Future Trend to Replace Chemical Products with Nutraceutical Food / Feed Additive: A Mini Review

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ABSTRACT
Since thousands of years, herbal products were used for medical purposes in old cultures. The present trend to re-discover the medical potential of herbs started to grow with the general awareness of the medical hazards of several chemical pharmaceutical preparations. Similarly, for several decades, antibiotics, Coccidiostat and other chemical feed additives were massively used in animal husbandry. However, due to their negative impact on consumer health, they were banned in many countries. The present work discusses some natural alternative available for use in human and veterinary medical fields. The number of commercially available herbal products increases rapidly in the markets worldwide and are expected to overtake the number of pharmaceuticals of chemical origin in food sector in the future.

Keywords: Coccidiostat, Disease control, Herbal, Nutraceutical, pharmaceuticals.

INTRODUCTION
In traditional medicine of old cultures like Egypt, China, India, and Greece, the use of medical plants to control human and animal diseases was well established (El-Sayed and Kamel, 2021). The cumulative experience over decades and centuries provides us with thousands of herbs/foodstuffs that possess medical/health benefits (called nutraceuticals). These include plant active substances (plant secondary metabolites) such as alkaloids, polyphenols, steroidal compounds (sapoines), glycosides, aromatic compounds (alcohols, ketones, etheric oils), flavonoids, in addition to trace elements, vitamins and minerals (Othman et al., 2019; El-Sayed et al., 2021a). One of the most commonly used herbs is garlic which was and still being commonly used in herbal medicine due to its high content of organosulfur compound mainly Allicin (S-allyl-L-propene thiosulfinate).

Allicin is a potent anti-inflammatory, antibacterial, antioxidant, and immunostimulant substance (Frankic et al., 2009; Alam et al., 2018), and broccoli is rich in sulforaphane, used for the prevention of cancer and atherosclerosis, and for the treatment of Alzheimer’s disease, and the improvement of the situation of autism. Table 1 is presenting other herbs which are also known to be potent antioxidants such as genistein (present in soybeans), epigallocatechin (green tea), resveratrol (grapes), melatonin (grapes and nuts), curcumin (Curcuma), indole (cruciferous vegetables), lycopene (grapefruits), and garcinol (Garcinia indica fruit) (El-Sayed et al., 2021a).

However, the use of herbal medications became less popular in the last century with the development of chemical pharmaceuticals. This is attributed to many factors related to the vegetation ecology such as the differences in the concentration of secondary plant metabolites in response to differences in water & soil nature, climatic conditions (temperature & humidity), altitude, subspecies of the used herb, method of extraction, harvesting & storage conditions. Moreover, the presence of several active ingredients in one plant complicates the complete understanding of the mechanism of action and interactions of herbal preparations. Furthermore, in addition to the previously mentioned factors, the inactivation of several active substances by light or the short shelf life of volatile & essential oils all these factors favoured the use of chemical substances (Soni et al., 2015; Zhao et al., 2016; Yang et al., 2018).
Table 1: Examples for investigated nutraceuticals which exert their action via epigenetic modulations:

