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Research review paper

Unexpected applications of secondary metabolites

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ABSTRACT

Secondary metabolites have been found to have interesting applications over and above their well-known medical uses, e.g., as antimicrobials, etc. These alternative applications include antitumor, cholesterol-lowering, immunosuppressant, antiprotozoal, antihelminth, antiviral and anti-ageing activities. Polyene antibiotics, such as amphotericin B, are of use as antiprion agents, antitumor drugs and against leishmaniasis. Other microbial natural products that show antibiotic activity are used against cancer e.g., doxorubicin, neomycin, β-lactams, bleomycin and rapamycin. Macrolide antibiotics, such as erythromycin, clarithromycin and azithromycin, improve pulmonary function in patients suffering from panbion cholitis. Pigments like prodigiosin and shikonin have antitumor activity, while violacein has anti-ulcer and antitumor activity and also acts as an antiprotozoal agent. Statins, in addition to lowering cholesterol and LDL levels, also decrease elevated C-reactive protein (CRP) levels independent of their cholesterol effects. Immunosppressants have many alternative effects: (i) Cyclosporin is proving useful in treatment of inflammatory disease such as asthma and muscular dystrophy. (ii) Rapamycin is extremely useful in preventing restenosis of stents grafted in balloon angioplasty. (iii) Tacrolimus and ascomycin help in treating inflammatory skin disease such as allergic contact dermatitis and psoriasis. Artemisinin, an antimalarial agent, is also showing antitumor activity. Other natural products, including those from plants (betulinic acid and shikonin), animals (bryostatins) and microbes (squalestatin and sophorolipids) have a multiplicity of potentially useful actions. Unexpected functions of known secondary metabolites are continuously being unraveled, and are fulfilling some of the needs of present day medicine and show great promise for the future.

Contents

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1. Introduction

Secondary metabolites, also referred to as natural products, are the products of metabolism not essential for normal growth, development or reproduction of an organism. These compounds serve to meet the secondary requirements of the producing organisms. They empower them to survive interspecies competition, provide defensive mechanisms and facilitate reproductive processes. Well known sources of secondary metabolites are plants, bacteria, fungi and marine organisms such as sponges, tunicates, corals and snails. Many secondary metabolites have proved invaluable as antibacterial or antifungal agents, anticancer drugs, cholesterol-lowering agents, immunosuppressants, antiparasitic agents, herbicides, diagnostics, and tools for research. Some of these have found to play a pivotal role in treatment or prevention of a multitude of biological disorders, many of which did not have any cure until these products were discovered.

In addition to their known activities and employment in combating disease, secondary metabolites reveal surprising additional activities which may be possible solutions to other diseases, some of which lack effective solutions. Many antibiotics, bacterial pigments, plant terpenoids, are also found to have anti-HIV, antitumor, anti-ageing, immunosuppressant, antiprotozoal and antihelminth activities, thus exhibiting multifarious applications in the sphere of medicine. Unraveling the novel applications of known secondary metabolites and exploiting a myriad of sources as microbes, plants and higher animals for screening new secondary metabolites are paving the way to treat "untreatable diseases", and help reduce mortality rates. In this review, we point out these other activities of useful secondary metabolites in the battle against life-threatening diseases in the hope that this will catalyze further efforts to apply these useful compounds against other forms of human disease. Of course, these further efforts will have to consider the possible toxicity of the compounds, resistance development and the possibility that humans may be resistant to them.

2. Antibiotics

Many antibiotics have a broad spectrum of activities (Table 1). For example, the majority of antitumor products used today in the fight against cancer were first discovered as antibiotics produced by microbes (Newman and Shapiro, 2008). These include actinomycin D (dactinomycin), anthracyclines (including daunorubicin, doxorubicin [adriamycin], epirubicin, pirirubicin, idarubicin, valrubicin, and amrubicin), glycopeptolides (bleomycin and phleomycin), the mitosane mitomycin C, anthracenones (mithramycin, streptozotocin, and pentostatin) and the endiyne calcheamycin attached to a monoclonal antibody (Mylotarg®).

