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New Antimicrobials of Plant Origin

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Infectious diseases account for approximately one-half of all deaths in tropical countries. In industrialized nations, despite the progress made in the understanding of microbiology and their control, incidents of epidemics due to drug resistant microorganisms and the emergence of hitherto unknown disease-causing microbes, pose enormous public health concerns. Historically, plants have provided a good source of antiinfective agents; emetine, quinine, and berberine remain highly effective instruments in the fight against microbial infections. Phytomedicines derived from plants have shown great promise in the treatment of intractable infectious diseases including opportunistic AIDS infections. Plants containing protoberberines and related alkaloids, picralima-type indole alkaloids and garcinia biflavonones used in traditional African system of medicine, have been found to be active against a wide variety of micro-organisms. The profile of known drugs like *Hydrastis canadensis* (goldenseal), *Garcinia kola* (bitter kola), *Polygonum* sp., *Aframomum melegueta* (grains of paradise) will be used to illustrate the enormous potential of antiinfective agents from higher plants. Newer drugs such as *Xylopia aethiopica*, *Araliopsis tabouensis*, *Cryptolepis sanguinolenta*, *Chasmanthera dependens* and *Nauclea* species will be reviewed.

INFECTIOUS DISEASE

World wide, infectious disease is the number one cause of death accounting for approximately one-half of all deaths in tropical countries. Perhaps it is not surprising to see these statistics in developing nations, but what may be remarkable is that infectious disease mortality rates are actually increasing in developed countries, such as the United States. Death from infectious disease, ranked 5th in 1981, has become the 3rd leading cause of death in 1992, an increase of 58% (Pinner et al. 1996). It is estimated that infectious disease is the underlying cause of death in 8% of the deaths occurring in the US (Pinner et al. 1996). This is alarming given that it was once believed that we would eliminate infectious disease by the end of the millenium. The increases are attributed to increases in respiratory tract infections and HIV/AIDS. Other contributing factors are an increase in antibiotic resistance in nosicomial and community acquired infections. Furthermore, the most dramatic increases are occurring in the 25–44 year old age group (Pinner et al. 1996).

These negative health trends call for a renewed interest in infectious disease in the medical and public health communities and renewed strategies on treatment and prevention. Proposed solutions are outlined by the CDC as a multi-pronged approach that includes: prevention, (such as vaccination); improved monitoring; and the development of new treatments. It is this last solution that would encompass the development of new antimicrobials (Fauci 1998).

Historic Use of Plants as Antimicrobials

Historically, plants have provided a source of inspiration for novel drug compounds, as plant derived medicines have made large contributions to human health and well-being. Their role is two fold in the development of new drugs: (1) they may become the base for the development of a medicine, a natural blueprint for the development of new drugs, or; (2) a phytomedicine to be used for the treatment of disease. There are numerous illustrations of plant derived drugs. Some selected examples, including those classified as antiinfective, are presented below.

The isoquinoline alkaloid emetine obtained from the underground part of *Cephaelis ipecacuanha*, and related species, has been used for many years as and amoebicidal drug as well as for the treatment of abscesses due to the spread of *Escherichia histolytica* infections. Another important drug of plant origin with a long history of use, is quinine. This alkaloid occurs naturally in the bark of *Cinchona* tree. Apart from its continued usefulness in the treatment of malaria, it can be also used to relieve nocturnal leg cramps. Currently, the widely prescribed drugs are analogs of quinine such as chloroquine. Some strains of malarial parasites have become resistant to the quinines, therefore antimalarial drugs with novel mode of action are required.

Similarly, higher plants have made important contributions in the areas beyond antiinfectives, such as cancer therapies. Early examples include the antileukaemic alkaloids, vinblatine and vincristine, which were both obtained from the Madagascan periwinkle (*Catharanthus roseus* syn. *Vinca roseus*) (Nelson 1982). Other cancer therapeutic agents include taxol, homoharringtonine and several derivatives of camptothein. For example, a well-known benzylisoquinoline alkaliod, papaverine, has been shown to have a potent inhibitory effect on the replication of several viruses including cytomegalovirus, measles and HIV (Turano et al. 1989). Most recently, three new atropisomeric naphthylisoquinoline alkaloid dimers, michellamines A, B, and C were isolated from a newly described species tropical liana *Ancistrocladus korupensis* from the rainforest of Cameroon. The three compounds showed potential anti-HIV with michellamine B being the most potent and abundant member of the series. These compounds were capable of complete inhibition of the cytopathic effects of HIV-1 and HIV-2 on human lymphoblastoid target cell in vitro (Boyd et al. 1994).