<table>
<thead>
<tr>
<th>Herbal Sources</th>
<th>Nutraceutical Active ingredient</th>
<th>Medical Effects</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leguminous plant foods</td>
<td>Genistein</td>
<td>antioxidant, anti-cancer, improve bone health, antilipogenic, hepato - protector</td>
<td>(Borradaile et al., 2002; Reinwald et al., 2010; Paul et al., 2017; Hanedan Uslu et al., 2019).</td>
</tr>
<tr>
<td>Grapes, nuts, pepper, tomato, germinated seeds, soybean</td>
<td>Melatonin</td>
<td>antioxidant, hepato -protector, anti-inflammatory</td>
<td>(Meng et al., 2017; Hanedan Uslu et al., 2019).</td>
</tr>
<tr>
<td>Red clover, soy, alfalfa sprouts, Cicer arietinum, peanuts, chickpea</td>
<td>Biochanin A</td>
<td>antioxidant, anti-cancer, neuro-protective, A prevents adipogenesis, anti-bacteria for healthy bone formation</td>
<td>(Su et al., 2013; Hanski et al., 2014)</td>
</tr>
<tr>
<td>Curcuma longa</td>
<td>curcumin</td>
<td>Antioxidant, immunomodulator, anti-inflammatory, anti-cancer, protective effect against chemotherapy induced side effects</td>
<td>(Catanzaro et al., 2018; Liu et al., 2018; Akter et al., 2019).</td>
</tr>
<tr>
<td>Echinacea purpurea, E. pallida or E. angustifolia</td>
<td>caffeic acid derivatives (phenolic compounds)</td>
<td>immunomodulator</td>
<td>(Catanzaro et al., 2018)</td>
</tr>
<tr>
<td>Green / white tea</td>
<td>epigallocatechin-3-gallate</td>
<td>Hepato-protector, anti-atherogenic, anti-oxidant, anti-cancer</td>
<td>(Pastoriza et al., 2017; Li et al., 2018; Rangi et al., 2018).</td>
</tr>
<tr>
<td>Cruciferous vegetables</td>
<td>Indole-3-carbinol</td>
<td>Antioxidant, hepato-protector, anti-atherogenic, anti-inflammatory, anti-arthritic, anti-cancer</td>
<td>(Lee et al., 2018).</td>
</tr>
<tr>
<td>Cruciferous vegetables (rutabaga, turnip, Brussels, broccoli, cabbage, sprouts, cauliflower, collard greens, kale, radish)</td>
<td>3,3'-diindolylmethane</td>
<td>Antioxidant, anti-angiogenic, anti-cancer, treatment of septic cardiomyopathy and side effects induced by irradiation therapy., reno-protective</td>
<td>(Lanza-Jacoby and Cheng, 2018; Xia et al., 2018; Lu et al., 2019).</td>
</tr>
<tr>
<td>Cruciferous vegetables such as broccoli, Brussels sprouts or cabbages in addition to papaya seeds, moringa,</td>
<td>Benzy! isothiocyanate</td>
<td>Antioxidant, anti-cancer, prevents obesity / fatty liver, and insulin resistance</td>
<td>(Alsanea &amp; Liu, 2017).</td>
</tr>
<tr>
<td>Cruciferous vegetables such as broccoli, Brussels sprouts or cabbages</td>
<td>Sulfuraphane</td>
<td>anti-cancer, anti-Helicobacter activity, prevents Alzheimer's Disease, protects from cardiovascular and neurodegenerative diseases and diabetes, reduces signs of Autism</td>
<td>(Kim &amp; Park, 2016; Yang et al., 2016; Lynch et al., 2017).</td>
</tr>
<tr>
<td>Grapes, Vitis vinifera, labrusca, mulberries, peanuts.</td>
<td>Resveratrol</td>
<td>Antioxidant, anti-atherogenic, anti-cancer, For the treatment of neurological disorders, cardiovascular diseases, skin disorders, metabolic diseases (obesity, Diabetes and non-alcoholic fatty liver disease)</td>
<td>(Markus and Morris, 2008; Ndiaye et al., 2011; Berman et al., 2017; Kim et al., 2017).</td>
</tr>
<tr>
<td>Tomatoes and other red fruits / vegetables (red grapefruits, red carrots, guava watermelons, papayas)</td>
<td>Lycopene</td>
<td>Antioxidant, protect cardiovascular system (antiatherosclerotic, anti-hypertensive, protective endothelial effects, antioxidant, anti-inflammatory, anti-apoptotic.</td>
<td>(Mozos et al., 2018)).</td>
</tr>
</tbody>
</table>
Another reason why the use of herbal preparations became less popular is the lack of understanding of their mode of action which remains unknown and needs to be elucidated in most herbal products. There are many reasons for this in opposite to chemical preparations. For instance, while conventional drugs are prepared and studied as single agents, herbal preparations contain several plant metabolites which exert their effect in combination or synergistic way (Bhikha and Glynn 2018).