2.1. β-lactams

The most well-known antibiotics are the β-lactams, i.e., penicillins and cephalosporins. Some β-lactam-based compounds also have activity as antitumor prodrugs (Xing et al., 2008). Also being considered are β-lactams as prodrugs that can specifically target tumor cells and as N-methylthiolated β-lactams which induce apoptosis (Kuhn et al., 2004). Apoptosis, also known as regulated cell death or programmed cell death, is different from necrosis in which cell death results from acute injury (Lederman, 2004). Apoptosis is required for normal development in which unneeded cells are eliminated. It occurs in three stages: (i) initiation occurs through activation of death receptors by a death signal such as damaged DNA; (ii) the enzyme caspase 3 is activated; (iii) caspase 3 cleaves effector molecules resulting in cell shrinkage, nuclear fragmentation and membrane blebbing. Induction of apoptosis is considered to be useful in fighting cancer.

2.2. Tetracyclines

Tetracyclines render prion aggregates susceptible to proteolytic attack (Borman 2002) and thus may be useful against prion diseases. Prion diseases include scrapie of sheep, spongiform encelopathy of cattle, Creutzfeldt–Jakob disease, fatal insomnia and Gerstmann–Struussler–Scheinker disease in humans (Forloni et al., 2002). These diseases, also known as transmissible spongiform encephalopathies (TSEs), are transmissible and cause neurodegenerative disorders of humans and animals for which no effective treatment is available. They are usually rapidly progressive and always fatal. They are associated with the conversion and accumulation of the alpha-helix rich prion protein (PrPC) into a beta-structure-rich, protease-resistant insoluble isoform (PrPSc) that is thought to be infectious. The normal isoform of this protein (PrP^c) is a copper-binding glycoprotein expressed at the surface of a number of cell types but principally neurons. The mechanism for the conversion of PrPC to PrPSc is poorly understood. PrPSc is a primary target for therapeutic strategies (Forloni et al., 2002). Both tetracycline and doxycycline reduce infectivity of prions. Although a number of other antiprion agents are known (e.g., quinacrine, polyanions, polyene antibiotics, anthracyclines [iododoxorubicin], chlorpromazine, Congo Red, tetrapyrroles, polyamines, antibodies and certain peptides), these are unable to pass the blood-brain barrier and/

Table 1
Alternative activities of antibiotics.

Antibiotic group	Unexpected activities
β-lactams	Antitumor (inducing apoptosis)
Tetracyclines	Antiprion, antimalaria
Aminoglycosides and macrolides	Pulmonary disease, immunomodulation, antitumor, antiparastic (leishmaniasis), antimalaria
Chloropeptins	Anti-HIV
Lincosamides	Antimalaria
Isoxazolidinones	Neurotransmission
Prodigines	Antiprotozoa, antimalaria, anticancer, immunosuppression
Polyenes	Imunomodulation, antiprion, antiviral, antitumor, anti-HIV, antiparasitic (leishmaniasis)
Coumermycins	Antitumor
Glycopeptides	Anti-HIV
Ansamycins	Anticancer, antiviral
Violacein	Antiprotozoal, antitumor, antiviral, anti-ulcer
Fosfidomycin	Antimalaria

or are toxic. The tetracyclines can pass through and are non-toxic. Tetracycline reverses abnormal physicochemical properties and abolishes neurotoxicity of PrP peptides *in vitro*. Hence, the ability of tetracycline to interact with PrP^{Sc} from patients with the new variant of Creutzfeldt–Jakob disease (vCJD) and cattle with bovine spongiform encephalopathy (BSE) was tested. The incubation with tetracycline hydrochloride or doxycycline hyclate at concentrations ranging from 10 μM to 1 mM resulted in a dose-dependent decrease in protease resistance of PrP^{Sc}. Thus, it can be concluded that tetracyclines reduce prion infectivity through a direct interaction with PrP^{Sc} and are potentially useful for inactivation of BSE- or vCJD-contaminated products and prevention strategies.

Doxycycline, a semisynthetic tetracycline, is useful against malaria (Schlitzer, 2008). A derivative doxycycline hyclate (Periostat®) is used against periodontis since it inhibits enzymes breaking down gum tissue (Golub et al., 1998).