The Development of Phytomedicines and the Ethnomedicinal Approach

The first generation of plant drugs were usually simple botanicals employed in more or less their crude form. Several effective medicines used in their natural state such as cinchona, opium, belladonna and aloe were selected as therapeutics agents based on empirical evidence of their clinical application by traditional societies from different parts of the world. Following the industrial revolution, a second generation of plant based drugs emerged based on scientific processing of the plant extracts to isolate "their active constituents." The second-generation phytopharmaceutical agents were pure molecules and some of the compounds were even more pharmacologically active than their synthetic counterparts. Notable examples were quinine from *Cinchona*, reserpine from *Rauvolfia*, and more recently taxol from *Taxus* species. These compounds differed from the synthetic therapeutic agents only in their origin. They followed the same method of development and evaluation as other pharmaceutical agents.

The sequence for development of pharmaceuticals usually begins with the identification of active lead molecules, detailed biological assays, and formulation of dosage forms in that order, and followed by several phases of clinical studies designed to established safety, efficacy and pharmacokinetic profile of the new drug. Possible interaction with food and other medications may be discerned from the clinical trials.

In the development of "Third Generation" phytotherapeutic agents a top-bottom approach is usually adopted. This consists of first conducting a clinical evaluation of the treatment modalities and therapy as administered by traditional doctors or as used by the community as folk medicine. This evaluation is then followed by acute and chronic toxicity studies in animals. Studies should, when applicable, include cytotoxicity studies. It is only if the substance has an acceptable safety index would it be necessary to conduct detailed pharmacological/ biochemical studies.

Formulation and trial production of the dosage forms are structured to mimic the traditional use of the herb. The stability of the finished product is given careful attention during the formulation of the final dosage form. This is a unique blend of the empiricism of the earlier first *generation* botanicals with the experimental research used to prove the efficacy and safety of second *generation* isolated pure compounds. Several pharmaceuticals companies are engaged in the development of natural product drugs through the isolation of the so-called active molecules from plant extracts.

PRESENT USE OF PLANTS AS ANTIMICROBIALS

It is estimated that today, plant materials are present in, or have provided the models for 50% Western drugs (Robbers 1996). Many commercially proven drugs used in modern medicine were initially used in crude form in traditional or folk healing practices, or for other purposes that suggested potentially useful biological activity. The primary benefits of using plant derived medicines are that they are relatively safer than synthetic alternatives, offering profound therapeutic benefits and more affordable treatment.

Therapeutic Benefit

Much of the exploration and utilization of natural products as antimicrobials arise from microbial sources. It was the discovery of penicillin that led to later discoveries of antibiotics such as streptomycin, aureomycin

and chloromycetin. (Trease 1972). Though most of the clinically used antibiotics are produced by soil microorganisms or fungi, higher plants have also been a source of antibiotics (Trease 1972). Examples of these are the bacteriostatic and antifugicidal properties of *Lichens,* the antibiotic action of allinine in *Allium sativum* (garlic), or the antimicrobial action berberines in goldenseal (*Hydrastis canadensis*) (Trease 1972). Plant based antimicrobials represent a vast untapped source for medicines. Continued and further exploration of plant antimicrobials needs to occur. Plants based antimicrobials have enormous therapeutic potential. They are effective in the treatment of infectious diseases while simultaneously mitigating many of the side effects that are often associated with synthetic antimicrobials. They are effective, yet gentle. Many plants have tropisms to specific organs or systems in the body. Phytomedicines usually have multiple effects on the body. Their actions often act beyond the symptomatic treatment of disease. An example of this is *Hydrastis canadensis*. *Hydrastis* not only has antimicrobial activity, but also increases blood supply to the spleen promoting optimal activity of the spleen to release mediating compounds (Murray 1995).

Economic Benefit

World wide, there has been a renewed interest in natural products. This interest is a result of factors such as: consumer's belief that natural products are superior; consumer's dissatisfaction with conventional medicines; changes in laws allowing structure-function claims which results in more liberal advertising; aging baby boomers; national concerns for health care cost.