Herbal products can exert their effect directly through the modulation of epigenomic activities, or indirectly through their effect on microbiome (prebiotic effect). For instance, microbial metabolites such as short chain fatty acids (SCFAs) are microbial by-products of ingested fibres. The SCFAs can support the mucosal immune response in the gut, utilized as energy source by intestinal epithelium, regulate the gut motility and reduce local inflammation by downregulating responsible genes (El-Sayed et al., 2021a).

The diet has a great influence on the naturally inhabiting micro-organisms (the gut microbiota). Their number and composition of change continuously in response to the nutritional status and certain medications. As an example, receiving high doses of antibiotics or changes in the dietary life style will dramatically change the number and composition of gut microbiome (El-Sayed et al., 2021b).

At present, due to the growing interest in phytogenic feed additives to replace chemicals, several herbal commercial products became available for therapeutic and prophylactic purposes. New technologies enabled the exact estimation of the content of the active ingredients. Presently, at least 25% of all drugs prescribed worldwide have a herbal origin (Rastogi et al., 2015). The growing interest in green farming and to replace the chemical products with natural product has many reasons such as the legal restrictions aiming to ban using antibiotics as feed additive growth promoter, growing resistance of pathogens against antibiotics and coccidiostats, the
chemical residues in the feed which harmfully affect the health of consumer, herbal products do not need withdrawal time as in most chemical preparations, the high safety of herbal products on animal health, and finally the absence of negative effect on the environment as many chemicals will be later excreted in manure to the environment to pollute soil and ground water (Rastogi et al., 2015; Mund et al., 2017; Okocha et al., 2018). While, some commercial products contain herb extracts, many manufacturers prefer to use the whole plant parts to supply the consumer with the full spectrum of the valuable active ingredients in the herb which usually interact in a synergistic way together (Rasoanaivo et al., 2011). For instance, the antimicrobial effect of Juglans regia (walnut) and Camellia sinensis (tea plant, tea shrub) increases when both substances are combined and can even eliminate multiple-resistance bacteria (Farooqui et al., 2015). Similarly, the antioxidant and anti-inflammatory effect of curcumin clearly increases when mixed with capsaicin (Setiawan et al., 2021).

Moreover, the involvement of many plants in one product aims usually to exert the required effect via several mode of actions and to overcome possible development of resistances (Rasoanaivo et al., 2011). In addition, mixing several plants together with the same effect and synergetic mode of actions in one product avoids the use of high amounts from one single plant in order to provide the same potential of the therapeutic effect. The use of a single plant or a selected part or a plant in large amounts not only enhances the development of resistance (as it has only one mode of action compared with multiple modes of actions upon using several plants) but may also to refuse the feed and change in the taste of the milk due to the excretion of plant metabolites in the milk. This can be seen when using the leaves of neem tree as immunostimulant or as growth promotor in cattle (Joint, 2006; Lakhani et al., 2019).

1. Herbal products in human medicine:

At least 15,000-20,000 herbs are known for their therapeutic properties in India (Bedi et al., 2016). They are mainly used to protect the heart, kidney, liver and nervous system from pathological disorders. Other plants can be used to treat infectious diseases as parasitic infestation or metabolic disorders such as diabetes type 2. The fields of their application include different ways. Firstly, the protection of heart (cardio-protective) (e.g. the herbs diosgenin, isoflavones, sulforaphane, carotinized, catechin, and quercetin) (Shah et al., 2019). Second, by supporting of the kidney functions (Renoprotectors). The old Chinese medical school used the roots of Astragalus membranaceus or Astragalus Mongholicus to treat renal disorders. Recent research revealed the presence of than 60 medical components in the plant roots (Zhong et al., 2013). Thirdly, supporting liver performance (hepato-protectors). Herbs including Silymarin (Silybum marianum or milk thistle), Andrographis paniculata, Solanum nigrum, Ocimum sanctum, and Phyllanthus niruri are the most commonly used herbal hepato-protectors worldwide. Their ability to revitalize exhausted liver cells is well documented (Saller et al., 2001; Pradhan and Girish, 2006; Bedi et al., 2016). Fourthly, Neuroprotective herbs such as Tianma (Gastrodia elata Blume) can be applied either to support patients following stroke or to improve the general performance of the nervous system (Kim, 2005; Manavalan et al., 2012). Fifthly, other herbal products such as origanum majorana, ferula persica wild, paconia officinalis, ferula gummosa bois, lavandula stoechas, cedrus deodara loudon, ferula asafoetida, caesalpinia bonduccella roxb, bryonia alba, cuscuta epithymum murray, and coriandrum sativum are characterized by their anticonvulsant effects and therefore can be used as Antiepileptics (Liu et al., 2017).