2.3. Aminoglycosides and Macrolides

Among the most well-known antibiotics are the aminoglycoside antibacterials. A surprising finding was that the antibacterial neomycin inhibits human angiogenin-induced angiogenesis in human endothelial cells (Hu, 1998). Angiogenesis is a process of blood vessel growth involved in initiation, development, and progression of many diseases, including cancer, metastasis, and diabetic retinopathy. It is a fundamental step in the transition of tumors from a dormant state to a malignant one. The mechanism appears to act via neomycin's ability to inhibit phospholipase C. Surprisingly, other aminoglycosides (gentamicin, streptomycin, kanamycin, amikacin and paromomycin) are inactive even though paromomycin differs from neomycin by merely having –OH at position 6 of the glucose ring instead of $–NH_2$.

Paromomycin is up for approval in the USA, Europe and India for visceral leishmaniasis ("black fever"), a parasitic disease, which kills 200,000 people per year in Africa, Latin America and India (Filmore, 2004). This aminoglycoside had been used as a broad spectrum antibiotic from the 1960s to the 1980s and then donated to WHO by Pharmacia/UpJohn. With the help of WHO, the Gates Foundation and the non-profit One World Health organization, its activity against leishmaniasis was proven.

Azithromycin, a very successful semisynthetic erythromycin-type antibiotic, has found use against malaria (Schlitzer, 2008). Macrolides, including erythromycin, clarithromycin and azithromycin, improve pulmonary function and lower exacerbation frequency in patients suffering from diffuse panbion cholitis (DPB), a progressive obstructive lung disease prevalent in Asia (Schultz, 2004). The effect appears to be due to immunomodulation, i.e., anti-inflammatory action. Before use of aminoglycosides, the ten year survival rate was below 50%; with them, it is above 90%. The immunomodulatory action is unrelated to their antibiotic effects (Shinkai et al., 2008). Erythromycin and clarithromycin are employed in Japan for sinusitis and chronic obstructive pulmonary disease, e.g., diffuse panbronchiolitis (Kadota et al., 1993). Erythromycin has been used to treat cystic fibrosis and bronchiectasis. The effects of the macrolides differ from those of classical immunosuppressants. That the effect is not related to their antibiotic activity was shown by the discovery of macrolide EM703 which has no antimicrobial activity but retains immunomodulatory action (Li et al., 2006).

Derivatives of erythromycin with little or no antibacterial activity can inhibit HIV replication and may be useful vs. AIDS (Komuro et al., 2008). Since 1981, 65 million individuals have been infected with HIV, resulting in AIDS-caused death of 25 million. In 2006 alone, 4.3 million people were infected and 2.9 million died. About 2.5 million people were newly infected with HIV in 2007 while 2.1 million people died. In 2007, over 39 million people had HIV infections. The number of people living with HIV is rising, because of population growth and the fact that drug treatment is prolonging life.

2.4. Polyenes

Activities of polyene antibiotics, other than for antifungal therapy, that are being studied include (i) immunomodulation by activating cells of the immune system; (ii) anti-HIV activity by inhibiting HIV replication; (iii) anticancer activity in killing of hepatoma cells, (iv) antiprion activity by reducing insolubility and protease resistance of PrP^{Sc} (Zotchev, 2003) and (v) antiviral activity. Amphotericin B is effective in treatment of transmissible spongiform encephalopathies (TSE) in transgenic mice expressing Syrian Hamster PrP (Mangé et al., 2000). It acts by delaying the accumulation of PrP^{Sc} and increases the incubation time of the disease after experimental transmission in laboratory animals (Demaimay et al., 1999). Amphotericin B inhibits the Japanese encephalitis virus (JEV) (Kim et al., 2004). This is important since no other drug against JEV is available. The sterol-binding activity of the polyene antibiotic nystatin results in activity against the obligate intracellular parasite *Leishmania donovani*. This parasite infects macrophages of the vertebrate host resulting in visceral leishmaniasis in humans, a major public health problem worldwide. The molecular mechanisms involved in internalization of *Leishmania* are still poorly characterized. Nystatin sequesters cholesterol and markedly inhibits binding and entry of non-opsonized *L. donovani* promastigotes into macrophages (Tewary et al., 2006).

2.5. Coumermycins

The coumermycin type antibiotic novobiocin binds to DNA gyrase at its ATP-binding pocket and inhibits bacteria by blocking ATP hydrolysis. It also has antitumor activity especially against breast cancer. New and more potent antitumor analogs have been synthesized (Donnelly et al. 2008).

