Antimicrobials of plant origin against TB and other infections and Economics of plant drugs – Introspection

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An overview on work published on antimicrobial activity of plants indicated that very limited work is reported on antimicrobial activities against multidrug resistant (MDR) pathogenic bacteria, especially the tuberculosis (TB) bacillus, Mycobacterium tuberculosis. But considerable work has been done with the methicillin-resistant Staphylococcus aureus (MRSA). Active principles from the tea tree oil plant, as well as the berberine found in many plants were reported to be effective against MRSA. For the control of many MDR pathogenic bacteria including M. tuberculosis, a systematic screening of plants would be the step towards drug-development from plants that would be economically viable too in the medicinal plant trade. In developing and developed countries phytodrugs with several commercial formulations are amply available, those are economical enough. A discussion on the economics of trade on medicinal plants is done that clarifies that raw products for healthcare are almost universally popular. It is discussed that crude plant extracts as antimicrobials are preferable, since resistance in pathogens would not be easy, for an array of compounds; and drug development for MDR-TB is need of the day.

Keywords: Antimicrobials, Phytodrugs, Multidrug-resistant bacteria, Mycobacterium tuberculosis, MRSA

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Millions of people of all age groups die each year from infectious diseases, tuberculosis, chest and respiratory disorders, wound suppuration, bacteremia, diarrhoea/dysentery and a few more, worldwide; and additionally, millions chronically suffer from several long-standing infections. On analysis, it is many a times found that some drug-resistant bacterium is the causative organism. As it is known, in a natural process, pathogenic bacteria become increasingly drug-resistant, and more often than not, these are the causative organisms of pre-mature death. Among notable and notorious ones, methicillin-resistant Staphylococcus aureus (MRSA) spearheads. Multidrug-resistant (MDR) MRSA, the representative of the major clonal complexes, is reported to be resistant to 23 antibiotics1, and is a great killer in aged and immunocompromised patients. Tuberculosis (TB) bacillus, Mycobacterium tuberculosis too nowadays imperils the health domain bitingly, due to the paradigmatic emergence of drug resistance. Drugs used for the treatment of TB are of two lines: 1. First line drugs: isoniazid and rifampicin as essential drugs; pyrazinamide, ethambutol and streptomycin as supplementary drugs. 2. Second line drugs: chemotherapeutics (ethionamide, thiacetazone, prothionamide and clofazimine), aminoglycosides (amikacin, kanamycin and debekacin), and other antibiotics (cycloserine, capreomycin and viomycin). Furthermore, any strain of M. tuberculosis, resistant to at least isoniazid and rifampicin is called a MDR; and MDR with additional resistance to a fluoroquinolone (ofloxacin or ciprofloxacin, Sparfloxacinc, Levofloxacinc and Moxifloxacinc) and one of the three second line injectable antibiotics (amikacin, kanamycin or capreomycin) is called extensively drug-resistant (XDR) strain. The extremely drug-resistant (XXDR) or pandrug-resistant (PDR) strain would be resistant to all the drugs used or available; this would be the last stage of TB resistance to currently used drugs. But, XDR-TB strains are reported occurring in 58% cases with TB patients in India2. A WHO survey reveals that of the 9.2 million new TB cases globally, about 3 millions occurred in Africa, 3 millions in Southeast Asia and about 2 millions in the Western Pacific region. India and China are reported to have the largest total
number of new cases, but South Africa had the highest rate of new cases in the world, with 9,400 cases per million. Unfortunately, patients with MDR/XDR-TB strains are nearly untreatable, as the second line drugs are used less often for more serious side effects and fewer efficacies; thus, those inescapably remain fatal\(^1\). Further, the XDR-TB strain readily gets transmitted to lacklustered human immune virus (HIV) infecteds with eventual high decimation rates of coinfecteds and a near-endemic spread of TB that being air-borne.

