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Plant-derived compounds in clinical trials

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Plants remain an important source of new drugs, new drug leads and new chemical entities. The plant-based drug discovery resulted mainly in the development of anticancer and anti-infectious agents and continues to contribute to the new leads in clinical trials. A total of 91 plant-derived compounds in clinical trials as of September 2007 are described in this review. A summary of the plant-based drugs launched during 2000–2006 is given.

Plants have been an integral part of the ancient culture of India, China and Egypt as medicine, and their importance even dates back to the Neanderthal period [1]. In the modern world, the finding of cinchona in 17th century, followed by digitalis, morphine, and so on, and then introduction of synthetic aspirin, a derivative of a plant-based drug, compelled human beings to believe in the wonders of the diverse floristic wealth [2]. A large number of plants used in the traditional medicine have now become a part of the modern world health care system [3]. Natural products offer large structural diversity [4], and modern techniques for separation, structure elucidation, screening and combinatorial synthesis [5–7] have led to revitalization of plant products as sources of new drugs. The introduction of herbals in the form of nutraceuticals and dietary supplements are also changing the plant-based drug market [8,9].

In the recent past, comprehensive reviews have appeared on natural products, including marine products in clinical trials [10–14]. This review describes plant-derived compounds, including herbal preparations in clinical trials as on September 2007, by disease area.

The market share of plant drugs

The global market for plant-derived drugs was worth an estimated $18 billion in 2005. BCC expects this figure to grow to nearly $19 billion in 2006 and more than $26 billion by 2011, at an average annual growth rate (AAGR) of 6.6% between 2006 and 2011 [15]. The U.S. accounts for 50% of the global plant-derived drug market and is expected to grow faster than other markets at an AAGR of 7.5% per year vs. 5.3% [16].

A total of 26 plant-based drugs were approved/launched during 2000–2006, which also include novel molecule-based drugs like Galanthamine HBr (Reminyl®), Miglustat (Zavesca®) and Nitisinone (Orfadin®) (Table 1).

Plant-derived natural products in clinical trials

For many centuries plants have been the main source of crude drugs used to cure or alleviate human sickness. In today's era of medicine engineering also, plants play an equally important role in drug discovery and development. The plant-derived compounds presently in clinical trials are discussed below for important therapeutic category (Figures 1 and 2).

Infectious and parasitic disease applications

Infectious and parasitic diseases are the second major cause of death, accounting for 15 million deaths each year worldwide [25]. Unlike antibacterials, which are dominated by antibiotics, plants have produced potential antiviral and antiparasitic drugs [26–28]. The drugs in clinical trials for different infectious and parasitic diseases are described below.

Artemisone/Artemifon (BAY 44-9585) in *Phase II*: This is a semi-synthetic antimalarial derivative of artemisinin that was first isolated from *Artemisia annua* (Asteraceae), a plant native to China, in 1971. Preclinical and clinical development of BAY 44-9585 (artemisone) is being done in collaboration with Medicines for Malaria Venture (MMV), Mahidol University, Bangkok and Bayer AG for the treatment of *Plasmodium*

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Table 1

Drugs approved/launched based on plant natural products during the period of 2000–2006[a]