2.6. Glycopeptides

Promising anti-HIV drugs include the aglycones of the glycopeptide antibiotics, vancomycin, teicoplanin and eremomycin (Balzarini et al., 2003).

2.7. Ansamycins

Ansamycins contain a chromophore which is benzene- or naphthalene-based connected via an ansa bridge so that one end of the chromophore is linked to the other end by an amide linkage. The chromophore is derived from a mC_7N structure coming from 3-amino-5-hydroxybenzoic acid (AHBA) produced via the aminoshikimate pathway. The polyketide pathway supplies any other part of the chromophore and the ansa bridge (Wu et al., 2008). The most well-known ansamycin is rifampin which is semisynthesized from rifamycin, produced by *Amycolatopsis mediterranei*, and is effective against mycobacterial infections such as TB. Another is geldanamycin produced by *Streptomyces hygroscopicus*. A semisynthetic product, 17-allylamino-demethoxygeldanomycin (17AAG) is being studied clinically against cancer (Solit et al., 2007). Rifamycin and geldanomycin also have antiviral activity *in vitro*.

2.8. Lincosamides

Clindamycin, a semisynthetic lincosamide (a derivative of the antibacterial lincomycin), is an effective antimalarial drug especially when used with quinine (Lell and Kremser 2002; Schlitzer, 2008).

2.9. Isoxazolidinones

The broad spectrum isoxazolidinone antibacterial D-cycloserine increases function of a receptor for the neurotransmitter glutamate (Anonymous, 2008) that is part of memory extinction. The

neurotransmitter is called the NMDA receptor. Use of cycloserine helps humans lower their fear of heights. Recently, it is being used to help US military veterans lessen post-traumatic stress disorder.

2.10. Pigmented antibiotics

Prodigines are red tripyrrole antibiotics containing a pyrrolylpyrromethane skeleton They are produced by Gram-positive and Gram-negative bacteria (species of *Serratia*, *Hahella*, *Pseudomonas*, *Vibrio*, *Streptomyces*, *Streptoverticillium*, *Actinomadura*, *Saccharopolyspora*, *Alteromonas* and *Pseudoalteromonas*). In addition to their antibacterial action, they have many other activities: antifungal, antiprotozoal, antimalarial, anticancer and immunosuppressive (Williamson et al., 2006). The compounds include prodigiosin, undecylprodigiosin, butyl-methyl-cycloheptyl prodiginine, cycloprodigiosin and cyclonoyl-prodigiosin. More than 30 genes are involved in their biosynthesis. They are being tested against cancer since they cause apoptosis in tumor cells (Péreg-Tomás et al., 2003). Prodigiosin, a product of *S. marcescens*, exerts an antitumor effect by arresting the cell cycle and inducing apoptosis (Zhang et al., 2005). It has shown activity against hematopoeitic, colorectal, gastric, and pancreatic cancer cells. Its activity against pancreatic cancer gives hope for cure of this fourth leading cause of cancer in the USA, killing 30,000 people per year. It is very deadly with a 5-year survival for only 3–5% of those with the disease. Median survival after diagnosis is less than 6 months. Prodigiosin also has immunosuppressive properties (Pandey et al., 2007).

Violacein, a toxic blue–violet pigment from *Chromobacterium violaceum* with antibacterial activity, also protects against protozoa, acts against the tropical pathogens *Trypanosoma cruzi* (which causes Chagas' disease) and *Leishmania* sp., shows antitumor activity, antiviral activity (vs. polio and herpes) and anti-ulcer activity (Sánchez et al., 2006; Durán et al., 2007). It is being studied as an agent preventing gastric ulcers when complexed with β-cyclodextrin which decreases its toxicity (Duran et al., 2003).

2.11. Chloropeptins

These antibiotics, produced by the soil actinomycete *Streptomyces* sp., WK-3419, were found to have anti-HIV activity (Tanaka et al., 1997). Chloropeptins I and II inhibit the binding between the viral exterior envelope glycoprotein gp120 and CD4 receptors on the target cell, thus interfering with the cytopathic effect of HIV in MT-4 cells. They also inhibit syncytium formation in co-cultured HIV-1-infected MOLT-4 cells. Chloropeptin I is synergistic in inhibition of the cytopathic effect when combined with other anti-HIV drugs such as zidovudine (AZT), didanosine (ddI), zalcitabine (ddC) and nevirapine.

