Active Nature Based Ingredients for Drug Discovery with Pivotal Role of Clinical Efficacy: Review and Prospective

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Abstract: There is much clinical and scientific interest in finding among natural products additional active ingredients as sources that could help develop new nature-based drugs and assist conventional and herbal drugs currently available for treating human diseases. Previous and current nature based drugs were derived preferentially from plants including fungi, in addition to bacteria, and rarely also products obtained from animals or maritime sources like algae. Future approaches will likely focus on new drugs using mostly phytochemicals contained in plants known for their potential of therapeutic efficacy, studied as traditional herbal medicines including the traditional Chinese Medicine (TCM). As a cautionary, new herbal drugs will only be accepted by consumers and regulatory agencies if efficacy for certain well defined diseases has been established using randomized controlled trials (RCTs) and if severe adverse effects had not been observed, providing thereby a favorable profile of benefits over risks. Additional clinical research should consider tropical plants with their amazing diversity and availability in high numbers of different plants in tropical forests although concerns currently emerge that plant numbers may be reduced and diversity be impaired due to political, economic, and ecologic tropical forest mismanagement. Much attention also focused more recently on the Sustainable Development Goal 3 (SDG3) that supplements the 2030 UN Agenda by inspiring ideologies and implementation concerning global health and wellbeing. In conclusion and considering these goals, new drugs derived from natural products could help improve health conditions and maintain wellbeing.

Keywords: Herbs, Tropical plant diversity, Herbal therapy, Randomized controlled trials, Antioxidants, Reactive oxygen species, Polyphenols, Herbal Traditional Chinese Medicine, Traditional herbal medicine.

1. INTRODUCTION

Plants are multifaceted products of nature exhibiting a variety of important properties essential for wellbeing in humans. Examples of benefits include: (1) with their chlorophyll actions and under the governance of sunlight, plants help provide ecological balance in the world ultimately achieved by their uptake of CO_2 and release of O_2 [1]; (2) these processes are linked with the production of glucose and sucrose as calories containing in plants such as fruits, vegetables, or grain, welcomed by humans primarily as food stuff [2,3]; (3) a few other plants may produce phytochemicals with herbicidal properties that could inhibit competing plants and may facilitate the growing of grain supplying the world population with enough food [4-11]; (4) among the plants under consideration is the fungus *Cordyceps militaris* with its now isolated cordycepin and its newly discovered herbicidal property [12]; this discovery could be important in the future for the Sustainable Development Goals (SDGs) and as a potential plant-based novel alternative to the disputed glyphosate, whereby this fungus has a long tradition of safe use as TCM (Traditional Chinese Medicines), food, and dietary product preferentially in the US [12]; and finally (5) the large group of promising herbal medicines including traditional ones, which present a variety of interesting aspects including efficacy and adverse effects as shown with a few reports as examples [13-21].

Much attention focused more recently on the Sustainable Development Goal 3 (SDG3) that supplements the 2030 UN Agenda by inspiring ideologies and implementation concerning global health and wellbeing [22]. Considering these goals, new drugs derived from natural products could help improve health conditions and maintain wellbeing. The development of new herbal therapeutics for severe human diseases or minor ailments requires an established pharmaceutical industry and researchers devoted to search for new drugs assisting or replacing existing pharmaceuticals. Plants with their abundant phytochemicals as well as other natural products represent an excellent source for drug research and development (R & D). Intuition will help search for nature based new drugs to be tested in randomized clinical trials for their efficacy and possible adverse reactions.

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This report provides a personal review on the past and current situation of nature based drugs, highlights the prospective how new drugs can be developed from various natural sources with a good benefit: risk constellation, and encourages approaches of uncovering active ingredients that can best be achieved using positive results of therapy efficacy during the course of randomized controlled trials (RCTs). In addition, encouraging results of effectivity should then allow isolation of the active ingredients(s) to be further refined by chemical modification(s) in order to improve efficacy and reduce possible inherited adverse effects.