Year	Generic name	Lead compound	Disease area	Company	Reference
2000	Exelon (Rivastigmine tartrate)	Physostigmine	Dementia–Alzheimer's disease	Novartis	[http://www.centerwatch.com/patient/drugs/druglist/], [17]
2000	Arteether (Artemotil®)	Artemisinin	Antimalarial	Brocacef	[18]
2000	Galanthamine HBr (Reminyl®)[b]	Galanthamine	Alzheimer's disease	Shire (U.K.), Johnson & Johnson (U.S.)	[18]
2000	Bexarotene	Retenoic acid derivatives	Cutaneous T cell lymphoma	Ligand Pharmaceuticals	[18]
2000	L-dopa-methyester (Levomet)	L-Dopa	Parkinson's diseases	Chiesi	[18]
2000	Malarone (Atovaquone; proguanil hydrochloride)[c]	Quinine	Antimalarial	GlaxoWellcome	[http://www.centerwatch.com/patient/drugs/druglist/], [17]
2000	Rapacuronium bromide (Raplon)	Tubocurarine	Neuromuscular blocking agent/anaesthesia	Akzo Nobel (Netherlands)	[18]
2001	Galanthamine HBr (Reminyl®)[b]	Galanthamine	Dementia–Alzheimer's	Janssen Pharmaceuticals	[http://www.centerwatch.com/patient/drugs/druglist/]
2002	Nitisinone (Orfadin®)	Leptospermone	Antityrosinaemia	Orphan Pharmaceuticals	[http://www.centerwatch.com/patient/drugs/druglist/], [19]
2002	Tiotropium bromide	Tiotropium	Chronic obstructive pulmonary disease	Boehringer Ingelheim	[19]
2002	Avinza (Morphine sulfate)[c]	Morphine	Pain	Elan	[http://www.centerwatch.com/patient/drugs/druglist/]
2003	Miglustat (Zavesca®)[d]	1-Deoxynojirimycin	Type1 Gaucher disease	Oxford Glycosides/Actelion/Celltech	[20–22]
2004	Spiriva HandiHaler (Tiotropium bromide)[c]	Tiotropium	Chronic obstructive pulmonary disease	Boehringer Ingelheim	[http://www.centerwatch.com/patient/drugs/druglist/], [http://www.drugs.com/newdrugs/]
2004	Apokyn (apomorphine HCl)[c]	Apomorphine	Parkinson's diseases	Mylan Bertek pharmaceuticals	[http://www.centerwatch.com/patient/drugs/druglist/; http://www.drugs.com/newdrugs/]
2004	Palladone (hydromorphone)		Moderate-to-severe pain	Purdue Pharma L.P.	[http://www.drugs.com/newdrugs/]
2004	DepoDur (morphine sulfate) extended release[c]	Morphine	Post-surgical pain relief	SkyePharma PLC and Endo Pharmaceuticals	[http://www.drugs.com/newdrugs/]
2004	Belotecan	Campthotecin	Ovarian & small lung cancer	Chong Kun Dang	[23]
2005	Tamibarotene (Amnolake)	Retenoic acid derivatives	Acute myelogenous leukaemia	Nippon Shinyaku	[24], http://www.nippon-shinyaku.co.jp/
2005	Abraxane (paclitaxel protien-bound particles)[c]	Paclitaxel	Breast cancer	American Pharmaceuticals Partners, Inc./American Bioscience	[http://www.drugs.com/newdrugs/]
2005	THC:CBD (Sativex)[e]	THC, CBD	MS pain	GW Pharma	[24]
2006	Taxotere (docetaxel) injection[f]	Docetaxel	Antineoplastic (head and neck cancer) and stomach cancer	Sanofis-Aventis	[http://www.drugs.com/newdrugs/]
2006	Duodote (atropine and pralidoxine chloride) injection	Atropine	Exposure to organophosphorous nerve agents (Antidote)	Meridian Medical Technologies	[http://www.drugs.com/newdrugs/]
2006	Exelon (rivastigmine tartrate)[f]	Phytostigmine	Dementia–Parkinson's	Novartis	[http://www.drugs.com/newdrugs/]
2006	Hycamtim (topotecan HCl)	Camptothecin	Cervical cancer	GlaxoSmithkline	[http://www.drugs.com/newdrugs/]
2006	Cesamet (nabilone)	Delta-9-THC	Chemotherapy nausea and vomiting	Valeant Pharmaceuticals International	[http://www.drugs.com/newdrugs/]
2006	Polyphenon E (Veregen) Ointment	Green tea polyphenol (catechin) extract	Genital and perianal warts	MediGene AG	[http://www.drugs.com/newdrugs/]

[a] New formulation (NDDS) and new indications of existing drugs are included.
[b] Galanthamine (Reminyl®) was approved for sale in U.K. and Ireland in 2000 and was approved for sale in U.S. by 2001 November and was launched in January 2002.
[c] New formulation or new salt form of an existing drugs.
[d] Miglustat (Zavesca) was approved in U.K. in 2002, launched by 2003 by Celltech, and approved in U.S. in 2003.
[e] Sativex launched in Canada, U.K. and in clinical trials in U.S.
[f] New indication of an existing drugs.