2.12. Fosfidomycin

Another antibiotic which has found use against malaria is fosfidomycin (Schlitzer, 2008). It is a structural analog of 2-C-methyl-D-erythrose-4-phosphate and inhibits a key enzyme in the non-mevalonate pathway used by the malaria parasite. When combined with clindamycin, it has shown success (Ruangweerayut et al., 2008).

3. Antitumor agents

In addition to unexpected activities of antibiotics, many other natural products have secondary activities with potential application in medicine (Table 2).

3.1. Anthracyclines

Doxorubicin is a member of the anthracycline group of anticancer compounds and is used in treating late stage tumors. Other members are bleomycin, daunorubicin, valrubicine, epirubicin and dactinomycin. Bleomycin also inhibits replication of hepatitis C virus (Rakic et al., 2006) and is active against HIV, including drug-resistant strains (Georgiou et al., 2006).

Table 2
Alternative action of secondary metabolites.

Secondary metabolite group/compound	Unexpected activities
Immunosuppressants	Antifungal, antitumor, anti-inflammatory, antimalarial, reversal of multidrug resistance to antitumor agents, nerve cell stimulation, stent-impregnation, neuroprotection, anti-atopic dermatitis (eczema)
Cholesterol-lowering agents (statins)	Stroke prevention, reduce development of peripheral vascular disease, antithrombotic, neuroprotective, anti-inflammatory, antiprion diseases, anti-multiple sclerosis, antitumor, antifungal, lower elevated C-reactive protein
Antitumor agents	Antiviral, including HIV, antifungal, memory enhancement
Artemisinin (antimalarial)	Antitumor
Shikonin (pigment for cosmetics)	Anti-inflammatory, antitumor, wound healing, anti-HIV replication
Sophorolipids (surfactants)	Antibacterial, antifungal, antitumor
Betulinic acid and derivatives	Antiretroviral, antimalarial, anti-inflammatory, antitumor

3.2. Taxol

Pacitaxel (Taxol), a plant alkaloid originally isolated from the Pacific Yew tree *Taxus brevifolia*, is one of the leading antitumor agents in use today, especially against breast cancer (Cisse and Mucke, 2009). In 1993, a taxol-producing endophytic fungus, *Taxomyces andreanae*, was discovered in *T. brevifolia*. Subsequently, fungal endophytes in a wide variety of higher plants were found to make taxol. Taxol prevents the depolymerization of microtubules during cell division in human tumor cells. The same effect has been observed in fungi; consequently, in nature, taxol acts as a fungicide.

3.3. Epothilones

The combination of anticancer and antifungal activity is also seen with the epothilones, compounds that have the same mode of action against breast tumors as taxol but are active against taxol-resistant tumors. Epothilones are 16-member ring macrolides produced by the myxobacterium *Sorangium cellulosum*. They bind to and stabilize microtubules essential for DNA replication and cell division, even more so than taxol. One epothilone (ixebepilone) has been approved by FDA. By preventing the disassembly of microtubules, they cause arrest of the tumor cell cycle at the GM2/M phase and induce apoptosis (programmed cell death). The mechanism is similar to that of taxol but they bind to β-tubulin at different binding sites and induce microtubule polymerization. The original development of the epothilones was for antifungal activity, but they made their mark against tumors (Goodin, 2008).

3.4. Bryostatins

These agents, found in extracts of the tiny colonial animal, i.e., the bryozoan *Bugula neritin*, are believed to be produced by the gamma proteobacterial symbiont *Endobugula sertula*. They have cytotoxic properties and are under investigation as anticancer agents. It has now been found that in numerous hematological and solid tumor cell lines, bryostatin-1 inhibits proliferation, induces differentiation, and promotes apoptosis. Furthermore, preclinical studies indicate that bryostatin-1 potently enhances the effect of chemotherapy. In many

cases, this effect is sequence specific. Bryostatin-1 is currently in phase I and phase II clinical trials (Kortmansky and Schwartz, 2003). Of relevance here is that bryostatins also are memory-enhancing agents. They have proved to be promising candidates for treatment for Alzheimer's disease, as tested on the snail Hermissenda, both for neurodegeneration, the underlying cause of the disease, and for the symptoms. The Food and Drug Administration (FDA) has given the Blanchette Rockefeller Neurosciences Institute (BRNI) the go-ahead to conduct Phase II clinical trials of bryostatin for the treatment of Alzheimer's disease patients (BRNI Press release; April 22, 2009).