2. LITERATURE SEARCH AND SOURCE

The PubMed database was used to identify relevant publications for the following terms: nature based drugs; herbal medicines; traditional herbal medicines; herbal Traditional Chinese medicine; herbal drugs. Manual search completed the electronic search. Limited to English language, publications were analyzed for suitability of this opinion article. The search was completed on 24 March 2020. The final compilation consisted of original papers, consensus reports, and review articles. The most relevant publications were included in the reference list of this article.

3. DEFINITIONS

Products used for treatment of severe diseases or minor ailments in humans need a clear definition for reasons of clarity, to be outlined briefly.

3.1. Conventional Drugs

Worldwide, conventional drugs commonly consist of a single chemical, had carefully been evaluated by the manufacturer and critically been approved by regulatory agency prior to marketing to be used in humans for therapy of their diseases.

3.2. Herbal Drugs

Variably from one country to the other but popular in European countries, herbal drugs receive a similar evaluation as conventional drugs and a less stringent regulatory approval before they are marketed and used for minor diseases and ailments. Herbal drugs usually represent extracts from a single herb,

3.3. Unspecified Herbal Products

In many countries, abundant different herbal products are on the market, most of these are erroneously called herbal dietary supplements although they are not destined to supplement the normal food; variable stringent manufactural and regulatory restrictions apply to these herbal products, to be used mostly for disease prevention rather than its treatment. Applicable to most herbal products, ingredients commonly include several herbs as mixture and rarely consist of a single herb.

3.4. Traditional Herbal Medicines

Traditional herbal medicines refer to the long historical use of these herbal medicines, which often comprise mixtures of many crude herbal substances containing abundant plant chemicals. In most countries, regulatory surveillance is incomplete.

3.5. Herbal Medicines

In general, herbal medicines is largely used as term for all medicinal products made specifically from herbs and includes both, herbal drugs and traditional herbal medicines.

3.6. Nature Based Drugs from other Sources

Drugs made from various other natural products such as bacteria, animals, and marine products may present as additional cornerstones of clinical medicine and should benefit from regulatory attention and control similar to conventional and herbal drugs.

4. EXPECTATIONS

Expectations are high to find additional active ingredients for new nature based drug candidates [14,23-27]. In first line, patients will benefit from new effective nature based drugs, but drug R & D will be costly for the pharmaceutical industry and require high prices of the drugs to be paid by the patients and the cost covering governmental health systems or health insurances. As the drugs are derived from natural sources including living organisms, problems may emerge due to a risky reduction of plant diversity caused by destruction of tropical and other forest areas resulting from political, economic, and ecologic forest mismanagement. Marine sources may become more important for new drugs and require good quality of marine living conditions without risky water pollution by synthetic chemicals including plastic microparticles.

5. OVERVIEW OF LISTED PREVIOUS AND CURRENT NATURE BASED DRUGS

It is amazing how many drugs have been made or developed from living organisms, considering drugs

Table 1: Selection of Drugs Derived from Natural Products: Plants Excluding Fungi

Natural product as drug source	Phytochemical/ Drug name	Action/ Previous or current clinical use	Reference/ First author
Artemisia annua	Artemisinin	Malaria	Tu [26]
Atropa belladonna	Atropine Hyoscyamine Scopolamine	Muscarine-antagonist Spasmolytic agent	Balandrin [28] Calixto [29] Farnsworth [31] Siddiqui [37]
Camellia sinensis	Caffeine Theophylline	ZNS stimulant Bronchodilator	Farnsworth [31] Teschke [40]
Camptotheca acuminata	Camptothecin	Antitumor agent	Wall [42]
Catharanthus roseus (formerly *Vinca*)	Vinblastine Vincristine	Antitumor agent	Balandrin [28] Farnsworth [31] Yuan [43]
Chondrodendron tomentosum	Curare	Muscle relaxant agent	Balandrin [28] Calixto [29]
Cinchona spp.	Quinine Quinidine	Malaria Antiarrhythmic agent	Balandrin [28] Farnworth [31] Siddiqui [37] Thomford [41]
Convalleria majalis	Convallatoxin	Cardiac diseases	Farnsworth [31]
Colchicum autumnale	Colchicine	Antigout agent	Balandrin [28] Farnsworth [31] Siddiqui [37]
Digitalis lanata	Acetyl-Digoxin	Cardiac diseases	Balandrin [28] Farnsworth [31]
Digitalis purpurea	Digitoxin	Cardiac diseases	Farnsworth [31]
Ephedra sinica	Ephedrine	Sympathomimetic agent	Balandrin [28] Farnsworth [31]
Erythroxylum coca	Cocaine	Local anaesthetic agent	Balandrin [28] Farnsworth [31]
Mucuna deeringiana	L-Dopa	Anti-Parkinsonism agent	Farnsworth [31]
Papaver somniferum syn. *opium poppy*	Codeine Morphine Papaverine	Antitussive agent Analgesic agent Antispasmodic agent	Balandrin [28] Calixto [29] Siddiqui [38] Thomford [41]
Pilocarpus spp.	Pilocarpine	Parasympathomimetic agent	De Abreu [30]
Physostigma venenosum	Physostigmine	Cholinesterase inhibitor Parasympathomimetic agent	Balandrin [28] Farnsworth [31]
Piper methysticum	Kawain	Anxiolytic agent Tranquilizer	Farnsworth [31] Sarris [35,36] Teschke [38,39]
Podophyllum peltatum	Etoposide	Antitumor agent	Farnsworth [31]
Rauwolfia vomitoria	Reserpine	Antihypertensive agent	Balandrin [28] Loba [35] Siddiqui [37]