Sales of products in this market have increased dramatically in the last decade. Sales of botanical products in the United States have reached $3.1 billion of the $10.4 billion dollar dietary supplement industry 1996 (NBJ June 1998). The industry anticipates growth on the order of 15–20% into the new millenium (Herbalgram 1996). This growth rate will be maintained in an industry that is still considered to be in its infancy. Many plants that were previously wildcrafted will need to be grown domestically to meet the demands of the consumer. This represents many opportunities for the cultivation of crops for this industry.

A market based illustration of the need for plant based antimicrobials is demonstrated by the dissection of the herbal products market. In reviewing the top botanicals used as antiinfectives, the primary botanical used as an antimicrobial is *Hydrastis* with sales of 4.7% in 1995 (Gruenwald 1997). While antiinfectives agents make up 24 % of the pharmaceutical market (1992 Census of Manufactures 1994).

A similar, analysis of *Hypericum* (St. John's wort), demonstrates the value of such an evaluation. Though *Hypericum* is an antiviral, it is primarily used for its antidepressant activity. In 1995 it was not among the top selling herbs (Gruenwald 1997). However, by 1997, it had become an overnight success, with sales increasing over 20,000% in the mass market sector (Aarts 1998). The meteoric increase in the sales of *Hypericum* is multifactorial, but one factor in its in popularity was the existence of an unexploited market opportunity. In 1994 21% of pharmaceuticals sold were for the conditions affecting the central nervous system (1992 Census of Manufactures). Most of the drugs sold in this category are for depression. During this period of time, none of the top selling herbs sold had a primary indication for depression. This market hole, coupled with the media exposure produced a market success.

Many market holes exist. When using the same strategy to look at antimicrobial agents there is a similar gap. If the market dissection for antiinfectives is viewed in the same light as the *Hypericum analogy,* then perhaps this market is prime for receiving new plant based antimicrobials.

The potential for developing antimicrobials into medicines appears rewarding, from both the perspective of drug development and the perspective of phytomedicines. The immediate source of financial benefit from plants based antimicrobials is from the herbal products market. This market offers many opportunities for those cultivating new crops, as many of the plants that are wildcrafted today must be cultivated to match the demands of this market. Again *Hydrastis,* one of the top selling antimicrobials in the US herbal market, represents an example of a herb that has undergone domestication. Originally this plant, native to eastern North America, was wild crafted. *Hydrastis,* has been used by Native Americans for many conditions, including as an antimicrobial for infections. Efforts to cultivate this plant were undertaken in order to supply the demands of the herbal products market and to battle it's threatened extinction.

It is vital to be in the position to capitalize on the phytomedicine market, providing environmentally responsible solutions to public health concerns presented by new trends in infectious disease. In order to be prepared, the industry must be able to sustainably harvest and supply the herbal market. That means we must be able to anticipate the market needs and develop products to satisfy this market.

PLANTS WITH PROMISING ANTIINFECTIVE ACTIVITY

In our organizations, our major emphasis has been on drug discovery from ethnomedicinal information using the "Third Generation Approach." This method differs in that the clinical evaluation in humans takes place before the precise active constituents are known but the chemical composition and safety of the extracts are determined before formulation into dosage forms.

Plants containing protoberberines and related biflavones used in traditional African system of medicine have been found to be active against a wide variety of micro-organisms. Many medicinal plants of Africa have been investigated for their chemical components and some of the isolated compounds have been shown to posses interesting biological activity. Some of these plants are discussed below.

***Garcinia kola*, bitter kola (Guttiferae)**

Garcinia kola, is found in moist forest and grows as a medium size tree, up to 12 m high. It is cultivated and distributed throughout west and central Africa. Medicinal uses include, purgative, antiparasitic, antimicrobial. The seeds are used in the treatment of bronchitis and throat infections. They are also used to prevent and relieve colic, cure head or chest colds and relieve cough. Also the plant is used for the treatment of liver disorders and as a chewing stick (Iwu 1993).

The constituents include—biflavonoids, xanthones and benzophenones. The antimicrobial properties of this plant are attributed to the benzophenone, flavanones. This plant has shown both anti-inflammatory, antimicrobial and antiviral properties. Studies show very good antimicrobial and antiviral properties. In addition, the plant possesses antidiabetic, and antihepatotoxic activities (Iwu 1993).

***Aframomum melegueta* (Zingiberaceae) Grains of Paradise**

This is a spicy edible fruit that is cultivated and occurs throughout the tropics. It is a perennial herb. The medicinal uses of *Aframomum* include aphrodisiac, measles, and leprosy, taken for excessive lactation and post partem hemorrhage, purgative, galactogogue and anthelmintic, and hemostatic agent (Iwu 1993). The constituents are essential oils—such as gingerol, shagaol, paradol. Studies show antimicrobial and antifungal activity and effective against schistosomes (Iwu1993).