4. Immunosuppressants

Immunosuppressants are valuable drugs which are produced by microorganisms and were first isolated as antibiotics. For example, rapamycin (sirolimus), tacrolimus (FK506), and cyclosporin A were discovered as antifungal antibiotics (High, 1994). However, they found their medical niche as immunosuppressants and are responsible for the success of the organ transplantation field. The antifungal and immunosuppressive activities may be unrelated since non-immunosuppressive derivatives have been obtained with good antifungal activity (Cruz et al., 2000). Two non-immunosuppressive analogs of cyclosporin are active against *Cryptococcus neoformans*. Like the immunosuppressive cyclosporin, they act by binding to cyclophilin A and inhibiting the action of the fungal calcineurin. A non-immunosuppressive analogue of tacrolimus also inhibits the fungus.

Cyclosporin A and tacrolimus convert the normally fungistatic activity of azoles (i.e., fluconozole) against *Candida albicans*, *Candida glabrata* and *Candida krusei* into fungicidal activity (Onyewu et al., 2003). They do this by inhibiting the protein phosphatase calcineurin. Even non-immunosuppressive analogs of tacrolimus have this ability. Non-azole drugs that inhibit other steps of ergosterol biosynthesis (terbinafine and fenpropimorph) are also improved in activity by immunosuppressants and their non-immunosuppressive analogs.

More than any group of microbial secondary metabolites, it is amazing how many additional potentially useful applications have been found for these compounds. Rapamycin has anticancer activity (Stoeltzing et al., 2006; Law, 2005; Sawyers, 2003; Brown et al., 2003; Wang et al., 2007). It and its derivatives specifically inhibit the mTOR (target of rapamycin) protein kinase as the mechanism in both immunosuppression and antitumor activities. Rapamycin and mycophenolic acid inhibit tumor growth by interfering with angiogenesis (Guba et al. 2002; Pray 2002; Chong et al., 2006). Furthermore, rapamycin shows synergy with protein tyrosine kinase (PTK) inhibitors such as Gleevac (Imatnib) which is used for leukemia but for which resistance is developing (Mohi et al., 2004). A rapamycin analog called temsirolimus (Toricel™) was approved for renal cell carcinoma (Rini et al., 2007). Rapamycin, cyclosporin A and tacrolimus also reverse multidrug resistance to antitumor agents in mammalian cells (Arceci et al. 1992).

Rapamycin has found a novel use in cardiology because rapamycin-impregnated stents are less prone to proliferation and restenosis which usually occur after treatment of coronary artery disease. The traditional treatment for coronary artery disease was the coronary artery bypass graft in which a vein from the leg is spliced around the heart blockage. The number of such surgical procedures dropped from 573,000 in 1995 to 519,000 in 2000. The drop was due to the use of cardiac stents (small metallic scaffolds) inserted into blocked arteries by threading them through the body from a small thigh opening, thus obviating heart surgery (balloon angioplasty). The stents are impregnated with rapamycin in a thin polymeric coating over the steel mesh. The drug is continuously eluted and prevents vascular smooth muscle cell proliferation, thus the cells cannot grow over the mesh (Ryan, 2003). As a result, stent restinosis is prevented. Such restinosis occurs in 15–60% of patients receiving bare stents (Vishnevetsky et al., 2004).

Cyclosporin A analogs are being clinically tested against the inflammatory disease asthma and are showing promising results (Eckstein and Fung, 2003). They exhibit decreased nephrotoxicity and have different pharmacology and metabolism.

Tacrolimus and rapamycin are also active in stimulation of nerve cells (Gold, 2000) and might find use for neurological disorders. Certain ascomycin derivatives made by combinatorial biosynthesis are being studied for nerve regeneration (Revill et al., 2002). Immunosuppressants have neuroprotective activity, i.e., they promote neurite outgrowth and protect neurons. Non-immunosuppressive analogs of rapamycin have been produced which retain neuroprotective activity (Ruan et al., 2008).