(Table 1). Continued.

Natural product as drug source	Phytochemical/ Drug name	Action/ Previous or current clinical use	Reference/ First author
Salix alba *Spiraea ulmaria*	Salicin, Aspirin Acetyl salicylic acid	Analgesic agent	Balandrin [28] Farnsworth [31] Koparde [32] Siddiqui [37]
Strophanthus gratus	Ouabain	Cardiac diseases	Farnsworth [31]
Taxus brevifolia syn. Pacific yew	Taxol Docetaxel Paclitaxel	Antitumor agent	Balandrin [28] Koparde [32] Thomford [41] Wall [42] Yuan [43]
Zingiber officinale (Ginger)	Gingerols	Antiemetic	Alamgir [27] Koparde [32] Lete [33]

that were previously and/or are currently on the market [23-25]. The success of new drugs is evidently the result of a good cooperation: Inspired by nature and refined by science. Indeed, the structure of many chemicals produced by nature had to be modified chemically in order to improve efficacy or eliminate risks of adverse effects.

To allow a better overview of nature based drugs, segments of specific natural sources are individually presented.

5.1. Plant Based Drugs

Most nature based drugs originated from phytochemicals found as ingredients of plants under clinical and scientific evaluation with focus on single specific chemicals (Table **1**) [26-43]. In some of these publications, interesting and exciting details are reported how active ingredients had been found in earlier times when sophisticated technical resources were absent. Discoveries emerged by chance and good luck, also in the course of scientific misfortunes, often outside of mainstream science, but mostly by intuition of devoted scientists and clinicians with their straight forward approaches. Needless to say, discoveries can be disappointing if the expected efficacy cannot be established in trials or major adverse reactions force removing drugs from the market. Besides these drawbacks, many drugs initially developed from active phytochemicals remain on the market and are successfully used for treating serious diseases with preference of malignancies (Table **1**). Herbal medicine received increasing attention with the discovery of *Artemisia annua* and the chemical Artemisinin as effective therapy of malaria, for which Youyou Tu was awarded with the Nobel prize for Physiology or Medicine in 2015 [26].

5.2. Fungi Based Drugs

As part of the large plant family, fungi also contain active chemicals from which herbal drugs are made (Table **2**) [27,29,32,37,41-48]. Respective drugs are mostly used as antitumor agents to treat patients with cancer, as agents for reduction of hypercholesterolemia known as effective statins, and as antibiotics for treatment of infectious diseases with Penicillin as the most known drug in the category of fungus related drug (Table **2**). Derivatives of Penicillin are important for infections caused by strains of bacteria resistant to Penicillin and considered as alternative therapy options [49]. This is a good example for partial or complete therapeutic failure of nature based medications, a problem known also for conventional drugs produced by chemical synthesis.