Virulent enteric bacteria (*Klebsiella*, *Salmonella*, *Pseudomonas*, *Shigella*, *Enterococcus*, *Vibrio* and a few more) are active in the non-hygienic poorer communities of developing countries; and these are the causative organisms of high infant mortality and out-breaks of inefrequent fervent episodes; these pathogens are also mostly MDR\(^4\)\(^5\) One burning example would be the emergence of community infections with *Clostridium difficile* reaching epidemic proportions in India\(^4\). Many factors including non-prudent antimicrobial use for some dramatic result in control of an infection are identified for such disasters; and by the by, people of poorer communities of the poorer countries often use medicines without a medical prescription. Further, many antimicrobials used for small animals (pets and food animals) are in use for humans. Eventually, a number of bacteria have become drug-resistant in animals as well as get transmitted to their owners. For example, drug-resistant strains of *Staphylococcus intermedius*, *Campylobacter* sp., *Salmonella* sp. and *Escherichia coli* have been cited as possible zoonotic concerns\(^6\). In dogs, *E. coli* strains are phylogenetically similar to pathogenic strains causing infection in human beings; more than 15% of canine fecal deposits in the environment contain *E. coli* strains related to virulent human strains\(^7\). Moreover, MRSA even has been isolated from family members and pets in the same household. Today, certain Gram-negative bacteria resistant to all the major classes of antibiotics have been emerged and these could be cited as ferocious PDR bacteria; such uropathogenic strains (more prominently, *Pseudomonas aeruginosa*, *Acinetobacter baumannii* and *Klebsiella pneumoniae*) cause utmost comorbidities and frequent immature mortality\(^8\). Of course, the term PDR is not yet consensus in literature, despite its clear etymological meanings, ‘resistant to almost all commercially available antimicrobials’, ‘resistant to all antimicrobials routinely tested’ and ‘resistant to all antibiotic classes available for empirical treatment’. May now be less spectacular, attack by such strains of bacterial pathogens would cause damnedest commotion in public health and extrication from such a gruesome infection would be a staggering victory for man.

In the last several decades, researches on antimicrobial activities of edible, non-edible and poisonous (lesser known and well known) plant species against several strains of both non-pathogenic and pathogenic bacteria, as well as fungal pathogens in *vitro* have been documented\(^9\)\(^16\). A search of the PubMed database (data from 1975 to 2010) yielded approximately, 1,500 reports that describe antimicrobial activities of plant species and their chemical constituents. Plant extracts have been tested against different strains of common pathogenic bacteria: *A. baumannii*, *Bacillus cereus*, *B. subtilis*, *Chlamydia pneumoniae*, *Enterococcus faecalis*, *E. coli*, *S. aureus* (the wild strain), *MRSA*, *Streptococcus pneumoniae*, *K. pneumoniae*, *P. aeruginosa*, *Helicobacter pylori* and a few more. The torrent of published data describing *in vitro* and clinical antibacterial activities of natural products is so vast that it could easily fill a book or two. But, very few isolated reports record antimicrobial activities of plant extracts on MDR pathogenic bacteria. Moreover, several reports on the use of phyto extracts for the control of MRSA are published, indicating a promise in the field of drug targeting or use phytodrugs as complementary medicines for MDR pathogens; but, very limited reports on the control of MDR or XDR *M. tuberculosis* are available. Herein, attempts for the identification of alternate/supplementary/complementary drugs from plants are discussed for MDR pathogenic bacteria including those published for the TB bacillus. ‘Reviews’ of reports on ethnomedicinal or antibacterial activities of plants are not aimed here. Single or conflated raw herbal products and their concoctions are used almost universally, which prompted the development of industry based user-friendly goods that lead emergence of ‘medicinal plant trade’ and associated tranche. The important objective of this paper is to call upon for systematic search for alternative and/or complementary drugs from plant sources for MDR and XDR *M. tuberculosis* and other MDR, XDR and nearly-PDR pathogens; public health scenarios are feared to shift from bad to abysmal in populous areas of the world, as conjectured from recorded shenanigans of XDR pathogens.
Antibacterial activities of plants on MDR pathogenic bacteria and MRSA