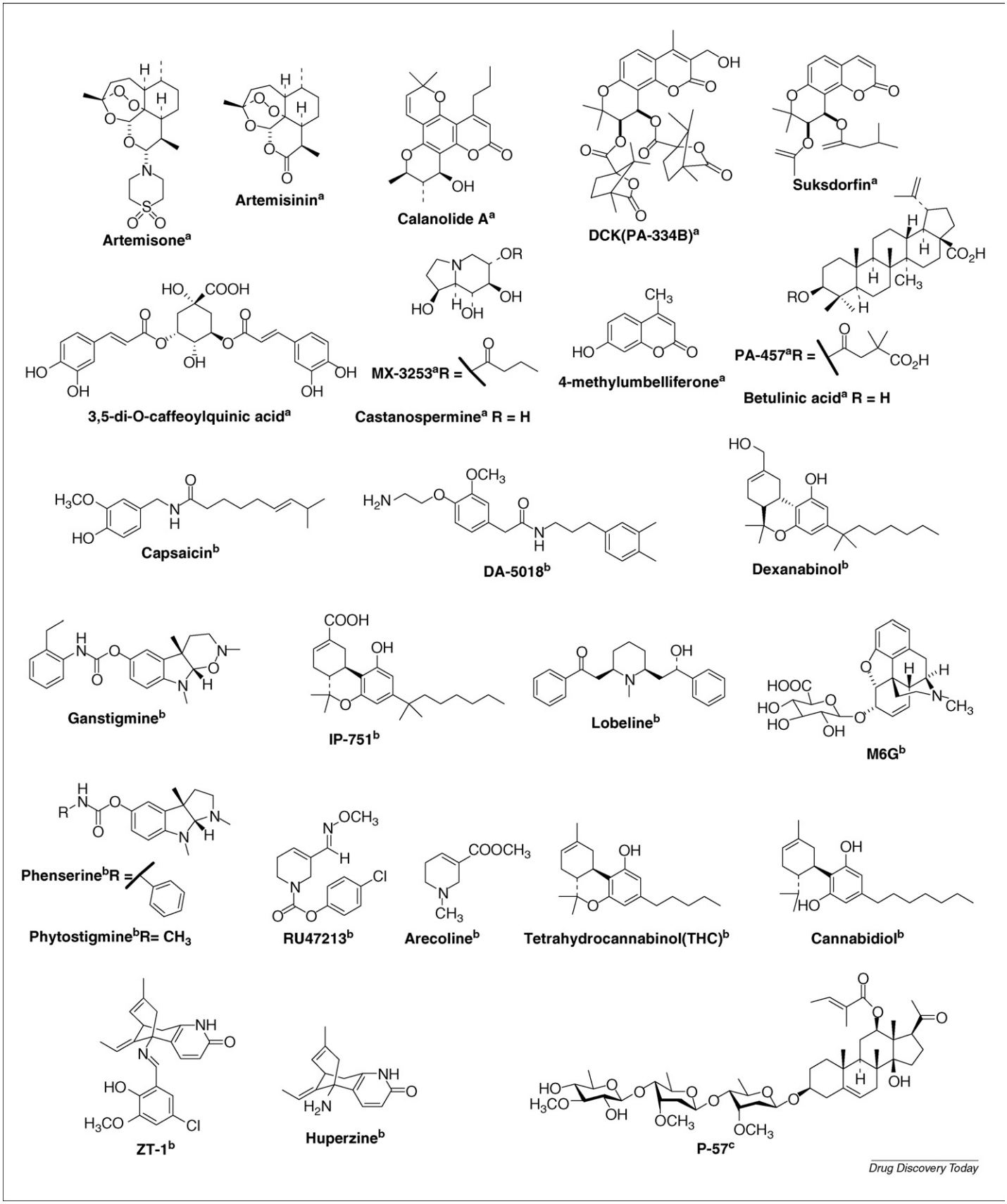

FIGURE 1

Plant-derived compounds launched in clinical trials. **(a)** Infectious and parasitic disease application, **(b)** pain and neurological disease application, **(c)** cardiovascular and metabolic disease application.

