

Phytomedicine: An abundant source of safe and efficacious therapeutics to revive local pharmaceutical production

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ABSTRACT

Background: Many health systems largely depend on phytomedicines. However, these therapeutic agents are being criticized because of the limited information on their quality, safety and efficacy.

Objectives: This review aimed to aggregate scientific evidence on the availability, safety and efficacy of phytomedicines, to reveal the available methods for optimizing their quality and to intensify the need for their local production.

Methods: About 1000 peer reviewed articles from 5 databases (Google scholar, Pubmed, Scopus, Web of Science and Science direct) were reviewed to extract relevant information on this subject of discussion.

Results: Over 50,000 plant species are known to occur in sub-Saharan Africa alone; and over 5,000 plants are already known to be used for medicinal purposes in Africa, but only a few have been adequately studied. African countries and institutions, including researchers have continued to document medicinal plants of importance as knowledge grows and new information emerge. Phytomedicines are known to be useful in managing many diseases but there are challenges of standardization, formulation and safe use in some instances. There are now several ways of addressing these challenges.

Conclusion: It is clear that our health system largely depends on traditional medicines and the world is returning to nature. Africa is rich in medicinal plants and the medicinal components can be converted to suitable dosage forms; hence, an enhanced production of phytomedicines could revive local pharmaceutical production.

Keywords: Phytomedicine, Local production, Safety, Efficacy, Africa

Phytomédecine: Une source abondante de thérapeutiques sûres et efficaces pour relancer la production pharmaceutique locale

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RÉSUMÉ

Contexte: De nombreux systèmes de santé dépendent largement des phytomédicaments. Cependant, ces agents thérapeutiques font l'objet de critiques en raison du manque d'informations sur leur qualité, leur innocuité et leur efficacité.

Objectifs: Cette étude vise à rassembler les données scientifiques sur la disponibilité, l'innocuité et l'efficacité des phytomédicaments, à mettre en évidence les méthodes disponibles pour optimiser leur qualité et à souligner la nécessité de relancer leur production locale.

Méthodes: Environ 1 000 articles évalués par des pairs provenant de 5 bases de données (Google Scholar, Pubmed, Scopus, Web of Science et Science Direct) ont été examinés afin d'extraire les informations pertinentes sur ce sujet de discussion.

Résultats: On recense plus de 50 000 espèces végétales rien qu'en Afrique subsaharienne, dont plus de 5 000 sont déjà utilisées à des fins médicinales. Cependant, seules quelques-unes ont fait l'objet d'études approfondies. Les pays et institutions africains, notamment les chercheurs, ont continué à répertorier les plantes médicinales importantes à mesure que les connaissances s'enrichissent et que de nouvelles informations émergent. Les phytomédicaments sont reconnus pour leur utilité dans la prise en charge de nombreuses maladies, mais des difficultés subsistent en matière de standardisation, de formulation et d'utilisation sans risque dans certains cas. Il existe désormais plusieurs moyens de relever ces défis.

Conclusion: Il est clair que notre système de santé repose en grande partie sur les médecines traditionnelles et que le monde se tourne à nouveau vers la nature. L'Afrique regorge de plantes médicinales dont les composants actifs peuvent être transformés en formes galéniques appropriées ; ce qui souligne la nécessité de relancer la production locale de phytomédicaments.

Mots-clés: phytomédecine, production locale, sécurité, efficacité, Afrique

INTRODUCTION

Phytomedicines are preparations containing herbal materials presented in dosage forms which on administration are meant to provide nutritional benefit, cosmetic benefit or to mitigate diseases in humans or animals. Herbal materials in common use include leaves, flowers, fruits, seed, stem wood, bark, roots, rhizomes as well as other morphological plant parts.¹ Rational phytotherapy is a modern concept of phytomedicine using standardized herbal preparations.²

The herbal material may be subjected to appropriate extraction process.^{3,4} The extract may be further subjected to concentration and/or purification. It may thereafter be presented without further processing and used in the forms such as decoctions, infusions and tinctures. In quest of ensuring the safety and efficacy of phytomedicines, the extract is formulated into appropriate dosage form like the conventional medicines.^{3,5} These includes solid dosage forms, semi-solid dosage forms, liquid dosage forms and aerosols as presented in Table 1.