5.3. Bacteria Based Drugs

It is an interesting phenomenon that drugs derived from bacteria often function as therapeutic agents for bacterial infections, aside from other indications targeting immune related diseases or cancer (Table **3**) [27,29,41,48-54]. Among the antibiotic producing bacteria, the Streptomyces species is the most active agent (Table **3**).

5.4. Animal Based Drugs

Various animal species provide drugs for treatment of a broad disease spectrum (Table **4**) [28,54-58]. On

Table 2: Selection of Drugs Derived from Fungi as Natural Products

Natural product as drug source	Chemical/ Drug name	Action/ previous or current clinical use	Reference/ first author
Aspergillus giganteus	α-sarcin	Antitumor agent	Endo [45]
Aspergillus niger	Jawaharene	Antibiotic Antitumor agent	Das [44]
Aspergillus proliferans	Proliferin	Antibiotic Anti-Tuberculosis agent	Woappi [49]
Aspergillus terreus and other fungi	Simvastatin Lovastatin Mevacor Pravastatin Atorvastatin	Anti-Cholesterolaemic agent	Calixto [29] Langdon [48]
Cephalosporium acremonium	Cephalosporin	Antibiotic	Langdon [48]
Claviceps purpurea	Ergotamine Lysergic acid diethylamide (LSD)	Anti-Migraine agent Hallucinogen	Langdon [48]
Fusidium coccineum	Fusidic acid	Antibiotic	Langdon [48]
Glarea lozoyensis	Caspofungin	Antimycotic agent	Langdon [48]
Isaria sinclairii (anamorph) with *Cordyceps sinclarii* (teleomorph)	Fingolimod Myriocin	Multiple sclerosis	Langdon [48]
Lentinula (syn. Lentinus) edodes, *syn. Shiitake mushroom*	Lentinan	Anti-Cholesterolaemic agent	Langdon [48]
Monascus purpureus	Compactin Mevastatin	Anti-Cholesterolaemic agent	Langdon [48]
Penicillium citrinum	Compactin Mevastatin	Anti-Cholesterolaemic agent	Calixto [29] Endo [45,46] Langdon [27]
Penicillium griseofulvum	Griseofulvin	Antibiotic	Alamgir [27]
Penicillium notatum	Penicillin Erythromycin Clarithromycin Amphotericin B	Antibiotic	Alamgir [27] Calixto [29] Koparde [32] Langdon [48] Siddiqui [37] Thomford [41]
Penicillium stoloniferum	Mycophenolic acid	Immunosuppressive agent	Langdon [48]
Psilocybe mexicana	Psilocybin	Anti-Stress agent	Langdon [48]
Tolypocladium inflatum	Cyclosporine A	Immunosuppressive agent	Calixto [29] Langdon [48] Thomford [41]

Table 3: Selection of Previously and Currently Marketed Drugs Derived from Bacteria as Natural Products

Natural product as drug source	Chemical/ Drug name	Action/ previous or current clinical use	References/ First author
Actinomyces	Augmentin	Antibiotic	Langdon [48]
Bacillus (syn. *Paenibacillus) polymyxa*	Polymyxin B Colistin	Antibiotic	Hancock [51]
Bacillus subtilis	Bacitracin	Antibiotic	Hancock [51]
Micromonospora sp.	Gentamycin	Antibiotic	Alamgir [27]
Streptomyces aureofaciens	Tetracycline	Antibiotic	Thomford [41]
Streptomyces erythreus	Erythromycin	Antibiotic	Chevrette [50]
Streptomyces fradiae	Neomycin	Antibiotic	Alamgir [27]
Streptomyces griseus	Streptomycin	Antibiotic	Alamgir [27]
Streptomyces hygroscopius	Rapamycin Sirolimus	Antiarteriosclerosis Immunosuppressive	Liu [53]
Streptomyces (syn. Amycolatopsis) mediterranei	Rifamycin Rifampicin	Anti-Tuberculosis agent	Henry [52]
Streptomyces nimosis	Tetracycline	Antibiotic	Chevrette [50]
Streptomyces nodosus	Amphotericin B	Antibiotic	Chevrette [50]
Streptomyces peucetius	Doxorubicin	Antitumor	Thomford [41]
Streptomyces orientalis	Vancomycin	Antibiotic	Chevrette [50]
Streptomyces tenebrarius	Tobramycin	Antibiotic	Alamgir [27]
Streptomyces tsukubaensis (soil bacterium)	Tacrolimus Rapamycin Rifampicin	Immunosuppressive agent Anti-Tuberculosis agent	Calixto [29]
Streptomyces venezuelace	Chloramphenicol	Antibiotic	Alamgir [27]