Cyclosporin A has activity against the malaria parasite *Plasmodium falciparum* in agreement with its genome containing sequences encoding cyclophilin and calcineurin (Berriman and Fairlamb, 1998; Dobson et al., 1999).

Ascomycins (immunomycins) were actually discovered earlier than the structurally related rapamycin and tacrolimus and are structurally related to rapamycin. They act as immunosuppressants, antitumor agents and antifungal agents. They never were commercialized as immunosuppressants. Novartis modified the structure of ascomycin, and produced Elidel®, an agent for inflammatory skin diseases (Petersen, 2005). It is successfully used as a topical drug to relieve atopic dermatitis (eczema) in children and also has use in Netherton syndrome. Launched in 2002, it already had sales of $349 million in 2004. Its anti-inflammatory action is also useful for topical treatment of allergic contact dermatitis and psoriasis. Tacrolimus is also being studied as a topical preparation for atopic dermatitis.

Cyclosporin A is being considered as a drug to correct mitochondrial dysfunction and muscle opoptosis in patients with collagen VI myopathies, which include muscular dystrophy (Merlini et al., 2008).

5. Cholesterol-lowering agents

The statins were first discovered in fungi. Compactin (mevastatin, ML-236B) was reported as an antifungal agent by Brown et al. (1976) from *Penicillium brevicompactum* and as a cholesterol-lowering drug by Endo (1985). The fungal fermentation products lovastatin (mevinolin, monocolin K, mevacor) produced by *Aspergillus terreus* and *Monascus ruber*, and compactin (mevastatin) from *Penicillium* spp. were found to be highly effective in reducing serum cholesterol in humans, especially cholesterol LDL levels. These compounds are potent inhibitors of 3-hydroxy-3-methylglutaryl-CoA reductase and block formation of all products of the mammalian polyisoprenoid pathway. They thus reduce the risk of cardiovascular disease.

Lovastatin, its related bioconversion compound pravastatin, its semisynthetic product simvastatin (Zocor), and its completely synthetic relative, atorvastatin (Lipitor) constitute the most economically successful drugs in the pharmaceutical industry. Of the above compounds, only compactin was not commercialized but instead was used as the substrate for the bioconversion to pravastatin. In addition to lowering cholesterol LDL levels, statins also lower elevated C-reactive protein (CRP) levels independent of their effect on cholesterol (Chan et al., 2004). This is important since half of all myocardial infarctions occur in patients with normal LDL levels. High CRP is associated with inflammatory response in atherosclerosis and is a predictor of future cardiovascular mortality.

Statins can also prevent stroke, reduce development of peripheral vascular disease, and have antithrombotic, neuroprotective and anti-inflammatory activities. They are showing beneficial effects in Alzheimer Disease, prion diseases, multiple sclerosis and cancer (Fogarty, 2003). The reduction of inflammation in Alzheimer's disease is unassociated with cholesterol levels. Statins do this by lowering isoprenyl intermediates which are involved in the disease (Hrastar, 2005). Their anti-inflammatory and neuroprotective properties may make statins useful for central nervous system (CNS) autoimmune

disorders such as multiple sclerosis (Youssef et al., 2002; Stuve et al., 2003; Wekerle, 2002; Brazil 2002). They inhibit production of pro-inflammatory molecules and are in clinical trials for multiple sclerosis. Experiments with oral statins showed efficacy in a mouse model of the disease. The anti-inflammatory effect appears to be independent of cholesterol-lowering.

Other activities being studied are stimulation of bone formation and antioxidation (Wrigley, 2004). Use of statins also leads to the decreased occurrence of sepsis. Simvastatin has an antibacterial effect against *Staphylococcus aureus* (Jerwood and Cohen, 2008). Against methicillin-resistant *S. aureus* (MRSA), the *in vitro* minimal inhibitory concentration (MIC) is 79 μg/ml whereas against methicillin-sensitive *S. aureus*, the value is 29 μg/ml. A statin derivative, fluvastatin, induces apoptosis in human tongue carcinoma cell line HSC-3, and is being considered as an antitumor drug (Fujiwara et al., 2008).