Sixthly, for the treatment of parasitic infestation, in sub-Saharan African countries, several herbs are used to treat malaria infestation including Tapinanthus dodoneifolius, Lophira lanceolata, Combretum collinum, Anthocleista nobilis, Celtis integrifolia, Ficus capræfolia, Oppilia celtidifolia, Securinega virosa, Terminalia avicenoides, and Cordia myxa. Others are common for the treatment of Trypanosomiasis such as (Striga spp., Lannea kerstingii, Cassytha spp, Securidaca longepedunculata, Terminalia avicenoides, Anchomanes diffornis, Parkia clappertonianna, Khaya senegalensis, and Pilostigma reticulatum), or against Schistosomiasis (e.g. Solanum nodiflorum, Apodytes dimidiata, Swartzia madagascariensis, Balanites maughamii, B. aegyptiaca, Combretum imberbe, C. molle, Warburgia salutaris, W. ugandensis, Uclea natalensis, Jatropha curcas, Sapindus saponaria, Gardenia thunbergia, Phytolacca dodecandra, and Berkheya speciosa) (Mwangi et al., 2017). Seventhly, supporting the urogenital system as diuretic such as amatymbica Eckl. & Zeyh., Carum carvi L., Coriandrum sativum L., Foeniculum vulgare L., Foeniculum vulgare Mill, Petroserinum hortense Hoffm, Petroserinum sativum Hoffm, Steganotaenia araliaceae Hochst, Apocynum venetum L., Carissa edulis Vahl, Achyrocline satureioides DC., Artemisia thusula Cav., Bidens odorata Cav., Centaurea phyllocephala Boiss., Cichorium endivia L., Helichrysum ceras, Hieracium pilosella L., and Mikania glomerata Spreng (Wright et al., 2007), other herbs are known to have Antilithiatic activity (such as Kalanchoe pinnata and Rotula aquatica) (Gilhotra et al., ), and even for the treatment of prostatic hyperplasia in men by Pumpkin seed oil
and saw palmetto oil (Hong et al., 2009). Eighthly, helping patients suffering from metabolic disorders as Diabetes mellities Type 2 to recover their normal / physiological metabolic activities. Several herbal plants exert a potential hypoglycemic effect such as Bauhinia forficata, Gymnema sylvestre, Ricinus communis, Swertia punicea, Combretum micranthum, Sarcopoterium spinosum, Parinari excelsa, Vernonnia anthelmintica, Elephantopus scaber, and Liriotype spicata and therefore are used for the control of blood sugar level in traditional medicine (Rao et al., 2010).

Ninthly, herbal products were even found efficient in controlling tooth caries. Commercial neem and tea tree oil toothpastes could prevent the multiplication of caries inducing bacteria Lactobacillus casei, Candida albicans, and Streptococcus mutans (Srichan et al., 2021).

2. Applications in veterinary sector:

With the boom of research in the field of herbal medical feed additives, key companies like BIOMIN Holding GmbH (Austria), Delacon Biotechnik GmbH (Austria), Cargill Incorporated (USA), and Life Circle Nutrition AG (Switzerland) became the major global players in providing potential phytopharmaceutical feed additives and feed preparations. For instance, Herb-All COCC-X® (Life Circle Nutrition AG, Switzerland) provided better performance than chemical coccidiostats and could efficiently reduce the severity of the intestinal lesions and the number of sporulated oocysts in the dropping of the poultry. Moreover, the potency of Herb-All COCC-X® in controlling coccidial infection increased with time and there was no need for rotation (Fayed and Rüegge, 2022). The addition of herbal feed additives may aim to treat a present disease, increase production and farm profitability or control diseases and prevent their emerge in the herd. In addition, herbal feed additives can also be added to bind mycotoxins (e.g. green algae), as anti-oxidant agents (e.g. green tea), as stomachic to increase appetite (e.g. chilli), and to support liver (silymarin) (Surai, 2015).