Table 1: Some dosage forms of phytomedicines

S/N	Solid dosage forms	Semi-solid dosage forms	Liquid dosage forms	Aerosols
1	Powders	Creams	Fluid extracts	Powder inhalers
2	Dry extracts	Ointments	Infusions	Inhalation liquids
3	Tea bags	Pastes	Decoctions	
4	Granules	Salves	Tinctures	
5	Pills	Gels	Emulsions	
6	Tablets		Syrups	
7	Capsules		Medicated oils	

Advancement in drug delivery is not limited to conventional medicines as phytomedicines are now available in the form of novel delivery systems such as phytosomes.⁶ Phytosomes are formed by complexing natural or synthetic phospholipids with plant extract in organic solvents. Nanotechnology has also been used to enhance the stability, delivery and bioavailability of phytomedicines. Nano dosage forms of herbal materials include polymeric nanocapsules (nanospheres and nanocapsules), liposomes, proliposomes, solid lipid nanoparticles and nanoemulsions.⁷

It is important to note that about 25 % of conventional medicines are derived from plant materials. However, recent reports have shown that such formulations can possess some form of toxicity which could be generated from the plant, plant product or the formulation.^{8,9} The toxicity and adverse effects associated with herbal formulations have been identified as some of the major

challenges that can affect the progress of phytomedicines.¹⁰

Phytomedicines have always been criticized for having little information on their quality, safety and efficacy. This study aimed to aggregate scientific evidence on the availability, safety and efficacy of phytomedicines, to reveal the available methods for optimizing their quality and to intensify the need for their local production.

METHODS

About 1000 peer reviewed articles from 5 databases (Google scholar, Pubmed, Scopus, Web of Science and Science direct) were reviewed to extract relevant information on this subject matter. There was no restriction on literature search on safety and efficacy of phytomedicines since this is universal. However, the search on the availability of medicinal plants was limited to information on indigenous African plants since local

production is being highlighted. Articles which were essentially on the chemistry of the phytomedicines were excluded.

FINDINGS

Documentation of african medicinal plants

Medicinal plants, as a key component of biodiversity, have been used in traditional African medicine to provide herbal remedies for a variety of ailments in various African cultures, and the potency of these plants can be traced back to prehistoric times. In ancient times, humans relied on nature for food and medicine. Nature has served as a repository of diverse medicinal plants that humans await in times of illness. The use of medicinal plants is rooted in African history, cultural beliefs and religion; and this is accepted among various subcultures before the advent of colonialism.¹¹⁻¹⁶

African medicinal culture involves the application of knowledge of the medicinal potential of plants acquired through trial-and-error experiments, experience, and many years of careful observation passed down from generation to generation.¹¹ This knowledge exists among cultures, tribes and families in the form of local legends. In the preparation of phytomedicines, it has been noted that, depending on the individual recipe, all or parts of the plant can be used, such as the whole plant, seeds, bark, leaves, roots, flowers, stems and fruits.^{12,17}

Over 50,000 distinct species are known to occur in sub-Saharan Africa alone, and the continent is home to more than a quarter of recorded angiosperm taxa in the world. Of the known species, more than 25 % has been used for several centuries in traditional medicine for the prevention and treatment of diseases. Africa presents a veritable treasure of cultural and genetic resources, including medicinal plants. Its unique and diverse indigenous cultures have produced a rich heritage of traditional knowledge on the use of plants for healing, for communications with the gods, and for food. The enormous biodiversity in its tropical forests, savannas, veldts, and unique environments of sub-Saharan Africa is due to its peculiar geography.¹⁸ It has been suggested that it is the great latitudinal range that gives Africa an enormous variety of climates, and that this variability is responsible for the continent's extreme diversity of ecosystems and biodiversity.

The continent is estimated to have about 216,634,000 hectares of closed forest areas with a calculated annual loss of about 1 % due to deforestation. Africa's vegetation can be classified into several phytochoria, that is, regions within which a substantial proportion of the plants are endemic species. The classes are: (1) Mediterranean North Africa, (2) South Africa, (3) Tropical Africa, and (4) Madagascar. Within tropical Africa, there are (1) Forests; (2) Seasonal tropical vegetation (which consists of woodland, bus grassland, shrublands); (3) Deserts; (4) Montane and Afroalpine ecosystems; (5) wetlands (6) Lakes and (7) Coastal vegetation.

