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Chapter
Natural Does Not Mean Safe
Onyenmechi Johnson Afonne and Emeka Chinedu Ifediba

Abstract
Medicinal plants are rich sources of natural products, the principal constituents in herbal medicines, utilized for the treatment and prevention of diseases. High consumer expectations for health care, in the face of soaring cost of conventional pharmaceuticals, have popularized herbal medicines in different regions of the world. The consumption of these botanicals and their products has recently gained much impetus with the assumption that since these active principles in them are natural, they are, therefore, safe. Assertive as this idea could be, scrutinizing the perspectives on which it is premised is critical in minimizing probable risk on human health. Most plant parts are repositories of natural toxins, phytosteroids, and bioaccumulated toxicants, all of which are driven by natural processes. Besides intrinsic toxicity possessed by phytotoxins, some innocuous chemicals in medicinal plants can be biotransformed to toxic components. Some chemicals in medicinal plants that are of safety concerns include the endocrine-disrupting chemicals such as phytoestrogens, bisphenol A, and phthalates, among others. The persistent, bioaccumulative, and toxic metals have also been identified in medicinal plants. Some of these chemicals have been found to cause metabolic derangement and carcinogenicity. It is, therefore, imperative that linking natural products to safety should rather be empirical.

Keywords: natural, safe, phytotoxin, phytoestrogen, dioxin, toxic metals

1. Introduction
Herbal medicines are the mainstay of complementary or alternative medicine in most developing and some developed countries [1–3]. The use of herbal medicine in history and in different cultures was premised on the discovery of medicinal plants by trial and error, serendipity, or by the observatory science of zoopharmacognosis [4, 5]. Plants have been used as drug by the primitive man and are presently in high demand with increasing acceptability globally. Currently, the demand for plant-derived products has increased across the world with the Middle East, Latin America, Africa, and Asia accounting for greater than 85% of the populations predominantly relying on herbal medicine for their health care needs [1]. Medicinal plants are a variety of plants with medicinal properties in some or all of its parts. Parts that have prominently contributed to these properties include the seeds, root, leaf, fruit, skin, and flowers [6, 7]. The rich contents of phytochemicals in medicinal plants have provided the basis for their use in herbal medicines. The World Health Organization (WHO) had defined herbal medicines to include herbs, herbal materials, herbal preparations, and finished herbal products that contain, as active ingredients, parts
of plants, other plant materials, or combinations thereof [8]. The production of plant secondary metabolites (PSMs) is a common phenomenon in the plant kingdom. These chemicals include a wide range of compounds, such as alkaloids, saponins, flavonoids, anthraquinones, terpenoids, coumarins, lignans, polysaccharides, polypeptides, and proteins [9]. Plant secondary metabolites are known to possess diverse physiological roles. They act as signaling compounds to attract pollinators or seed dispersers and defense against threats such as microbes, insects, predators, and abiotic (radiation, temperature, and drought) stress [9–12]. The presence and diversity of these compounds in plant materials are inducible by natural selection (or processes) and new breeding methods that accentuate these protective/adaptive mechanisms [13]. Most of these products found in medicinal plants surely provide a diverse chemical space for drug discovery and management of many health conditions [14, 15]. The search for these products is attracting interest globally especially from Asia, Africa, or Latin America [16].