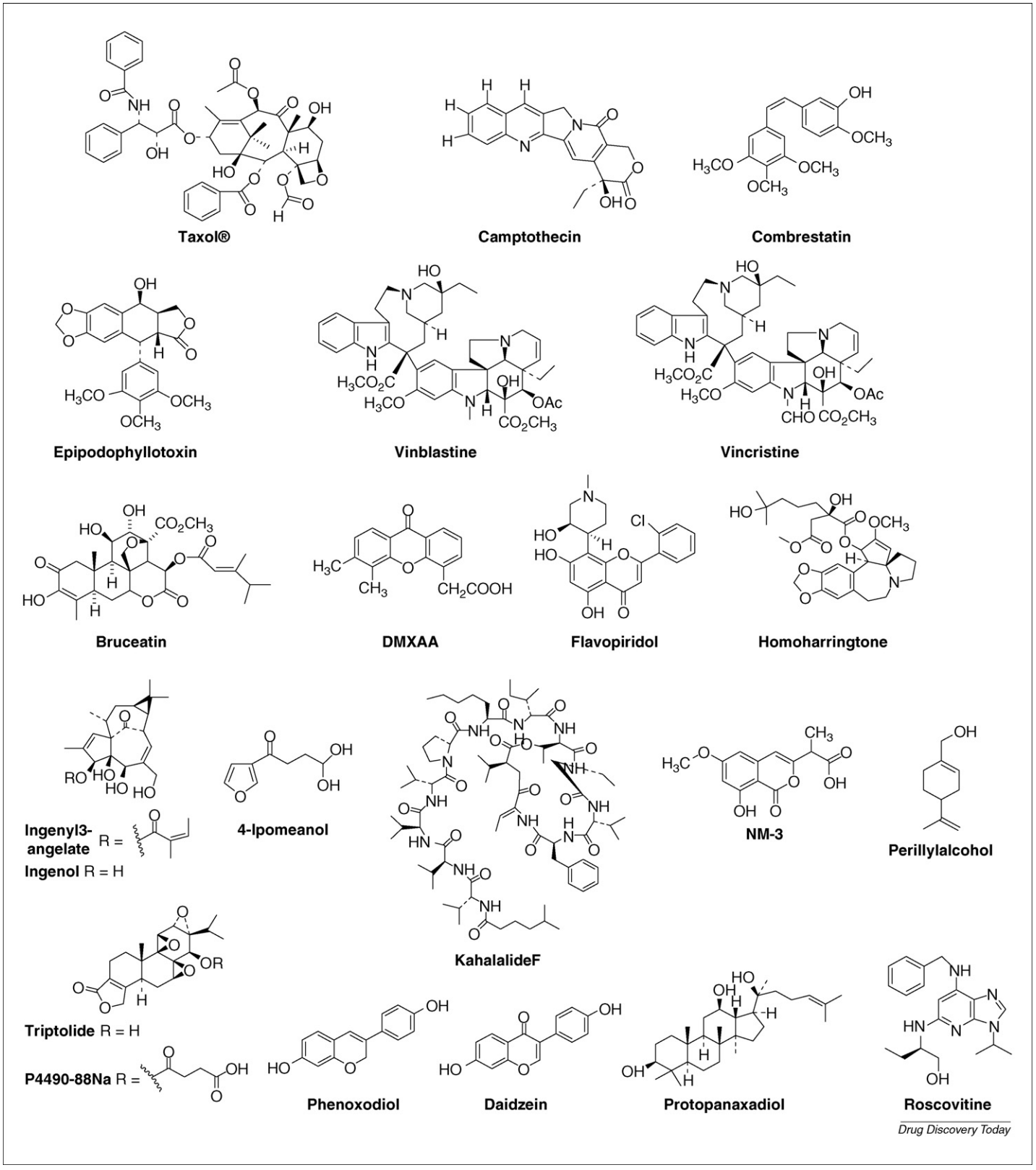

FIGURE 2

Plant-derived anticancer drugs launched/in clinical trials.

falciparum infection. Artemisone inhibits sacroplasmic reticulum Ca^{2+} transporting ATPases (SERCAs), specifically the SERCA of the malarial parasite (pfATP6), and, in addition, a free radical-based mechanism is proposed for its action [29]; [http://www.public-health.tu-dresden.de/dotnetnuke3/Portals/0/VKliPhaDresden%202005.pdf].

Calanolides in *Phase II*: Calanolide A, an anti-HIV coumarin, was isolated by the National Cancer Institute from the fruit and

twigs of the tree *Calophyllum lanigerum* var. *austrocoriaceum* (Guttiferae). This compound was licensed to Sarwak Medichem Pharmaceuticals (SMP) and was being evaluated in combination with other anti-HIV agents. Calanolide A also has an activity against all *Mycobacterium tuberculosis* strains tested and may allow more efficient treatment of patients with both HIV and tuberculosis. The related coumarins calanolide B (costatolide), dihydrocalanolide B and oxocalanolide are also under preclinical development by Sarawak Medichem and NCI. The development of Calanolide A and its related compounds is on hold, and the fate will be decided by the Sarawak government, who now owns SMP and its HIV-therapeutic candidates [30,31].