Most papers on antimicrobial activities of plants did not record drug/antibiotic-sensitivity profile of the used pathogenic bacteria and those were often wild drug-sensitive strains from some standard culture collection centre like, American Type Culture Collection (ATCC) or National Collection of Type Cultures (NCTC). Further, antimicrobial records on clinical isolates of pathogenic bacteria without any antibiogram are apt to be regarded as exercises of simple academic interest and not works of ‘drug-targeting’, or it could be concluded that the described works were on drug/antibiotic sensitive pathogens. Further, antimicrobial activities of isolated compounds, essential oils, alkaloids, flavonoides, sesquiterpene, lactones, diterpenes, triterpenes and naphthoquinones have been recorded. Most of these studies do not examine systematically the therapeutic potentialities of plant extracts. There is also a consensus that work with non-pathogenic bacteria are not coveted in Medical Microbiology. In many papers, there is a lack of uniformity in the criteria of assessment of antimicrobial activities of plants, with eventual contradictions of results. Most studies describe ‘minimum inhibitory concentrations (MIC)’ of phyto extracts against a bacterium instead of both MIC and ‘minimum bactericidal concentration (MBC)’ or lethal concentration — the most sought after requirements in drug-targeting. Moreover, evaluation of host toxicity (cyto-and genetic-pathology) is an essential corollary, when it is aimed that phytochemicals (because of an array of natural chemicals) would be suitable candidates for drug-targeting as antimicrobials against MDR pathogens, as an array of natural compounds of non-microbial origin can never be won over by any bacterial cell machinery. But, dearth of systematic or pragmatic approach in reported antimicrobial work with pathogens in vitro does not go well with the medical paradigm. Obviously, the vast published information on antimicrobial activities of phyto extracts would definitely be guiding further work on searches for new drugs for the control of MDR incarnations of M. tuberculosis and other pathogenic bacteria. At all the time, it would be prudent to take recourse to plants (and animals) systematically for some avant-garde natural drugs for the holistic control of MDR bacteria, or else are we heading to a post-antibiotic era with the ‘butterfly’ theory of chaos in issues of healthcare and management of infections, as bacteria evolve faster than all higher organisms.

1. An Indian report describes a systematic work done in vitro control of ATCC and MDR strains of E. coli, K. pneumoniae, Streptococcus mutans, S. bovis, E. faecalis, P. aeruginosa, S. aureus, Salmonella typhimurium, and the fungus, Candida albicans using ethanolic extracts of five plants, Acacia nilotica (L.) Willd. ex Delile, Syzygium aromaticum (L.) Merrill & Perry, Cinnamomum zeylanicum, Terminalia arjuna (Roxb.) wt. & Am and Eucalyptus globules Labill. The most potent antimicrobial plant was A. nilotica with a MIC range of 9.75-31.3 µg/mL.

These studies with a few plants provide ample evidences that extracts from specific plants would control MRSA (Fig. 1):

2. A crude methanol extract of Garcinia nigrolineata Planch. ex T. Anderson had antibacterial activity against MRSA. An ethanol extract of Garcinia kola Heckle. (Bitter kola) was tested against MRSA; MIC value of the extract was of range, 0.08 - 1.8 mg/mL, while the MBC value ranged from 0.135 to 4.2 mg/mL. Thus, Bitter kola was recorded to be strongly active against MRSA.

3. A 50% ethanol extract of the dried fruits (with chebulagic acid, chebulinic acid, corilagin, gallic acid, punicalagin, terchebulin, and terminalic acid) of...
Terminalia chebula Retz. (local, Haritaki) inhibited the growth of MRSA, with a MIC value of 31.3 mg/mL. This plant, native to India has been used in traditional medicines to treat respiratory tract infections. It was reported that 66 clinical isolates of S. aureus were susceptible to tea tree oil (TTO) from Melaleuca alternifolia (Maiden & Betch) Cheel; of the isolates tested, 34 were MRSA and 32 were mupirocin-resistant S. aureus; the MIC and the MBC values were 0.25% and 0.50% diluted oil, respectively. Moreover, some of the naturally occurring compounds in the oil, including 1, 8-cineol (4.5-16.5%), terpinen-4-01 (29-45%), y-terpinene (10-28%) and a-terpineol (2.7-13.0%), were recorded to show a reduced growth pattern of MDR S. aureus, in vitro, without any bacterial resistance to the oil even at a concentration of 2.5% (v/v). Thus, the TTO appears to be a viable alternative as a topical agent to eradicate MRSA colonization in wounds.