The curious expression that PSMs are natural products underpins the belief that as “natural” products, medicinal plants are “safe” or “safer” than conventional medicines. Indeed, some PSMs in medicinal plants are intrinsically toxic [17, 18] or are activated by enzyme systems in humans to toxic compounds [19]. There are also certain classes of PSMs with endocrine-disrupting capabilities [20–22]. This perspective that links natural to safety underscores core health issues in the use of herbal medicines. First, adverse effects resulting from the consumption of herbal medicines are usually not reported since consumers generally regard them as safe and, therefore, would not attribute symptoms to their use [23]. Second, the increased toxicity of conventional drugs when taken concomitantly with these “safe” products can also ensue. The abuse of these natural products is also inevitable, posing an incremental risk of toxicity since consumers usually care less about the quantity (dose) and frequency of herb intake. Besides PSMs, “natural processes,” such as adsorption and absorption, introduce environmental toxic substances into plant systems, thereby expanding the profile in the chemical composition of plant species. Environmental changes and pollution effects are major determinants in this regard and are critical in the definition of “nature” and “natural” and the safety attributed to their products. A subset of these xenobiotics is carcinogenic and can also cause metabolic derangement in humans on exposure beyond certain threshold. Regulation governing the production and sale of herbal medicines vary from one country to the other under regulatory categories, such as health foods, dietary supplements, natural health products, and functional foods [8]. These categorizations do not suggest safety in anyway but an approach for control and marketing. Therefore, leveraging on the nominal representation of the word “natural” in defining safety is not only ambiguous but also deceptive. Empirical data have shown that natural does not always mean safe in the premise of utility of medicinal plants for therapeutic consequences.

2. Naturalness of herb constituents

The concept of natural is contested by different perspectives cutting across different fields of learning. However, nature may be considered under different possible definitions: pristine ecology and life processes [24]. The definition of nature as pristine ecology is questionable given the successive cataclysmic evolution that gradually disequilibrated the ecology of the primitive man. Natural as life processes governed by
the laws of science (physics, chemistry, and biology) will provide a better platform for this discourse. Therefore, in the light of herbal medicines, the word “natural” suggests essentially that the product is comprised of ingredients produced by nature processes and not the work of man or interference from man. Excitingly, processes suggest activities and reactions that can be conditioned by the environment. The environmental conditions in which a plant grows influence its phytochemical composition and distribution [11, 13]. Second, anthropogenic activities contaminate air and land in addition to agricultural practices (irrigation, fertilization, and pest control), all of which can induce stress to the subsisting plant organisms [12]. The environment and its activities describe nature and could represent natural in this manner since it facilitates life processes. These processes, however, reflect an ecosystem situation and exposure that is far from that of a pristine environment. Safety of constituents of biological organisms, plants inclusive, in such environment should be considered with caution.

3. Safety of herbal constituents

3.1 Natural plant toxins (phytotoxin)

Phytotoxins are toxic plant secondary metabolites employed for defense by the plant kingdom and are also similar to anthropogenic micropollutants in terms of persistence and toxicity [25]. The distribution of these natural products is diverse but present in most plant families used for medicinal purposes [19, 26]. They also differ in biological function and toxicities. Common classes of phytotoxins include the alkaloids, cynogenic glycosides, saponins, furocoumarins, lectins, solanines, and chaconine [9]. Sources of some of these chemicals from plant species, such as *Atropa belladonna*, *Datura* spp., *Digitalis* spp., *Papaver somniferum*, and *Strophantus gratus*, are well documented [17, 27]. Apparently, no correlation exists between toxicity and chemical diversity [28], but these toxins might contribute to mixture toxicities and have the potential to overtake anthropogenic chemicals in their overall risk because of constant and ubiquitous production in plants. Since the presence and diversity of these compounds in plant materials are inducible by natural selection [13], medicinal plants with high local abundance often induced by human activity might be of great concern. Phytotoxins cause a variety of adverse effects and pose a serious health threat to man [25] ranging from acute poisoning to long-term health consequences. They mediate their biological activities through mechanisms such as covalent modification of proteins and DNA bases (e.g., furanocoumarins), nonlinam-covalent modification of proteins, and interaction with biomolecules [27]. The common adverse health effects of these phytotoxins in man had previously been reviewed [18, 29] (Table 1). Besides phytotoxins with intrinsic toxicity, the metabolic activation of certain inert classes of natural plant products can unmask potential toxicities. Most of these potential herbal toxins are mainly found in chemical classes, such as the pyrrolizidine alkaloids, furanoterpenoids, anthraquinones, bisbenzylisoquinolines, alkenylbenzenes, flavonoids, and alkaloids. Their activation is mainly mediated by hepatic cytochrome P450 and in few cases by intestinal bacteria leading to the generation of toxic and reactive metabolites capable of binding to cellular macromolecules/reduction systems with a consequent formation of intermediate complexes and resultant toxicities. A comprehensive review of the activation, mechanisms, and subsequent toxicity of these pretoxic compounds has recently been undertaken by Wang et al. [19] and summarized in Table 2.
### 3.2 Phytosteroids