Crofelemer (CAS 148465-45-6) in *Phase III*: It is an oligomeric proanthocyanidin derived from the latex of *Croton lecheri* (Euphorbiaceae) and being developed by Napo's partners, Trine Pharmaceuticals Inc. and AsiaPharm Group Ltd., to treat different types of diarrhoea. Crofelemer, is in various stages of clinical development for four distinct product indications, including (a) CRO-HIV for AIDS diarrhoea in Phase III, (b) CRO-IBS for diarrhoea irritable bowel syndrome ('D-IBS') and CRO-ID for acute infectious diarrhoea (including cholera) in Phase II and (c) CRO-PED for paediatric diarrhoea in Phase I. It has a novel anti-secretory mechanism of action that blocks chloride ion secretion via cystic fibrosis transmembrane conductance regulator (CFTR) channel, normalizes water flow in the gut treating diarrhoea and thereby preventing dehydration Recently, Napo obtained Special Protocol Assessment (SPA) agreement from U.S. FDA for Crofelemer in HIV/AIDS Diarrhea Assessment [http://www.prnewswire.com/, http://www.napopharma.com].

DCK (PA-334B) in *Phase I*: It is a 3-hydroxymethyl-4-methyl khellactone coumarin derivative, a modified form of suksdorfin, which is isolated from methanol extracts of *Lomatium suksdorfii* (Apiaceae). DCK (PA-334B) is a nanomolar inhibitor of both primary clinical and drug resistant HIV-1 isolates. Panacos pharmaceutical has nearly completed the required preclinical studies for IND filing [31].

3,5-di-O-caffeoylquinic acid in *Phase I*: It was isolated from *Inula britannica* (Asteraceae). China's Academy of Military Sciences is carrying out clinical trial, which acts as an irreversible inhibitor of HIV and Hepatitis C integrase. It can be synthesized chemically and is also expected to be examined in combination with existing drugs for the above-mentioned two infections [32].

MX-3253 (*celgosivir*, *MBI-3253*, *6-O-butanoylcastanospermine*) in *Phase II*: It is a semi-synthetic derivative of castanospermine, an alkaloid originally isolated from *Castanospermum australe* (Fabaceae). The Canadian company MIGENIX is evaluating it for the treatment of patients with chronic Hepatitis C. MX-3253 is an orally active inhibitor of α-glucosidase I, a mammalian enzyme that affects the early stages of glycoprotein processing. Recently, the Phase II clinical trial as combination therapy with peginterferon α-2b and ribavirin in Chronic Hepatitis C Genotype-1 Non-responder Patients has been completed [http://www.migenix.com/, http://www.hepatitis-central.com].

4-Methylumbelliferone in *Phase II*: An umbelliferone (7-hydroxycoumarins) derivative present in many plants such as manna ash, sweet woodruff, German chamomile, celery, parsley, amongst others, is being developed for the treatment of Hepatitis C and B by M T Medical Institute of Health, University of Texas Health Science Center at San Antonio and BioMonde Preparations Limited. Products containing 4-methylumbelliferone as their active substance have been available in the U.S.A. and Europe since 1990, as dietary supplements under the trade names Heparvit®, Heparmed®, DetoxPro®) [http://www.mtmedical.org/, http://www.clinicaltrial.gov/ct].

Milk Thistle in *Phase II*: The *Silybum marianum* (Asteraceae) has been used for centuries for diseases of the liver and biliary tract. A standardized extract of milk thistle (Silymarin) is being evaluated by the National Center for Complementary and Alternative Medicine (NCCAM). Silymarin has flavonoids silybinin, silydianin and silychristin as active constituents that work as antioxidants (scavenging free radicals) and inhibit lipid peroxidation. Studies also suggest that they protect against genomic injury, increase hepatocyte protein synthesis, decrease the activity of tumour promoters, stabilize mast cells, chelate iron and slow calcium metabolism [http://www.hepatitis-central.com/, http://www.clinicaltrials.gov/].

PA-457 (*Bevirimat*) in *Phase IIb*: It is 3-*O*-(3′,3′-dimethylsuccinyl) betulinic acid, a semi-synthetic derivative of the plant triterpenoid betulinic acid isolated from the leaves of *Syzygium claviflorum* (Myrtaceae). Panacos Pharmaceutical is developing its lead compound PA-457 as an antiviral drug. The antiretroviral activity of PA-457 is due to a novel mechanism of action, blocking a late step in processing of the Group-specific antigen (Gag) protein. The resulting virus particles are structurally defective and are incapable of spreading infection around the body. PA-457 is a new class of HIV drugs called maturation inhibitors [11,33]; http://www.panacos.com].