top are hormones of animals to be used in humans as replacement therapeutics for missing hormones due to endocrine insufficiency leading to low or subnormal hormone levels measurable in the blood of affected patients, conditions that commonly help establish the correct diagnosis and provide respective hormone substitution. An exemption is the diabetes mellitus, diagnosed by increased blood glucose levels rather than by insulin measurements; early studies in animals identified low insulin production, findings that later allowed synthesis of insulin applicable as substitution therapy in patients with diabetes mellitus. For emergency treatment after bites from poisonous snakes respective lifesaving antitoxins are available prepared with the help of other animals (Table **4**). Therefore, animals facilitate treatment of some diseases in humans, but vice versa, animals have benefits from drugs established in humans that are also effective in animal diseases.

5.5. Marine Based Drugs

Drugs obtained from living marine organisms are mostly used for treating patients with cancer, but for some drugs more valid clinical trials are needed (Table **5**) [27,55,59-61]. Active ingredients derived from different algae species are in the pharmaceutical pipeline with drugs targeting cancer [59-61]. Considering algae with their active ingredients destined as possible drugs, some interesting aspects are under discussion [59]. It has correctly been outlined that the coexistence of several species of marine living organisms in their habitats of limited extent triggers their competition among each other, forcing sessile organisms such as algae to adopt chemical means in order to defend themselves against predation or overgrowth of competing species, or to subdue motile prey species for ingestion; for all these purposes, different chemical classes are synthetized powerful

Table 4: Selection of Previously and Currently Marketed Drugs Derived from Natural Products of Animals Excluding Marine Ones

Natural product as drug source	Chemical/ Drug name	Action/ Previous or current clinical use	References/ First author
Bothrops jararaca (Brazilian pit viper)	Captopril Enalapril	Antihypertensive agent	Balandrin [28] Bozoghlanian [55] Calixto [29]
Capra aegagrus hircus syn. Goat	Antithrombin	Anti-Coagulant agent	Bozoghlanian [55]
*Celosia argenta (*formerly *cristata)* syn. Rooster combs	Hyaluronic acid	Antiarthritic agent Wound repair agent Skin healing agent	Bozoghlanian [55]
Crotalus durissus terrificus syn. South American rattlesnake spp.	Crotamine	Antibiotic Antitumor agent	Bozoghlanian [55] Costa-Neto [56]
Epipedobates tricolor syn. South American poison dart frog	Tebanicline	Analgesic agent (trial)	Bozghlanian [55]
Heloderma suspectum (Reticulate Gila Monster)	Exenatide	Anti-Parkinsonism Antidiabetic agent	Bozoghlanian [55]
Hirudo medicinalis syn. Leech	Lepirudin	Antithrombotic agent (de-listed)	Bezoghlanian [55] Costa-Neto [56]
Mammals such as bear, bovine canine, porcine	Insulin Thyroid hormones Other hormones Heparin Ursodiol	Diabetes mellitus Thyroid diseases Various diseases Anti-Coagulant Cholelithiasis Primary biliary or sclerosing cholangitis	Bozoghlanian [55]
Leiurus quinquestriatus syn. Deathstalker scorpion	Clorotoxin	High-grade glioma (Phase II)	Bozoghlanian [55]
Reptiles (various)	Polyvalent antisnake venom	Antitoxin	Alamgir [27] Amin [54] Ferraz [57] WHO [58]
Sistrurus miliarius barbouri, syn. Rattlesnake	Eptifibatide	Antithrombotic agent	Bozoghlanian [55]

chemicals with great pharmacological potential [59]. Therefore, algae and other marine organisms represent a perfect tool of natural products ready to be tested as drugs for treating human diseases.