Most of the plants found in Africa are endemic to the continent, with the Republic of Madagascar having the highest rate of endemism, 82 %. The island contains over 12,000 species in its original forest areas, and 4,900 of these species are found only on that island. There is therefore an urgent need to document not only the uses but also the constituents and pharmacological activities of these plants. Over 5000 plants are known to be used for medicinal purposes in Africa, but only a few have been studied.¹²⁻¹⁸

African countries and institutions, including researchers have continued to document medicinal plants of importance as knowledge grows and new information emerge. In this respect, there exist the African Herbal Pharmacopeia,¹⁹ regional,^{20,21} as well as Pharmacopoeias of different African countries.^{20,22,23} Other reliable source of documented medicinal plants includes that of Iwu.¹⁸ In his book "Handbook of African Medicinal Plants", 2000 plants used in African traditional medicine have been documented. From the Alma-Ata Declaration (1978) to the Declaration of Astana (2018), and the re-affirmation in Mozambique, 2003, African heads of government have laid emphasis on development of herbal medicines, with establishment of institutions for phytomedicinal research and development being core. Several African countries have taken steps to actualize these declarations.²⁴ For example, Nigeria established an agency, Nigeria Natural Medicine Development Agency (NNMDA) which is responsible for among other things, the documentation of medicinal, aromatic and pesticidal plants (MAPPs). The agency has documented several MAPPs. It also has a Herbarium which at the moment holds 3,267 physical voucher specimens and 2,650 digitalized voucher specimens.²⁵ The work of Ogunwande *et al.*²⁶ also revealed the diversity of medicinal plants in Nigeria.

Determinants of safety and efficacy of phytomedicines

Phytomedicines have been perceived to be effective and safe because they are of natural origin hence their increased and wide use. However, this statement is not readily justified until scientific evidence emerges and certain knowledge gaps are then filled. Clinical efficacy studies must be conducted on herbal medicines in order to evaluate their effectiveness.

The safety and efficacy of phytomedicines largely depend on their quality which is why quality assurance and control are vital. This is largely dependent on the method of extraction, and on whether purification and isolation were carried-out or not. Lack of standardization in the production process and variation in methods of processing have significant effects on safety and efficacy of phytomedicines.^{27,28}

Plant materials contain various constituents some of which are known to be toxic.¹⁰ It is impossible to assume that herbal medicines are completely safe, though they may cause fewer adverse events than conventional medicines. The efficacy and safety of phytomedicines either positively or negatively are determined by the compounds they contain. Variation in content and proportions of active chemical components may exist in same plant species from different location.^{27,28}

Toxicity has been observed with the medicinal herbs (Ginseng, Ginkgo biloba) and poisonous herbs (Digitalis). For these group of herbs, knowledge of their dosage and rationale behind their use needs to be clearly defined. Several adverse effects have been associated with some of these phytomedicines hence the increased need for strict regulation of their use globally. Toxicity of phytomedicines most times usually arises from manufacturing procedure which could be due to wrong manufacturing method, contamination or wrong dosage.²⁹

The safety and efficacy of phytomedicines are also influenced by the dosage forms in which they are presented. For instance, liquid dosage forms are highly unstable and easily attacked by microbes because of the high water content affecting their safety and efficacy.

Research guidelines for evaluating safety and efficacy of phytomedicines

Due to the knowledge gap regarding scientific studies to prove the efficacy and safety of phytomedicines, the

World Health Organization produced a document on research guidelines to be used to evaluate the safety and efficacy of phytomedicines. The main goal is to ensure and promote the judicious and appropriate use of these preparations. The guidelines states that research into the safety and efficacy of herbal medicines can be in form of non-clinical studies or clinical trials. Animals can be used to evaluate the pharmacological and pharmacodynamic activity of phytomedicines. With regards to safety, various toxicity tests such as acute, long term, local and special tests can be utilised.³⁰ Efficacy studies conducted on phytomedicines could take the form of case reports, case series, animal studies and randomized clinical trials.