2. 1. The therapeutic applications of herbs include:

Therapeutic application of herbs can be summerized as follow:
(1) antimicrobial activity (e.g. Azadirachta indica (neem plant) and Origanum vulgare) even against multiple resistant bacteria. The neem extract is commercially available as soap, oil, spray or capsules.
(2) support the digestion and anti-diarrhoea (e.g. Myristica fragrans (nutmeg), Elettaria caromomum (Caradamom), Coriandum sativum L (Coriander) and Cinnamomum zeylanicum (Cinnamon)) (Tipu et al., 2006). Commercial herbal anti-diarrheal preparations such as Diaroak®, Salcochek® (Ayurved Limited) and Herb-All GUT® (Life Circle Nutrition) are now available in the market and can be efficiently used to treat non-specific diarrhea in calves (Ranaut et al., 2018).
(3) liver support: Several plants are known for their hepatoprotection such as Boerhavienia diffusa, Silymarin, Yakrit Botus viz. Andrographis paniculata, Eclipta alba, Phyllanthus niruri, Tephrosia purpurea, and Picrorhiza kurroa. They support normal physiological functioning of liver and decrease the harmful effect of chemical feed contaminants as mycotoxins, or pesticides (Hadiya et al., 2010).
(4) anti-parasitic effect (anthelmintic and coccidiostats): Herbal anthelmintics are known since long time and are still in use in traditional medicine such as Allium sativum (Lillaceae), Acacia albida (Fabaceae), Adhatoda vesica (Acanthaceae), Alangium lamarkkii (Angliaceae), Albizia anhemlanticca, Artemisia mesatlantica (Asteraceae), Bixa orellana (Bixaceae), and Butea monosperma (Fabaceae) (Jain et al., 2013). Recently, commercial herbal coccidiostats like Herb-All COCC-X® (Holarrhena antidysenterica and Allium sativum) were developed. They showed more coccidiostat efficiency than chemical coccidiostats in poultry and rabbits (Jung et al., 2021; Fayed and Rüegge, 2022). The presence of a mixture of herbs in one commercial product is very important to prevent the development of resistance (Mushtaq et al., 2017). Similar results were achieved in another study where ZeeCox delivered the same anticoccidial effect as ionophores (Palavesam et al., 2021).
(5) Treatment of mastitis: As several herbal products possess antimicrobial potential, they were applied in mastitis therapy. The herbs can be applied topically or via intramammary infusion. They delivered superior results in comparison to antibiotics and could reduce the somatic cell count in milk (SCC) (Mushtaq et al., 2017).

At present commercial herbal products for the treatment of mastitis are available such as the intramammary infusion Phyto-Mast® (herbal IMM, Bovinity Health LLC, Narvon) (Mullen et al., 2014). The therapeutic application in veterinary field is also well documented. Treatment of mastitis in dairy cattle can be achieved by the topical application or intramammary infusion of several plants such as garlic, Taraxacum mongolicum, Viola patrinu, Scutellaria baicalensis, Foliium isatidis, Lonicera japonica, Angelica dahurica, Angelica dahurica, Captis chinensis, Phellodendron amurense, and Rheum officinale are also used for the treatment of bovine mastitis in old China (El-Sayed and Kamel, 2021). (6) stimulating innate immunity in

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farm animals (e.g. cinnamon (Cinnamomum cassia), mustard (Brassica juncea), dandelion (Taraxacum officinale), and safflower (Carthamus tinctorius)) (Lillehoj et al., 2018). Among the commonly used commercial herbal in the last years the immunostimulant Winters® (by PDN GmbH, Germany) which contains a large cocktail of essential oils including Anise, Eucalyptus, Ginger tincture, Oreganum oil, Peppermint oil, Rosmarin extract, Caraway oil, Tea tree oil, Thyme oil, Artichoke tincture, and Silybum marianum tincture (according to the homepage of manufacturer). (7) Treatment of non-infectious diseases such as urolithiasis especially in poultry. Supplementation of commercial products which consist of both herbal and inorganic ingredients such as Fetorin® could improve the redox status, renal function, immune and anti-inflammatory responses in diseased poultry (El-Sebai et al., 2021).