6. ACTIVE INGREDIENTS

6.1. General Considerations

Plants synthesize abundant structurally different metabolites [62] that might be further processed used eventually as drugs [28]. It is generally agreed that chemicals produced by living, chlorophyll containing terrestrial organisms like plants, or corresponding marine organisms like algae, can be classified as primary and secondary metabolites [28,59,62], whereby proteins and nucleic acids are generally not part of these categories [28]. Primary plant metabolites originate from a variety of cellular chemicals and their modifications occurring during plant growth; instead, secondary plant metabolites are derived from primary metabolites and are functionally more active as compared to primary plant metabolites. The high functional power of the secondary metabolites is the result of own defense mechanisms, attacks of competitors, and biotic stress, conditions that make secondary metabolites more valuable as potential drugs [28,59].

Much recent interest and speculation focused on plant antioxidants as well as the assumed role of reactive oxygen species (ROS) possibly triggering or perpetuating in humans a variety of diseases including cancer and degenerative disorders [63]. After

Table 5: Selection of Previously, Currently, and Potentially Marketed Drugs Derived from Natural Marine Products

Natural product as drug source	Chemical/ Drug name	Action/ Previous, current, or potential clinical use	References/ First author
Aplidium albicans syn. Sea squirt spp.	Aplidine	Antitumor agent	Bozoghlanian [55]
Bugula neritina (marine animal)	Bryostatins	Antitumor agent (experimental/ Phase II)	Alamgir [27]
Cephalosporium acremonium (maritime fungus)	Cephalostatinsa	Antibiotic	Alamgir [27]
Coho salmon	Calcitonin	Postmenopausal osteoporosis Hypercalcaemia Paget's disease	Bozoghlanian [55]
*Cryptotethya (*syn, *Tectitethya) crypta* syn. Caribbean sponge	Cytarabine Trabectedin Eribulin Brentuximab	Anti-Lymphoma agent	Bozoghlanian [55] Jimenez [60]
Discodermia dissoluta (marine sponge)	Discodermolide	Antitumor agent (experimental)	Alamgir [27]
Dolabella auricularia (marine gastropod mollusk)	Dolastatins	Antitumor agent (trial)	Alamgir [27]
Ecteinascida turbinata syn. Sea squirt spp.	Trabectedin	Antitumor agent	Bozoghlanian [55]
Eleutherobia sp. (coral)	Eleutherobin	Antitumor agent (experimental)	Alamgir [27]
Marine Algae (multiple species)	Multiple chemicals	Antitumor agents and others (all experimental)	Alves [59] Jimenez [60] Poopa [61]
Marine *Cyanobacterium Lyngbya majuscula*	Curacin A	Antitumor agent (experimental)	Alamgir [27]
Pufferfish	Tetrodotoxin	Analgesic (experimental)	Bozoghlanian [55]
Salmon	Protamine sulfate	Anti-Heparin agent	Bozoghlanian [55]

gastrointestinal uptake, it is speculated that plant antioxidants could attempt reducing or preventing organ injury through neutralizing reactive oxygen species (ROS), which might be generated in excess within living organisms. With respect to plant antioxidants, their two elements are often poorly differentiated from each other, namely plant antioxidant profiles and plant antioxidant activities that are mostly used as interchangeable terms and need clarification [63]: (1) the antioxidant profile is determined by the variety of polyphenols and usually quantified as mg polyphenols per 100 g fresh weight that describes the content of polyphenols of a plant part, and within the group of polyphenols, the most studied ones are flavonoids; (2) the antioxidant activity reflects the biological power, whereby herbal polyphenols modify as antioxidants various physiological and pathological parameters related to special targets in humans, poorly assessable in diseases because mostly evaluated using *in vitro* systems or experimental animal models with questionable valid translation of these data to humans.

6.2. Experimental Versus Human Studies

Active ingredients are commonly mentioned in titles of publications on herbal therapy without a clarifying association with human disease or therapy. In fact, many of these reports on active ingredients describe results, which are not derived from studies in sick or healthy humans. In order to avoid superfluous ambiguity, it is recommended that in future publications a clarifying statement is included regarding animal or human study. Alternatively, the title should have at the end a question mark if an interesting proposal is made from results based on an animal study but with uncertain transfer to humans [64].