Categorisation of safety of phytomedicines

The safety of phytomedicines can be influenced by different factors. The guidelines of WHO provide the principles for assessing safety of phytomedicines based on contaminants and residues which could be in form of toxic metals and pesticide residues respectively. The guideline establishes limits for these contaminants and residues in phytomedicines.³¹

Apart from heavy metal composition of these phytomedicines, there could also be interaction with synthetic drugs. St John's wort is known to interfere with CYP 450 metabolizing enzymes; therefore, drugs that are substrate for this enzyme have the possibility of interacting with the phytomedicine.

Also, the safety of phytomedicines can be compromised when adulterated with pharmaceutical substances in order to increase their efficacy thereby leading to increased toxicity; for example, fenfluramine in a herbal slimming product. To combat the issue of adulteration and thereby guaranteeing the quality, safety and efficacy of herbal products, DNA barcoding and metabarcoding can be used to identify specific species in these complex herbal products.²⁹ Special precaution needs to be taken regarding the administration of herbal medicines in specific patient groups (elderly, paediatrics, pregnant and breastfeeding mothers).

Some manifestations of toxicity arising from the use of phytomedicines

Different types of toxicity have been observed with herbal formulations. For example, there have been reports that some Chinese herbal medicines cause

nephropathy; therefore, care must be taken with the consumption of these herbs.³² Toxicity related to phytomedicines could arise from substitution of one of

the ingredients with a more toxic one.³³ Some toxicity manifestations arising from the use of phytomedicines are shown in Table 2.

Table 2: Some manifestations of toxicity arising from the use of phytomedicines

S/N	Plant	Therapeutic use	Toxicity manifestation
1.	Yun-cai tea	Hyperlipidemia	Gastrointestinal adverse event ³⁴
2.	<i>Aristolochia spp,</i>	Inflammation, snake bite	Carcinogenicity
3.	<i>Ginkgo biloba</i>	Tinnitus and hearing loss	Carcinogenicity, allergic reactions, bleeding, genotoxicity
4.	<i>Piper methysticum</i>	Anxiety, insomnia	Hepatocellular damage ³⁵
5.	<i>Ephedra sinica</i>	Asthma, cold	CNS, cardiovascular and liver toxicity. ³⁶
6.	<i>Aconitum species</i>	Diabetes and stroke	Tachycardia and fibrillation
7.	<i>Tussilago farfara</i>	Cough	Liver cirrhosis and hepatic veno-occlusive disease ³⁶
8.	<i>Echinacea purpure</i>	Upper respiratory infections in children	Rashes ³⁷
9.	<i>Garlic (Allium sativum)</i>	Hypertension and hypercholesterolaemia	Epidural haematoma
10.	Ginseng	Diabetes, inflammation, anxiety	High blood pressure, agitation, insomnia and Stevens-Johnson syndrome. ³⁶
11.	Alfa alfa (<i>Medicago sativa</i>)	Homeopathy	Systemic lupus erythromatosus-like syndrome
12.	Ispaghul (<i>Plantago ovata</i>)	As laxative	Asthma and bronchial constriction
13.	Liquorice (<i>Glycyrrhiza glabra</i>)	Respiratory and gastrointestinal ailments	Sodium and water retention
14.	<i>Silybum marianum</i>	Liver cirrhosis, hepatitis	CNS and liver toxicity. ³⁶
15.	Yoyo Bitters®	Diabetes, hypertension, GIT disorders	Liver toxicity, excessive potassium loss predisposing to arrhythmias
16.	<i>Hypericum perforatum</i>	Anxiety, sleep disorders	Hypomania and palpitations. It is contraindicated in pregnancy due to its effect on the uterus. ³⁶