In traditional folk medicine, oily extract of Hypericum perforatum L. (St. John’s wort) is used for topical treatment of wounds, burns and myalgia, and its alkaloid, hyperforin (lipophilic phloroglucin-derivative of hyperforin) at a concentration of 1 mg/mL has been recorded to inhibit the growth of MRSA. Berberine, obtained from a number of plants including, Coptis chinensis Franch., Berberis vulgaris L. and Hydrastis Canadensis L., was also active against MRSA in vitro. Berberine inhibited the growth of S. aureus, with a MIC value of 25.0 mg/mL. Sub-inhibitory concentrations of berberine were potentiated by the flavones, chrysosplenol-D and chrysoplenetin from Artemisia annua L. This potentiation was recorded to be effective due to the inhibition of a MDR pump in MRSA, an intrinsic mechanism of multiple drug resistance. This is an example of synergistic effects of phytochemicals against MRSA.

The antimicrobial activity of a berberine-containing extract from rhizome of Coptis chinensis Franch. was found effective against sortase (a surface protein-anchoring transpeptidase), from S. aureus ATCC 6538 (wild strain), with a MIC value of 8.7 mg/mL.

Crude extracts of 10 plants from Brazil were screened for antibacterial activity of 7 clinical MDR microorganisms utilizing as control ATCC strains. Ethanol extracts of plants, Geissospermum argenteum Woodson in. A.C.Sm., Uncaria guianensis (Willd. ex Schult.) DC., Brosimum acutifolium Huber, Copaifera reticulate Lindl., Licania macrophylla Aubl., Ptyocpetalum olacoides Benth. and Dalbergia subcymosa Ducke, were effective against MDR S. aureus, MDR P. aeruginosa and the S. aureus ATCC strain 6538. As it is known, MDR P. aeruginosa, an uropathogen (mostly infecting females, rarely males), causes the fatal bacteraemia in immunocompromised patients.

Work done on phytodrugs against TB bacillus

The first line drugs for M. tuberculosis (Fig. 2) (see Introduction) are administered all at a time for 6-8 months in a module of ‘combination chemotherapy’ for the fear of development of resistance and the resultant failure of treatment. In patients who are taking inadequate/irregular drug dosages, mutations occur sequentially as follows: one in 10^6 cells for isoniazid, 1 in 10^7 rifampicin, 1 in 10^13 for double resistance to isoniazid and rifampicin, 1 in 10^18 for triple resistance to isoniazid, rifampicin and pyrazinamide, and 1 in 10^23 for quadruple resistance to

![Microphotograph of TB bacillus, Mycobacterium tuberculosis on an oil-immersion smear slide stained with Ziehl-Neelsen or acid-fast staining of a clinical sample. Bacilli are long and rod-shaped; a bacillus is indicated by a black arrow; magnification, X 2250.](image-url)
isoniazid, rifampicin, pyrazinamide and ethambutol. A patient with TB when acquires approximately \(10^{23}\) bacteria in the body, resistant mutations appear spontaneously and independently to all 4 cited drugs, which would be the rare PDR or XXDR strain. Before such a stage, the patient dies and the PDR/XXDR strain is reported from nowhere. Clearly, a XDR strain mostly emerges independently, as in \(10^{13}\) cells. But, if one resistant cell becomes resistant to two or more drugs simultaneously in a specific chance factor, all TB-cells in the body slowly get replaced by a progeny of the resistant cell or the XDR strain. This has occurred indeed, as conjectured from the gauntlet of XDR-TB strain in the public health domain in India. This computation is based on published rates of spontaneous mutations known for bacteria. Gene transfer mechanisms, particularly bacterial transformation of DNA of multiple antibiotic resistances- (mar-) locus (originally from \(E. coli\)) and associated transposon are operative in nature, involving phylogenetically related and distant pathogenic bacteria. Apart from acquired resistances, an intrinsic resistance in \(M. tuberculosis\) has been attributed to impermeable mycolic acid containing envelopes that contribute to higher rates of mutations. Distressingly, before the patient dies, intractable MDR/XDR \(M. tuberculosis\) strain(s), as if with Promethean abilities escape to and nimble in community through air covertly, without any tangible control; it is now feared that MDR/XDR strains can spread to an epidemic level.

1. From Mexico, activities of several plant species, \(Artemisia ludoviciana\) Nutt., \(Chamaedorea tepejilote\) Liebm. ex Mart, \(Lantana hispida\) Auct. non Kunth, \(Juniperus communis\) L. and \(Malva parviflora\) L. against MDR \(M. tuberculosis\) as well as the sensitive (to these 4 drugs) strain, H37Rv have been reported. The n-hexane extract of \(L. hispida\) at 25 \(\mu\)g/mL inhibited the growth of MDR TB bacillus, and this plant among the ones used, was considered as a potential source of anti-mycobacterials.