Squalestatin (zaragozic acid) is a fungal natural product which lowers cholesterol by a mechanism different from those described above which inhibit 3-hydroxy-3-methylglutaryl-CoA reductase; it inhibits squalene synthase. Low concentrations of squalestatin reduce the cholesterol content of the neurons and prevent the formation of PrP^{Sc} in three prion-infected cell lines (ScN2a, SMB and ScGT1 cells). It has been shown to cure prion-infected neurons and to protect against prion neurotoxicity. These observations suggest that squalestatin is a potential drug for the treatment of prion disease (Bate et al., 2004). Uninfected neurons treated with squalestatin became resistant to the otherwise toxic effect of PrP peptides, a synthetic miniprion (sPrP106) or partially purified prion preparations. The protective effect of squalestatin, which was reversed by the addition of water-soluble cholesterol, correlated with a reduction in prostaglandin E_2 production that is associated with neuronal injury in prion disease. These studies indicate a pivotal role for cholesterol-sensitive processes in controlling PrP^{Sc} formation, and in the activation of signaling pathways associated with PrP-induced neuronal death. Squalestatin also alters the intracellular trafficking of a neurotoxic prion peptide by shifting the prion protein from Golgi/ER to the degradative lysosomes and the neurotoxicity of this PrP peptide is dependent on trafficking to specific organelles where it activates specific signal transduction pathways (Wilson et al., 2007). Squalestatin also inhibits Ras farnesyl-protein transferase (FTase) which is believed to play an important role in development of progeria, a rare genetic disease characterized by premature aging in children, and various forms of cancer (Dufresne et al., 1993).

6. Other agents

6.1. Artemisinin

Artemisinin is a compound extracted from the wormwood plant, *Artemisia annua* L and is a leading antimalarial agent. In addition to this antimalarial action, it has been shown to selectively kill cancer cells *in vitro* and retard the growth of implanted fibrosarcoma tumors in rats (Singh and Lai, 2004).

6.2. Shikonin

Shikonin, a naphthaquinone pigment produced by cell culture of the plant *Lithgospermum erythrorhizon*, is widely used in the cosmetic industry. It also has anti-inflammatory, antitumor, wound healing, and anti-HIV replication activity (Chen et al., 2003; Lee et al., 2008).

6.3. Betulinic acid

Betulinic acid, a naturally occurring pentacyclic triterpenoid, is found in the bark of several species of plants, e.g., *Ziziphus mauritiana*, *Betula pubescens*, *Inonotus obliquus*, and cinder conk. It has antiretroviral, antimalarial, and anti-inflammatory properties, and potential as an anticancer agent by inhibition of topoisomerase (Noda et al., 1997). Betulin appears to be highly selective against tumor cells because the interior pH of tumor tissues is generally lower than that of normal tissues, and betulinic acid is only active at those lower levels. Fulda and Debatin (2005) reported that once inside the cells, betulinic acid induces apoptosis) in the tumors. A betulinic acid derivative was also shown to have anti-HIV activity.

6.4. Sophorolipids

Sophorolipids are surfactants produced by yeasts which have application in the food, cosmetic, pharmaceutical, and cleaning industries (Van Bogaert et al., 2007). They also have antibacterial, antifungal and antitumor properties. Production of sophorolipids by *Candida bombicola* is amazingly high, i.e. 400 g/L.

7. Final comments

Secondary metabolites have primarily been known for their extensive use as antibacterial and antifungal agents for the past 60 years. Other extremely successful applications of secondary metabolites are as antitumor agents, immunostimulants, and cholesterol-lowering agents, among others. Unexpected functions of known secondary metabolites are being unraveled and they have interesting applications in many life-threatening diseases such as prion diseases, Alzheimer's disease, cancer (hepatoma, breast, hematopoietic, colorectal, gastric, pancreatic, leukemia, renal cell and other carcinomas, and fibrosarcoma), pulmonary disease, cardiovascular disease, parasitic diseases and viral diseases such as AIDS. Since most of the compounds discussed here have been successfully used in humans, the relatively low degree of toxicity gives great hope that these unexpected activities will be exploitable as future cures for the terrible diseases confronting humans today, e.g., Alzheimer's disease, multiple sclerosis, cancer, parasitic diseases, cystic fibrosis, viral diseases and many others. Like the almost miraculous appearance of penicillin on the scene in the 1940s, we can look forward to a new era in medicine by taking advantage of molecules that are with us today as well as new derivatives to be made by chemists and microbial molecular geneticists.

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