Another class of specialized secondary plant metabolites, which can affect human health, is the phytosteroids. These compounds can potentially bind to steroid receptors in animals/humans and, thus, trigger or repress downstream receptor-mediated signaling events [22]. Phytosteroids, usually diverse in structures from endogenous steroid, can act as agonists, antagonists, or agents with both agonist/antagonist activities for steroid receptors [30, 31]. Some of these phytosteroids are the culprit of receptor promiscuity and may also interfere with steroid metabolizing enzymes, gifting this class of compounds a complex modulatory ability on the endocrine and reproductive systems [22]. A prominent subclass of phytosteroids is termed phytoestrogen because of their similarity to the female hormone, estrogen. These estrogen-like substances are the basis for the use of some plants for medicinal purposes [32] and include such classes as isoflavones (e.g., genistein, diadzein, glycitein, and biochanin), lignans (e.g., sesamin, enterodiol, and enterolactone), coumestans (e.g., coumestrol, plicadin, and wedelolactone), and certain classes of phytoalexins (e.g., medicarpin) (Figure 1) [33]. Phytoestrogens have been isolated and identified in herbal medicines [34, 35] for the relief of menopausal symptoms and the prevention of osteoporosis and heart diseases [36]. Apparently, they also improve serum triglycerides, total cholesterol, low-density lipoprotein, apolipoproteins A-1

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**Table 1.**

Some phytotoxins and common adverse effects.

<table>
<thead>
<tr>
<th>Class</th>
<th>Common sources</th>
<th>Common toxicity</th>
<th>Mechanism</th>
<th>Sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xanthin alkaloids</td>
<td>Bumexiaceae, Rubiaceae, Thesaceae</td>
<td>Stimulate heart rate, force of contraction, and cardiac arrhythmias at high concentration</td>
<td>Inhibits CAMP phosphodiesterase and adenosine receptors</td>
<td>[9, 29]</td>
</tr>
<tr>
<td>Furocoumarins</td>
<td>Leguminosae, Rutaceae, Apiaceae, Moraceae</td>
<td>Phytophotodermatitis</td>
<td>DNA alkylation</td>
<td>[9, 27]</td>
</tr>
<tr>
<td>Lectin proteins</td>
<td>Leguminosae</td>
<td>Interferences with digestion and absorption of nutrients</td>
<td>Bind to cell surface</td>
<td>[9, 27]</td>
</tr>
<tr>
<td>Cyanogenic glycosides</td>
<td>Leguminosae, Gramineeneae, Raucoace</td>
<td>Diarrhea, convulsion, death in severe case of large acute exposure</td>
<td>HCN produced poisons mitochondrial respiratory chain</td>
<td>[27, 29]</td>
</tr>
<tr>
<td>Solanine and chaconine</td>
<td>Solanaceae</td>
<td>Hallucinations, hypothermia, fever</td>
<td>Reversible inhibition of cholinesterase</td>
<td>[9, 29]</td>
</tr>
<tr>
<td>Sesquiterpen lactones</td>
<td>Asteraceae, Convolvulaceae, Rutaceae, Umbellifera</td>
<td>May be genotoxic</td>
<td>DNA oxidation</td>
<td>[27, 29]</td>
</tr>
<tr>
<td>Saponins</td>
<td>Araliaceae, Fabaceae, Plantaginaceae, Scrophulariaceae, Solanaceae</td>
<td>Diarrhea, excessive salivation</td>
<td>Complex membrane, cholesterol</td>
<td>[27, 29]</td>
</tr>
</tbody>
</table>