6.3. Variability of Active Plant Ingredients

Plants commonly contain abundant different polyphenols, and their anti-oxidative and related properties are thus expected as is the large list of assumed benefits [63,64]. This list includes properties of lifespan extension and features of antiobesity,

antilipocyte, antipancreatic lipase, antidyslipidemia, antiatherosclerosis, antidiabetes, antihypertension, antitumor, and antioxidative properties [63,64]. In face of limited RCT availabilty in patients with defined diseases, claimed efficacy remains mostly elusive [17,40,43,63-76]. Consequently, a gap is evident between data from experimental plant studies and the real world of human conditions and diseases, considered as clinical challenges and worth to be illustrated with a few examples.

6.4. Special Clinical Challenges

Interactions of polyphenolic plants with human conditions including their diseases are complex and require tentative discussions because related evidence often is circumstantial because lack of respective studies. Well established and quantitatively verified by chemical analyses is only the high amount of polyphenols contained in many plants [63,64,77-83]. Concomitantly, hypotheses prevail that many human toxic, degenerative and chronic diseases may be triggered by ROS, but only a few of these are considered as perfect preventive or curative targets for plant polyphenols [84-101].

6.4.1. Longevity

There are speculations that In addition to genetic factors plant polyphenols could contribute to longevity, an interesting phenomenon observed in various countries and areas [63,64,95-98] including the Japanese Okinawa [64]. To overall disappointment, although some relationship between the use of polyphenolic plants and longevity can be assumed, a causal association could not validly be established [63]. Of course, this question is hardly to be assessed because the study group must be followed up for over several decades, likely without financial support by the pharmaceutical industry. In addition, a large number of individuals will have to be included in this cohort because the possible polyphenolic effect over the existing genetic factors may be small.

6.4.2. Cancer

A similar dilemma exists for ROS, polyphenolic plants, and human cancer prevention or treatment. It has been speculated that human carcinoma may be caused through metabolic interactions that lead to the generation of ROS [99-101]. Again, this thesis is difficult to evaluate in human cancer tissue and may vary from one cancer type to the other. A critical review evaluated clinical and pre-clinical studies based on polyphenol administration and led to the conclusion that controversial and contradictory prevailed, with overlap of cancer treatment and prevention seen as confounding factors [102]. Another review article summarized that evidence from epidemiological studies is inconsistent, especially when considering the results of prospective cohort studies [103].

6.5. Specific Plant Issues

Among the many natural products derived from plants and used for medicinal purposes, a few plants merit further consideration for general understanding and basic discussion. These are *Camellia sinensis* with its extracts, *Ginger officinale* including Ginger shell (*Alpinia zerumbet*), *Polygonum multiflorum*, and Piper methysticum.

6.5.1. Green Tea

Derived from leaves of *Camellia sinensis*, green tea is among the top of the worldwide appreciated beverages with a low risk of adverse events if consumed in usual amounts although rare liver injury has been reported [40]. Whether polyphenols derived from green tea as beverage are of benefit to the health is unlikely but still a matter of debate, because efficacy is mostly assumed from experimental data [40,65,66-76]. Therefore, green tea as beverage can be consumed, but health benefits are not to be expected [40]. Similarly, expectations improving efficacy by using green tea extracts (GTE) rather than the common green beverages were not fulfilled, especially regarding weight loss [40]. Instead, severe liver injury caused by GTE became a major clinical issue [91,104,105], leading to the advice not using the risky GTE [40].

6.5.2. Ginger

Ingredients derived from *Ginger officinale* [27,63,64,77] including Ginger shell (*Alpinia zerumbet*) [63,64,77] are of potential interest to be used as drugs. Both plants are edible and likely without health risks. Phytochemicals of *Alpinia zerumbet* interfere experimentally with fat cells, which might be useful to reduce fat and body weight, whereas results of other experimental studies suggest positive and promising effects of longevity, to be confirmed in humans using strict study protocols as outlined recently [64]. In Japan, with JIPAN Ginger® containing *Alpinia zerumbet* from Makise Medical Center in Osaka, a nonregistered herbal medicine is available, but clinical data are not provided according internet information [64].