***Xylopia aethiopica*, Ethiopian Pepper (Abbibacceae)**

An evergreen, aromatic tree growing up to 20 m high with peppery fruit. It is native to the lowland rainforest and moist fringe forest in the savanna zones of in Africa. Largely located in West, Central and Southern Africa. Medicinal uses of the plant are, as a carminative, as a cough remedy, and as a post partum tonic and lactation aid. Other uses are stomachache, bronchitis, biliousness and dysentery. It is also used externally as a poultice for headache and neuralgia. It is used with lemon grass for female hygiene. It is high in copper, manganese, and zinc (Smith 1996).

Key constituents are diterpenic and xylopic acid. In studies, the fruit as an extracts has been shown to be active as an antimicrobial against gram positive and negative bacteria. Though it has not been shown to be effective against *E. coli* (Iwu 1993). Xylopic acid has also demonstrated activity against *Candida albicans* (Boakye-Yiadom 1977).

***Cryptolepis sanguinolenta* Lindl. Schltr. (Periplocaceae)**

A shrub that grows in the rainforest and the deciduous belt forest, found in the west coast of Africa. Related species appear in the east and southern regions of the continent. Its main medicinal use is for the treatment of fevers. It is used for urinary tract infections, especially *Candida*. Other uses are inflammatory conditions, malaria, hypertension, microbial infections and inflammatory conditions, stomach aches colic (Iwu 1993).

Active principals identified are indo quinoline alkaloids. Studies show inhibition against gram negative bacteria and yeast (Silva 1996). Additionally studies have shown this plant to have bactericidal activity. Clinical studies have shown extracts of the plant were effective in parasitemia. Recent in vitro study shows activity against bacteria specifically, enteric pathogens, most notably *E. coli* (but also staphylococcus, *C. coli, C. jejuni*, pseudomonous, salmonella, shigella, streptococcus, and vibrio) and some activity against *candida* (Sawer 1995). It has shown histamine antagonism, hypotensive, and vasodilatory activities (Iwu 1993). In addition it has demonstrative antihyperglcyemic properties (Brierer 1998).

***Chasmanthera dependens* Hoschst (Menispermaceae)**

A woody climber that grows wild in forest margins and savanna. The plant is cultivated. It is used medicinally for venereal disease, topically on sprained joints and bruises and as a general tonic for physical and nervous debilities. The constituents include berberine type alkaloids, palmatine, colombamine, and jateorhizine. Studies show that the berberine sulfate in the plant inhibits lieshmania.

***Nauclea latifolia* Smith (Rubiaceae)**

It is a shrub or small spreading tree that is a widely distributed savanna plant. It is found in the forest and fringe tropical forest. Medicinal uses are as a tonic and fever medicine, chewing stick, toothaches, dental caries, septic mouth and malaria., diarrhea and dysentery (Lamidi 1995).

Key constituents are indole-quinolizidine alkaloids and glycoalkaloids and sapponins. There are studies showing the root has antibacterial activity against gram positive and negative bacteria and antifungal activity (Iwu 1993). It is most effective against Corynebacterium *diphtheriae, Streptobacillis* sp., *Streptococcus* sp., *Neisseria* sp., *Pseudomonas aeruginosa, Salmonella* sp. (Deeni 1991).

***Araliopsis tabouensis* (Rutaceae)**

It is a large evergreen tree found throughout west tropical Africa. Its medicinal use is for the treatment of sexually transmitted diseases. The bark infusion is drunk for gonorrhea in the Ivory Coast (Irvine 1961). Its major constituents are alkaloids. Seven alkaloids have been isolated from the root and stem bark (Fish 1976).

CONCLUSION

Thomas Jefferson wrote that “The greatest service which can be rendered any country is to add a useful plant to it’s culture.” Plants have forever been a catalyst for our healing. In order to halt the trend of increased emerging and resistant infectious disease, it will require a multi-pronged approach that includes the development of new drugs. Using plants as the inspiration for new drugs provides an infusion of novel compounds or substances for healing disease. Evaluating plants from the traditional African system of medicine, provides us with clues as to how these plants can be used in the treatment of disease. Many of the plants presented here show very promising activity in the area of antimicrobial agents, warranting further investigation.

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