HCN, hydrocyanic acid; cAMP, cyclic adenosine monophosphate.
Despite these benefits, animal data had also revealed that phytoestrogens have a wide range of adverse molecular, cellular, behavioral, developmental, and reproductive effects at doses and plasma concentrations comparable to that in humans [20, 36, 38, 39]. Based on the estrogenic potential of phytoestrogens, exposure can disturb normal sexual differentiation in fetus and cause menstrual disturbances in females or low sperm counts in males. Owing to the potential interactions between phytoestrogens and the thyroid gland, it is possible that the thyroid function of hypothyroid individuals consuming high levels of phytoestrogen- or goitrogen-rich foodstuffs and supplements may be adversely affected [22]. Exposure to phytoestrogens may have a modest adverse effect on carotid intima media thickness (CIMT) progression particularly in postmenopausal women at an increased risk of developing atherosclerosis [37]. The harmful effects of phytoestrogens is a subject of scientific contestation; however, these effects depend on the exposure (type, amount consumed, and bioavailability), ethnicity, hormonal status (age and sex and physiological condition), and health status of the consumer [33]. Besides the phytoestrogens, ligands for receptors of hormones, such as progesterone, thyroid, and gluccocorticoids (Figure 2), have also been identified in botanicals [21, 22, 40]. Effects from phytoprogestins (e.g., apigenin), phytoandrogens (e.g., drupanol), and phytocorticoids (e.g., ginsenoside) in medicinal plants are also gaining attention. The promiscuity of these plant-sourced ligands for steroid receptors have been
Figure 1.
Structural classes of phytoestrogens. Source: Domínguez-López et al. [33].

Figure 2.
Other examples of phytosteroids. Source: Dean et al. [22].
reported [22, 41] and have the potential to precipitate side effects leading to cardiovascular disease, stroke, water retention, and weight gain.

3.3 Bioaccumulated toxicants

The abuse of the natural ecosystem by a massive use of materials and energy to meet the demands of the world’s growing population has led to a continuous and significant contamination of water, soil, and air. Industrial and agricultural activities are hugely responsible for the release of millions of tons of chemicals known as persistent, bioaccumulative, and toxic (PBT) into the environment. The interactional forces driving the relationship between the three environmental compartments (water, soil, and air) determine the fate of these pollutants, which undoubtedly have become part of nature. Medicinal plants grown in contaminated areas are usually susceptible to concentrating PBT chemicals. Dioxin, dioxin-like polychlorinated biphenyls (PCBs), some indicator PCBs [42, 43], metals [44–46], and phthalates [47–49], among others, are common environmental pollutants that can accumulate in plants in substantial and health-threatening quantities. Exposure to dioxins and dioxin-like substances has been associated with an avalanche of toxic effects during developmental stages, immuno-toxicity, and adverse changes in thyroid and steroid hormones and also in reproductive functions [43]. Toxic metals found in botanicals may pose low health risk in one dose of herbal preparations [50] but can have a significant contribution to total body heavy metal burden [51, 52]. Major threats to human health from heavy metals are commonly associated with exposure to lead, cadmium, mercury, and arsenic [53] and have been linked to indicators such as decreased immunity, cardiac dysfunction, fetal malformation, and impaired psychosocial and neurological behavior [52]. Phthalates, globally used as plasticizers readily accumulate in medicinal plants [47, 48], have been found to be potent endocrine disruptors. In addition to endocrine-disrupting abilities, phthalates also possessed teratogenicity, carcinogenicity, and mutagenicity effects [54, 55]. Other toxicants with bioaccumulative capacities in medicinal plants abound. Some of these agents can bind covalently to enzymes and induce the production of reactive oxygen species (ROS), thus leading to negative health effects in humans [56].