2. 2. Application for the increase of farm profitability:

In addition to their therapeutic potential, herbs can also be used to increase animal production, for instance herbal galactagogue are herbs which can be supplemented to increases milk production such as Cuminum cyminum (Cumin), Curcuma aromatica, Curcuma zeodharia, Curcuma mangga, Cysterus rotundus, Pulvaria tuberose, Withania somnifera, Arundo donax, Asparagus racemosus, Cissampelos pareira, Eclipta alba, Solanum nigrumon, Foeniculum vulgare, Ipomea digitata, Lepidium sativum, Polygonum convolvulaceum, Curcuma zeodharia, Curcuma mangga, Cysterus rotundus, Pulvaria tuberose, Withania somnifera, Arundo donax, Asparagus racemosus, Cissampelos pareira, Eclipta alba, Solanum nigrumon, Foeniculum vulgare, Ipomea digitata, Lepidium sativum, and Nigella sativa (Nurdin et al., 2011; Behera et al., 2013).

Moreover, herbal feed additives can be used as alternative of antibiotic growth promoters in feedlots and broilers. They improve feed conversion ratio (FCR), and body weight gain. Field trial reports carried out in Switzerland revealed that the herbal hepatoprotector Herb All LIVER® could not only protect the liver cells against the harmful effects of chemicals but could also aid in revitalization and detoxification of exhausted liver cells (Mahanta et al., 2016).

In poultry, herbal feed additives are added to increase egg production in laying hens. Traditional medical plants in China as A. membranaceus dried root (Radix Astragali), Salvia miltiorrhiza Bunge, and Cnidium monnieri fruit (Cnidii Fructus) are commonly used for this purpose (Xiao et al., 2019).

2. 3. Supplementation to prevent/ control diseases:

Commercial herbal products can also be supplemented to prevent or to decrease the prevalence of certain diseases in the farm. For instance, (1) herbal teat dips which are commonly used to control mastitis (e.g. Cinnatube (teat sealant, New AgriTech Enterprises, Locke) and Phyto-Mast (herbal IMM, Bovinity Health LLC, Narvon)) (Mullen et al., 2014). (2) Herbal insect repellents and insecticides: the most famous example worldwide is the neem tree. The use of insect repellents and insecticides helps to control insect-borne diseases in farm animals, prevents the loss of blood due to blood sucking insects, and decrease the negative effects of stress resulting from the insect bites (Tipu et al., 2006). (3) Herbal mycotoxin binders: while some herbal products can be used to support the liver cells and to minimize the effect of mycotoxins present in the feed, other commercial products tend to combine herbal extracts with non-organic mycotoxin binders such as Mycofix (Biomin GmbH) which combines (according to the manufacturer) inorganic substances (bentonite and diatomaceous earth), enzymes (fumzyme), yeast and living bacteria (Eubacterium strain BBSH 797) to maximize the binding potential (Pietri et al., 2009).

CONCLUSION

Since centuries, herbal medicine was used to treat man and animal diseases. However, herbal products lost their position due to several factors such as the improper standardization of their content of active ingredients. Recently, due to public health hazards, several countries started to restrict the use of certain pharmaceutical preparations in human medicine. Similarly, several chemical feed additives are banned to be used in farm animals worldwide for the same reason. Based on the cumulative experience in traditional medicine, current research focused on the construction of novel synergetic herbal formulations, and to develop -in parallel- advanced laboratory tools for their standardization. This, in turn, brought old herbal formulations back to life to provide an efficient alternative to chemical preparations. The current work describes the medical application of herbal products in human and veterinary medicine.

Declaration of Conflicting Interests

The authors revealed that there is no potential conflicts of interest.

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