Some herbal remedies and their therapeutic uses

Different countries have different plants that are peculiar to them. For instance, *Artemisia annua* has been in use for ages in China for the management of malaria.³⁸ *Azadirachta indica* sometimes called neem, is originally from India and some part of the Southeast Asia but has spread widely and is now grown in the tropical and subtropical regions. It is used for different purposes.³⁹ In Nigeria, it is used for the treatment of malaria and skin infections. On the other hand, the 10 most commonly used phytomedicines in the United States are echinacea,

ginseng, *Ginkgo biloba*, *Allium sativum* (garlic), St John's wort, peppermint, ginger, soy, chamomile, kava kava. Out of these phytomedicines, Echinacea, ginseng, peppermint, ginger and chamomile do not have conclusive scientific studies relating to their efficacy. Soy has been shown to be ineffective in treatment of menopausal symptoms. However, extensive clinical trials have proven the effectiveness of garlic on lipid-lowering and its protective effect on the cardiovascular system.³³ Therapeutic uses of some phytomedicines are shown in Table 3.

Table 3: Therapeutic uses of some phytomedicines

S/N	Plant	Therapeutic use
1.	<i>Allium sativum</i>	Hyperlipidemia ³³
2.	<i>Jatropha curcas</i> , <i>Gossypium hirsutum</i> , <i>Physalis angulata</i> , <i>Delonix regia</i>	Malaria ³⁸
3.	<i>Radix echinacea</i>	Common cold
4.	<i>Hedera helix</i>	Bronchial inflammation ⁴⁰
5.	<i>Nigella sativa</i>	Asthma symptoms and pulmonary dysfunction
6.	<i>Andrographis paniculate</i>	Upper respiratory infections ³⁸
7.	<i>Cinnamomum zeylanicum</i> ,	Allergic rhinitis ⁴¹
8.	<i>Malpighia glabra</i>	Allergic rhinitis ⁴¹
9.	<i>Bidens Pilosa</i>	Allergic rhinitis ⁴¹
10.	<i>Ginkgo biloba</i>	Cancer, Alzheimer's disease.
11.	<i>T. angelica</i> herbal	As laxative
12.	Niprisan [®]	Sickle cell disease
13.	Ciklavit [®]	Sickle cell disease
14.	<i>W. ugandensis</i> bark	Dental ulcer
15.	<i>Alchornea glandulosa</i>	Gastric ulcer
16.	<i>Azadirachta indica</i>	Gastric ulcer
17.	<i>Angelica sinensis</i>	Gastric ulcer
18.	<i>Croton lechleri</i>	Gastric ulcer
19.	Tea tree oil	Oral care ⁴²
20.	Turmeric, aloe vera	Oral care ⁴²
21.	<i>S. indicus</i> extract	Plaque psoriasis ⁴³
22.	Viron [®] (herbal tablet formulation)	Hepatitis C infection
23.	Glucos Cut [®] (herbal tea consisting green tea, mulberry leaf, stevia, rooibos tea and <i>Gymnema sylvestre</i>)	Diabetes ⁴⁴
24.	Canephron [®] N	Cystitis, urinary tract infection ⁴⁵

Phytomedicines such as Ginkgo biloba have been implicated in the prevention and management of cancer. It has been observed that most patients on conventional cancer therapy still use herbs in an attempt to leave no stone unturned in their quest for healing. Also, patients use some herbs to alleviate the adverse effects observed with conventional therapies. In terms of safety, due to the narrow therapeutic index of some of these medicines, the likelihood of drug-herb interaction is increased. Therefore, oncologists managing patients on conventional anticancer treatment regimens need to be aware of possible herbal medicines patients may be taking. It is also critical that patients take those herbs that have been well proven to be effective in the treatment of cancer. Though studies have been done to show the safety and effectiveness of herbal medicines, robust clinical studies are required to substantiate claims. Clinical studies which showed positive results have been conducted on popular phytomedicines such as ginseng, feverfew, saw palmetto and chamomile, but more extensive double blind randomised clinical studies are required.

DISCUSSION

According to the report of Agrawa *et al.*,⁴² as many as 80 % of the world population depend on phytomedicine for their primary healthcare needs. Also, in the developed countries, plants are the source of more than 25 % of prescription and over-the-counter medicines.⁴² Hence, the production of indigenous medicines and the use of medicinal plants carry considerable economic benefits in the treatment of various diseases.