4. Naturalness and herbal processing

The preparation of herbal medicines from medicinal plants requires processes such as boiling, roasting, squeezing, and soaking [7, 57]. This is believed to mitigate exaggerated pharmacological actions, alleviate side effects, modify energy properties, mask disagreeable odors, or prolong the shelf life of crude herbs [58]. Herbal processing has been leveraged most of the times as detoxifying processes important for those herbs that are known to contain toxic or undesirable chemical components [59]. For example, steaming and frying may degrade heat-sensitive toxic, while fermentation and aging may result in enzymatic degradation of the toxic ingredients. Despite these positive implications of processing, such practices may also uncover a type of metabolite-deficiency-induced toxicity since the pharmacological potencies of herbal medicinal preparations had been touted as one served by synergistic interactions of disparate constituents in an extract [60, 61]. Adjuvants are also often added to enhance therapeutic effects or minimize drug toxicity, thereby broadening the spectrum of clinical application of the processed drugs. Commonly used adjuvants include vinegar, honey, wine, brine, ginger juice,
bran, and rice [58, 62]. For example, according to Li et al. [63] approximately 19.4% adverse events, associated with traditional Chinese medicine use between 1949 and 2008 in China, are reported to be ascribable to improper processing. It is believed that adjuvants participate in chemical or physical transformation that improves pharmacological effects, or alter the pharmacokinetic behavior, to provide an enhanced therapeutic effect or counteract drug toxicity [58]. Therefore, concoction, decoction, infusion, and homogenization, among others, are processes that can alter the natural constituents of medicinal plants and thereby introduce a twist in this concept of “natural.”

5. Discussion

The safety of medicinal plants has been enmeshed in scientific controversies. While the promoters of “natural is safe” paradigm persisted, different authors had previously justified why natural does not really mean safe in the context of phytotherapy. Most contributions in this regard presented evidence-based toxicity bordering on inherent toxicity of plant constituents [64–66] and herbal–drug interactions [23, 60]. However, the present paper premised this safety concerns on a definition of natural as a process influenced by the immediate habitat of the plant. The impact of the environment and processing procedures are indeed critical players of nature that determine the safety of medicinal plants. However, the general consensus by all authors is that some popular medicinal plant materials contain harmful substances, which may be classified into phytotoxins, phytosteroids, and bioaccumulated toxicants.

6. Conclusion

The folkloric use of medicinal plants has been justified by their constituents of active principles. However, the safety attributable to these natural products is overestimated. There are harmful substances found in plant materials as a result of natural processes. Unfortunately, these processes are reflecting an ecosystem situation and exposure that is far from that of a pristine environment. However, these facts seem to be overshadowed by the views of the “naturalists” who understand nature as pristine, pure, and harmless. Exposure to these natural toxins through herbal preparations and its attendant risks to human health may surge higher under this assumption that if a compound is natural, it is automatically safe. Caution should, therefore, be taken in the use of medicinal plants for treatment of various health conditions against the backdrop of poor regulation of herbal medicines.

We recommend the scientific determination of the safety profile of medicinal plants before use in therapy. In addition, appropriate regulatory agencies should intensify the monitoring of these phytomedicines to ascertain that they meet set regulatory standards, as their being natural does not mean being safe.

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Conflict of interest

The authors declare no conflict of interest.

Author details

Onyenmechi Johnson Afonne* and Emeka Chinedu Ifediba
Nnamdi Azikiwe University, Awka, Nigeria

*Address all correspondence to: oj.afonne@unizik.edu.ng
References


[41] Austin JR, Kirkpatrick BJ, Rodríguez RR, Johnson ME, Lantvit DD, Burdette JE. Baicalein is a phytohormone that signals through the progesterone and glucocorticoid receptors. Hormones and Cancer. 2020;11:97-110


[43] Olatungi OS. Evaluation of selected polychlorinated...
biphenyls (PCBs) congeners and dichlorodiphenyltrichloroethane (DDT) in fresh root and leafy vegetables using GC–MS. Scientific Reports. 2019;9(538):1-10. DOI: 10.1038/s41598-018-36996-8


[57] Alebie G, Urga B, Worku A. Systematic review on traditional medicinal plants used for the treatment of malaria in Ethiopia: Trends and perspectives. Malaria