2. Extracts of 17 traditional Australian medicinal plants were tested for anti-mycobacterial activity against \(Mycobacterium fortuitum\) and \(M. smegmatis\). Four extracts viz, aerial parts of \(Pterocaulon spachelatum\) Cass., bark and leaves of \(Acacia ligulata\) A. Cunn. ex Benth., leaves and stems of \(Eremophila alternifolia\) A. Cunn. ex Benth. and leaves of \(Eremophila longifolia\) (R. Br.) F. Muell., were reported to have strong activity against other species, \(M. smegmatis\) only, while the two \(Eremophila\) extracts were active against \(M. fortuitum\). The MIC values ranged from 20 to 66 \(\mu\)g/mL.

3. Seven medicinal plants were screened for their anti-mycobacterial activities. The MIC values of four plants namely, \(Artemisia afra\) Jacq. ex Willd., \(Dodonea angustifolia\) Lf., \(Drosera capensis\) L. and \(Galenia africana\) L. ranged from 0.781 to 6.25 \(\mu\)g/mL, against \(M. smegmatis\). Ethanol extracts of \(G. africana\) had the best activity with a MIC value of 0.78 \(\mu\)g/mL and a MBC value of 1.56 \(\mu\)g/mL. MIC values of ethanol extracts of \(D. angustifolia\) and \(G. africana\) against \(M. tuberculosis\) were recorded at 5.0 and 1.2 \(\mu\)g/mL, respectively. The mammalian cytotoxicity lethal concentration value of extract from \(G. africana\) was reported to be 101.3 \(\mu\)g/mL against monkey kidney cells. The ethanol extract of \(G. africana\) with flavone, 5, 7, 2'-trihydroxyflavone had the best anti-mycobacterial activity. The MIC value of this compound was reported as 0.031 \(\mu\)g/mL, against \(M. smegmatis\) and as 0.10 \(\mu\)g/mL, against \(M. tuberculosis\).

4. Anti-tubercular activity of extracts of Colombian medicinal plants (\(Lippia origanoides\) Kunth and \(L. alba\), \(Swinglea glutinosa\) (Blanco) Merr., \(Hyptis mutabilis\) (A. Rich) Briq., \(Achyrocline alata\) (Less.) DC., \(Piper auritum\) Kunth and \(P. bogotense\) C. Dc., \(Cananga odorata\) (Lam.) Hook.f. & Thomson have been reported. Essential oils from \(A. alata\) and \(S. glutinosa\) were the most active antimicrobials with MIC values of 62.5±0.1 and 100±36 \(\mu\)g/mL, respectively. Carvacrol, thymol, \(p\)-cymene, 1, 8-cineole and limonene were the major components, most often identified in these plant extracts.

All the plants screened for anti-mycobacterial activity in vitro so far had promising results. Incidentally, the drug-targeting endeavour from plant sources for the control of TB is very much neglected, particularly with plants available at the gamut of forest patches in diverse Indian climatic zones, despite the estimated infection dynamics of XDR/MDR \(M. tuberculosis\) strains in unhygienic rural communities and urban slums of India. Reminded that, MDR/XDR TB strains decimate drastically in 25 - 44 years age group, worldwide; thus, a prudent stratagem would be to search new avant-garde drug(s) or to revise the current therapeutic module of combination chemotherapy for the control-crusade of this bacillus now.

