence suggests that some TAMs possess anticancer and anti-inflammatory properties (Akindele et al., 2015; Dzoyem and Eloff, 2015). Using metabolomic approaches to expand and confirm findings from such initial studies would be essential in the development of novel therapeutics against cancer and several other diseases in Africa and elsewhere. The integration of metabolomics approaches in the study of TAMs by African scientists may contribute immensely to the advancement of research, early diagnosis, preventive treatment and personalized medicine on the continent.

5. Using metabolomics to ensure quality control of TAMs

Standardization and quality control assurance of herbal products are essential in the protection of the integrity of the products and in meeting pharmaceutical quality. Standardization and quality control are also essential to ensure the reproducibility of the effect of active ingredients (Heyman and Meyer, 2012). The main parameters required for certifying the quality and safety of herbal products may include, but may not be limited to: (a) definitive identification and taxonomic classification of plants e.g. through DNA bar coding and fingerprinting, (b) identification of the main bioactive constituents, (c) determination of the structure of the major constituents, (d) standardization of single extract or multi-compound extract fingerprints, and (e) harmonization of standardization criteria under the relevant state and international authorization bodies (Heyman and Meyer, 2012; Slater et al., 2015). From the criteria it becomes evident that standardization of herbal products could be quite difficult to achieve given the numerous factors that could influence the standardization process. Thus, it becomes important to optimize all aspects of the process from plant cultivation, harvesting, sample preparation to analysis. Spectroscopic and chromatographic techniques could be adopted to facilitate the quality control process. Using these high-throughput techniques it becomes possible to generate a standardized metabolic fingerprint of any given herbal product (Sheridan et al., 2012). Metabolic profiling methods could then be used to identify the multiple constituents of the herbal product making up the metabolic fingerprint. These techniques, may therefore aid in obtaining relatively accurate, reliable and reproducible assessment of herbal products for clinical use (Sheridan et al., 2012).

6. Working at the metabolite level: benefits and limitations

6.1. Benefits

Metabolite measurements are crucial given their importance as components of biochemical pathways, the significance of some metabolites in human diet and their potential role as biomarkers for a wide range of biological conditions (Hall, 2006). Improvement in our ability to characterize changes in metabolite contents from seemingly unconnected pathways is facilitating our understanding of how cells prioritize and partition important nutrients in different conditions. Several studies are implicating metabolites in mediating gene expression (Baier et al., 2004; Lancien and Roberts, 2006), and demonstrating their key role in determining responses to perceived stress and developmental cues (Panicot et al., 2002). Moreover, there are suggestions from yeast-based studies indicating that metabolites can also influence protein stability and act as mobile cellular and intracellular signals (Fafournoux et al., 2000). There is also little doubt that the phenotype of biological systems are largely determined by their metabolic composition (Fernie, 2007), providing a strong reason to invest time, funds, and research efforts into furthering our understanding of how this phenomenon is mediated. The fact that metabolomic entities operate at a level directly impacting biological function is the key reason necessitating its application in the study of TAMs for establishing the disease-modifying actions of these products.

6.2. Limitations

Set against the numerous advantages of metabolomics is the fact that measurement of metabolites could be difficult, mostly due to their dynamic behavior as well as the diversity of their chemical nature (Stitt and Fernie, 2003). The chemical diversity of metabolites is much more than that of nucleic acids and proteins given the enormous diversity in their structure. This structural diversity therefore confers a broad range of chemical properties, which may be a problem when finding suitable extraction buffers. This diversity also implies that there is no single extraction procedure that does not cause substantial loss of some cellular metabolites (Fernie, 2007). In addition, there is no single metabolomics platform existing currently that can measure all metabolites (Fernie, 2007). Another major disadvantage in the study of TAMs at the metabolite level has to with the greater metabolic diversity in plants. In this regard, while the genome of *Arabidopsis* has approximately the same number of genes as humans, the metabolic diversity in the former is far greater than the latter (De Luca and St Pierre, 2000). The plant kingdom contains over 200,000 metabolites (De Luca and St Pierre, 2000) with individual species having about 15,000 metabolites (Hartmann et al., 2005). Given that currently existing metabolite profiling methods cover only a fraction of the full metabolite complement of the cell, this represents a key limitation.

7. Integrating metabolomics approaches into TAMs research: challenges and solutions

While metabolomic platforms could play crucial roles in the advancement of research on TAMs, their adoption may be hindered by a number of factors. Among these factors are limited resources and research funding. The cost of metabolomic technologies such

as NMR and mass spectrometers can be a critical barrier to the application of metabolomics approaches in research and clinical use of TAMs in Africa. However, African universities and hospitals could benefit from organizations such as Adéquation (http://adequationgermany.embl.de/), Seeding Labs (http://seedinglabs.org/), and TReND in Africa (http://trendinafrica.org/), which supply second-hand medical and laboratory equipment in good condition (Quansah and Karikari, 2015a,b). In addition, African governments need to commit to supporting local scientific research with at least 1% of each nation's gross domestic product as indicated by the African Union (Quansah and Karikari, 2015a).

Another potential impediment to the use of metabolomics approaches in TAMs-based research may be the lack of well-resourced scientists with metabolomics know-how. Metabolomics research remains relatively new to most research and clinical institutions in Africa. As such, many institutions on the continent may lack appropriately trained scientists. However, national training programs on metabolomics could be organized in various African countries to train a few local researchers and clinicians, who could then lead metabolomics research in their respective institutions. Moreover, training programs organized under the H3Africa (Human Heredity and Health in Africa; http://www.h3africa.org/) initiative and other similar initiatives could be expanded to accommodate metabolomics research approaches. Addressing these challenges would be crucial in the adoption of metabolomics to improve TAMs research on the continent.

8. Conclusion

The steady growth of the global market for traditional medicines suggest that increased research utilizing modern research technologies may be essential to improve our understanding of the composition, efficacy, safety and tolerability of traditional African medicines, if they are to have a more global appeal. Metabolomics platforms offer an excellent means of determining the composition and holistic effect of TAMs on biological systems, therefore representing a means for Africa to extend the clinical use of TAMs and for the discovery of novel drugs that may be specific for local populations.

Conflict of interests

The authors declare that there is no conflict of interest in relation to the publication of this paper.

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