Safety and efficacy issues with phytomedicines are related to insufficient information, poor or lack of standardization and poor stability. The methods of improving their quality therefore must be considered in those directions. The following approaches can be employed to improve the safety and efficacy of phytomedicines:

1. Information

Sufficient information should be obtained before going into herbal formulation. The active ingredient must be investigated to determine appropriate method of extraction, purification, isolation and formulation. The stability profile must also be investigated so that appropriate measures will be taken to ensure the stability hence ensuring safety and efficacy.

2. Standardization

Standardization is key to optimizing safety and efficacy. For non-standardized preparations, accuracy of dosing cannot be guaranteed. There is either under or over-dosage. Use of under-dose will not elicit the desired effect while over-dose can lead to toxicity. Besides, the presence of undesired component in the formulation can also lead to toxic effect. The formulation must be standardized to contain a known amount of the active principle in a given quantity of the formulation.

3. Enhanced stability

Various approaches can be utilized in modifying the dosage form of phytomedicines in order to improve the stability. These include the use of plant polysaccharides as excipients in the formulations, the use of long chain fatty acids derived from plants, application of protein coating substances, and the use of aqueous soluble cellulose derivative to coat the herbal active in liquid preparations. Other approaches are: the use of viscosity enhancers such as xanthan gum, the use of chelating substances such as PVP, and the use of antioxidants.⁶

Phytosome formation is a recent technology that can be used to improve the stability of herbal products. Phytosome is a liposome-like structure formed by complexation of natural or synthetic phospholipids with herbal extract in organic solvents such as acetone using methods such as rotary evaporation process, solvent ether-injection process or anti-solvent precipitation process. Phytosome formation has been used for preparation of ginkgo flavonoids, gingoic acids and ginkgolides to enhance cognition improvement ability of the formulation.⁶

Nanotechnology is at the forefront in addressing stability problem of phytomedicines, hence optimizing the effectiveness of the formulation. An example is the formulation of nanoparticles of breviscapine (used for managing cardiovascular conditions); this approach is used to increase the half-life of this herbal active. Another application is the formulation of the anticancer agent Tripterygium wilfordi, as a liposome for enhanced stability. Formulation of microcapsules has also been used to enhance stability of phytomedicines.⁶

The high water content in liquid phytomedicine is one of the major factor responsible for their poor stability. Hence, any approach that will reduce the moisture content should improve the stability. Therefore, formulation of a phytomedicine as a semi-solid or solid is

a method of optimizing safety and efficacy as water is known to catalyse degradation which can lead to reduction in activity or formation of toxic product. Three different topical preparations (ointment, cream, gel) from the leaves of *Tridax procumbens* L. and nuts of *Areca catechu* L. have been prepared by Lokesh *et al.*³⁷

Solid dosage forms are generally more stable than semi-solid and liquid products. An anti-diabetic plant extract (*Ipomoea digitata*) has been formulated into tablets and evaluated for its biological/pharmacological activity. The formulation was done to present the phytomedicine in a dosage form that will contain a known amount of the herbal active with known a specified expected activity.⁴⁶ Fruit extract of *G. gnemon* has also been formulated into capsules and evaluated following standard procedures. The capsules passed weight uniformity test, a pointer to dosage uniformity.⁴⁷ Formulation as solid dosage form will go a long way in ensuring the quality and stability of phytomedicines.

In summary, the use of medicinal plants in the unprocessed forms like teas, powders, infusions and decoction is common but a vast majority have not been converted to standardized dosage forms. While roughly 25 % of modern prescriptions are plant-derived, majority of the 250,000 known plant species remain unavailable in commercial formulations.⁴⁸

CONCLUSION

Phytomedicines arguably are safer, more dependable, and have lesser side effects than conventional medicines; the reason being that, they are of natural origin, with most of the herbs serving as condiments or food for man and animals. They have found widespread application in human and animal health, despite the availability of conventional therapies, put full stop after the sentence. Many potent and novel compounds isolated from plants are still the drug of choice for various conditions like cancer, HIV et cetera. It is important that more stringent, robust and well-designed trials are conducted to assess safety and efficacy of phytomedicines. It is clear that our health system largely depends on phytomedicines. With African continent being endowed with medicinal plants, local production of phytomedicines in commercial formulations needs to be intensified so as to revive local pharmaceutical production.

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