**Economics of plant drugs**

The first category of plant drugs are simple crude extracts and their popular à la carte menu-like
concoctions with modalities, idiosyncratic to ‘medicine and disease’ that are often lent from literature of folklore-medicines recorded from different parts of the world, and the majority of aborigine-people still depend primarily on plants in under developed areas of developing countries. Large proportions of plant drugs are very popular for their performance standards, and are in use by the elite mass without any institutional (scientific/clinical/pharmaceutical) evaluation (physio-and cytotoxicity studies in both single and repeated uses). Two epitomes would be: the use of the decoction of internodes of the anti-diabetic, *Tinospora cordifolia* (Thunb.) Miers (Guduchi/Guluchi, local names) in India, and the ginseng (*Panax ginseng*, L., root is best known to lower blood sugar and cholesterol levels, protect against stress, enhance strength and promote relaxation) from the East world with a remarkable popularity in the USA. Other examples would be Indian ‘chuyavanprash’ and many Brazilian, American and Chinese health-boosting formulations, concocted with many herbal products that have been growing slowly popular. Several of these have some planned clinical evaluations of treatment modality, therapy and in the marketing of patented formulations. Moreover, several pharmaceutical companies are busy worldwide in preparing and marketing several combinations of natural products as medicines for different purposes, parallel to the scientific exactitude of drug preparations and uses followed in modern medical sciences. Many phytochemical based drugs constitute the considerable sources of economy in several states of the USA, India, Brazil and China, and that should be also occurring in equal or lesser dimensions in many other countries. Planned commercial medicinal plant growing establishments are slowly developing at several states in India, apart from government approved collections of plants of curio from forest.

The second category of phytodrugs is the class of pure chemicals. Notable examples are many that are established scientifically: quinine and quinidine from *Cinchona*, reserpine from *Rauwolfia*, morphine and codeine from *Papaver somniferum* L., vinblastine and vincristine from *Catharanthus roseus* (L.) G. Don, atropine from *Atropa belladonna* L., digoxin from *Digitalis purpurea* L. and taxol from *Taxus*, to state a few in succinct. Today, plants provide about a 25% of the drugs prescribed worldwide and 121 active compounds procured from plants are in current use. Of the 252 basic and essential drugs recognized by the WHO, an 11% drugs exclusively are of plant origin and a significant number are synthetic drugs, obtained from natural precursors. In addition, a 60% of anti-tumor and anti-infectious drugs already on the market or under clinical trial are of natural origin. The vast majority of these drugs cannot yet be synthesized economically and are still obtained from wild/cultivated plants. Further, compounds (muscarine, physostigmine, cannabinoids, yohimbine, forskolin, colchicines and phorbol esters), obtained from plants are important tools used in pharmacological, physiological and biochemical studies. Several plant chemicals have been developed, evaluated and find their own places as pharmaceutical agents. The burning example would be the quinine that lends itself for further chemical manipulations for preparations of different variants suiting to progressively resistant strains/species of *Plasmodium*, the malaria parasite.

It is estimated that plant materials either are present in or have provided models, for further development of a 50% of western drugs used worldwide. As it is known, the primary benefits of using plant based medicines are comparatively safer than synthetic alternatives, as pure chemicals as drugs in chemoprophylaxis have non-target adverse effects on host, for an instance in TB medication, whereas phytochemicals are safer as those have instances of traditional uses as ethnic medicinal literature. Nevertheless, certain phytochemicals also have both known and unknown toxic effects on the human body. Thus, the drug-targeting endeavour with certain phytochemicals (obtained from non-edible plants) needs due host toxicity testing with animal systems and mammalian cell lines, before use for man. Moreover, plant based antimicrobials have enormous therapeutic potentials, as seen in the literature published so far. For an instance, antioxidative properties of antimicrobial-producing plants are often reported, which is a boon of phytomedicines in mitigating or ameliorating some cryptic ailment/disorder at an initial stage, along with general heath conditioning. Further, phytochemicals usually have multiple beneficial effects, often acting beyond a symptomatic treatment of diseases. For example, *Hydrastis canadensis* L. (orange root), has not only antimicrobial activity, but also increases blood supply to the spleen to release mediating compounds.
Antimicrobial herbal drugs have a promising marketing potential as bacterial resistance to phytochemicals is effective as a drug for an ailment, plant resources are not required in such exaggerated amounts; here research is needed for selected plants. Moreover, when the information of century-old uses of certain plants as therapeutic resources could be taken into account, during drug preparation the rigorous checking of host toxicity of the particular plant product as drug should be redundant. For example, a pure drug as an antimicrobial from a plant, *Hydrastis* (L.) are gaining importance in the tide of present love for organic products over synthetics. Further, leaves of the Indian laburnum (*Cassia fistula* L.) are gaining importance in the market as an ingredient in preparations of purgatives, the original information lent from Indian Vedic and folklore literature.