6.5.3. Polygonum Multiflorum

Bioactive ingredients of *Polygonum multiflorum* Thund., PM in short, have well been described for this herbal TCM that is popular in China and included in the Chinese Pharmacopeia, but liver injury associated with its use is a major clinical issue [93,106-108]. In addition and associated with a lacking Cochrane report, valid results from RCTs are limited, and efficacy of PM in clinical settings has not been published [106]. Consequently, the use of PM cannot be recommended because the benefit; risk ratio is negative.

6.5.4. Kava

Extracts containing kavalactones and prepared from the rhizome of Kava (*Piper methysticum*) have a long history as an anxiolytic herb and as a regulatory approved herbal drug in many European countries, but in Europe the herbal drug was banned due to discussions around liver injury cases awaiting final court decision of lifting the ban [35,36,38,39,109-117]. Early problems emerged because the German regulatory agency used outdated causality assessment methods for liver injury, which led to heavy discussions. Kava as herbal product remained on the market in the US [114] and is available in other countries including Australia [35,36].

7. DESIRED PRAGMATIC APPROACHES

A few suggestions for plants as natural source will help ensure that pragmatic steps in the right order are undertaken. It is useless to accumulate *in vitro* data of ROS or antioxidants found in plants without establishing their beneficial properties in humans. Instead, the starting point should focus on herbal medicines with assumed potential therapeutic efficacy verified through clinical trials. Only then studies on the active ingredient(s) are warranted, not *vice versa*.

7.1. Principle Aim

Provided the search of active ingredients is successful with established efficacy, the principle aim is without any question to approach drug registration by the national regulatory agency and then international registration, best under the guidance of Europe with EMA (European Medicines Agency) as the most professional agency with special expertise for herbal drugs, or the US FDA (Food & Drug Administration). However, international registration requires harmonization of basic requirements and agreement among various regulatory agencies.

7.2. Studies on Efficacy

In connection with herbs, RCTs are a major issue [118-121]. Using traditional medicines for a long period should allow experts in the field for an initial filtering of plants and other nature based medicinal products that might be effective for treatment of certain diseases. Subsequently, these products under consideration should undergo clinical evaluations using RCTs. If these trials are successful and provide a good benefit: risk profile, the used products should be analyzed for the single ingredient responsible for their clinical effectivity, repeating the RCT. If financial resources are limited and a repeat RCT is not feasible, then the crude medicinal product should be marketed as herbal drug after regulatory approval and should remain under regulatory surveillance.

7.3. Adverse Effects Including Liver Injury

Pharmacovigilance aiming to detect adverse effects is an important cornerstone in the setting of consumer safety, required not only for common drugs but also for herbal drugs and medicines, as outlined in detail [122]. For causality assessment of non-hepatic adverse effects, the use of the Naranjo method is recommended that is not suitable for liver injury cases [122]. For liver injury, however, the updated version of RUCAM (Roussel Uclaf Causality Assessment Method) is the preferred algorithm assessing causality [123-126]. Liver injury due to herbal TCM is a major clinical issue in Asia [16,17,19,20,21,91,104-108, 127-131], with rare cases observed in Germany where good product quality has been ascertained [13].

7.4. Product Quality

High product quality is essential for all nature based medicinal drugs and products, as recommended for herbal medicine [105]. Whether genetic predisposition or low quality of herbal TCM products caused potentially by contaminants or adulterants are responsible for the high rate of liver injury in Asia remains to be established.

8. CONCLUSIONS

Our planet is covered by abundant products made from living organisms with their sophisticated facilities allowing synthetize structurally complex chemicals, part of these likely represent active ingredients and could theoretically be used as nature based medicines for treating human disease. It is now up to clinicians, scientists and the pharmaceutical industry to promote

R & D of new drugs, in line with the view: Inspired by nature, refined by science.

AUTHORS' CONTRIBUTIONS

The first draft of this article was prepared by R.T. and edited by T.D.X., who provided additional stimulating discussion aspects and added other references. Subsequently, both authors agreed to submit the final version of this article.

CONFLICT OF INTEREST STATEMENT

Both authors declare that they have no conflict of interests with respect to this article. There was no funding of this article.

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