As seen often, the development of therapeutic materials from plants is hard and expensive, particularly when aimed for active compounds, as done for *Papaver somniferum* L., for example; 50 kg of raw materials are required for getting 500 mg of a pure compound. Bioassay, toxicology, *in vivo* evaluation and full preclinical and clinical studies required 2 kg of pure compounds obtained from 200 tons of raw materials. People from Microbiology, Botany, Biochemistry, Biotechnology, Organic Chemistry and Pharmacology must involve together, for the creation of drugs from plant sources. When a crude plant extract in place of its pure plant product as drug should be redundant.

Antimicrobial activity of plants should be involving diverse molecular mechanisms, as diverse phytochemicals in crude form would have different mechanisms of toxicity to bacteria, not easily possible for a prokaryote (bacterium) with a limited mechanisms of breaking down of the panoply of phytochemicals *in vivo*. On the contrary, plant extracts, tantamount to a large armamentarium would have a holistic approach of toxicity to pathogens, as exemplified in the published reports. A burning example of a top-selling antimicrobial in the herbal US market is *Hydrastis*, which has been used by Native Americans and this plant is in cultivation to supply the demands of its herbal products. Furthermore, *Ocimum*-based cough syrups and *Aloe vera* (L.) Burm. f., -based cosmetic preparations are preferred over synthetic chemical-based ones in India, in the tide of present love for organic products over synthetics.
population cannot afford to the conventional modern medicinal system. Secondly, modern medicinal system sometimes lands at ineffective therapy, leading to the alternate or complementary use of comparatively cheaper folklore system of natural products. Obviously, for treatments of viral diseases and cancer, interest seen in alternative therapy is enormous: the searches of 50,000 plant samples against the HIV and 33,000 plant samples for anti-tumor activity have been carried out by Natural Cancer Institute, USA. Presently, established companies, Merck, CIBA, Glaxo, Boehringer, Syntax and Unichem have a specific R & D section in each, for the search of new drugs from natural systems.

Raspberry (Fragaria dulcis Sommerf. ex Hornem., Rosaceae) leaf tea with the active principle, fragine was much praised in Europe for pregnant women, as the tonic is effective in strengthening the muscles of the pelvic floor; this traditional brew, once popular has now been lost from the cultural memory of modern European women disciplined for hospital childbirth. It could be that many similar plants and their uses in hands of Indian rustic tribals, for example, must have been lost due to both creeping of modernism to aborigine societies, and the diminution of diverse forest flora for multiple obvious reasons. In the developing world, useful lesser known or unknown wild plants and their traditional ethnomedicinal information must be at jeopardy. Thus, trials of gathering ethnomedicinal information must continue, as followed till date, along with possible scientific verifications.

Secondly, tissue culture methodology in Botany has helped mass propagation of many plants, loved by horticulturists, and the cash plant tobacco, which is much worked upon in genetics too, for the increase of nicotine content and leaf size in the commercial interest, is much improved. This plant is grown in Japan, West Europe and North America in vats by cigarette companies. Thus, no time is wasted for it, in ploughing, sowing, watering, nurturing, harvesting and shipping the product. But, no medicinal plant has gone up commercially so high, and consequently is not favoured as the tobacco plant is. The suspicion is that, albeit its popularity American ginseng (Panax quinguefolius L.) that is regulated in the international trade might not rise to the industrial height of the tobacco in future. It is ridiculous that we have preferred the semi-poisonous, carcinogenic tobacco to develop to this extent for no human good!

Future directions

Indeed, we have not yet exploited plant resources with prescient to the extent needed for the control of MDR pathogens, despite information on their raging nosocomial and communal spreads to notorious standards. Many a times, phytochemicals are not as effective as drugs of some synthetic chemical/microbial source, but their enormous types should allow synergistic effects in combinations for the control of pathogens. A purified active principle can be used as a base chemical for further modification, for effectivity. At all the time, systematic screening of plants is necessary for alternative/supplementary/complementary drugs, as the rapid emergence of MDR pathogenic bacteria, particularly invincible MDR/XDR-TB bacilli are widespread, perniciously. Considerations on economics of phyto drugs clearly indicated a promising market would be waiting ahead during fight with adept against the avalanche of MDR avatars of pathogenic bacteria and a considerable number of viral and fungal attacks. Chemicals like berberine or TTO could be taken up for further drug development against TB. Some large pharmaceutical company could further initiate development of suitable supplementary/complementary drugs from phytochemicals with sanguinity for MDR/XDR pathogens.

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