PYN6 in *Phase I*: This is a fraction isolated from a single plant and is being developed by Phynova as an antibacterial. In the preclinical screening assays conducted in China *PYN6* has shown activity against major classes of infectious bacteria that have acquired resistance to current front-line antibiotics, such as methicilin-resistant *Staphylococcus aureus* (MRSA) [http://www.phynova.com].

Sho-saiko-to (H09) in *Phase II*: It is a standardized aqueous extract from the roots of *Scutellaria*, *Glycyrrhiza*, *Bupleurum* and ginseng; the pinella tuber; the jujube fruit and the ginger rhizome. It is manufactured and supplied by Honso Pharmaceutical Co. Ltd. Japan and is under clinical studies to determine its effect on Hepatitis C patients. SST is known to have anti-fibrotic effect through inhibition of lipid peroxidation in hepatocytes and stellate cells in animal studies. It reduces aminotransferase levels, increases hepatic levels of superoxide dismutase and the incidence of hepatocellular carcinoma in hepatitis and liver cirrhosis patients [34]; [http://honsousa.com/Sho-saiko-to.htm, http://hepatitis-central.com].

Sutherlandia frutescens in *Phase I*: A shrub of the Fabaceae family was evaluated for its anti-HIV activity by the Medical Research Council of South Africa. The principal active constituents of *S. frutescens* include L-canavanine, GABA and D-pinitol. *In vitro* studies have shown effects of *S. frutescens* on CYP3A4, P-gp and PXR and produce nearly complete inhibition of CYP3A4 (96%) [35]; [http://www.newscientist.com, http://www.clinicaltrials.gov].

Pain and neurological disease applications

In the modern world, neurological disorders, such as Alzheimer's disease, Parkinsonism, migraine, epilepsy, multiple sclerosis, and so on, are highly prevalent. It is estimated that in 2000, mental and neurological disorders accounted for 12% of the total disability-adjusted life years (DALYs) lost because of all diseases and injuries. By 2020, it is projected that the burden of these disorders will have increased by 15% [http://www.who.int/whr/2001/]. Some of the earliest drugs used for this category include opiate alkaloids from *Papaver somniferum*, tropane alkaloids like cocaine from *Erythroxylon coca*, galanthamine from *Galanthus nivalis* and the anticholinestrase agent physostigmine from *Physostigma venenosum*, and so on. The plant-derived drugs presently in clinical trials for this category are discussed below.

DA-5018 in Phase II: It is a synthetic capsaicin analogue that is being developed by the Korean company Dong-A Pharmaceuticals as a non-narcotic analgesic. Capsaicin causes the burning sensation associated with eating chillies by binding to the ion channel receptor transient receptor potential vanilloid (TRPV1) formerly vanilloid receptor subtype1 (VR1) [11]; [http://www.donga-pharm.com/].

Dexanabinol in *Phase III & II*: It is being developed by Pharmos as a neuroprotective product. Dexanabinol is a non-psychotropic dextrocannabinoid, currently undergoing Phase III clinical trials as a treatment for traumatic brain injury and Phase II testing as a preventative agent against post-surgical (CABG) cognitive impairment. Dexanabinol is an antioxidant, anti-inflammatory and a weak and safe *N*-methyl-D-aspartate receptor antagonist [http://www.rddirections.com, http://pharmalicensing.com/article].

Ganstigmine (CHF2819) in *Phase II*: It is a novel AChE inhibitor derived from genserine, for which animal models suggest significant neuroprotection independent from its cholinergic activity. Chiesi Farmaceutici had been testing ganstigmine hydrochloride in Phase II for the treatment of AD; however, the company discontinued development of the drug candidate in order to focus resources on other therapeutic areas [http://www.centerwatch.com, http://integrity.prous.com/].

IP-751 (*Ajulemic acid*, *CT-3*) in *Phase II*: It is a synthetic analogue of the THC metabolite, THC-11-oic acid developed by Atlantic Technology Ventures, U.S.A. and is currently at Indevus in Phase II clinical trials for the treatment of neuropathic pain. It is also undergoing clinical trials for treatment of tremor and spasticity in multiple sclerosis. IP-751 appears to inhibit COX-2 and other inflammatory cytokines, particularly interleukin-1β, TNF-α and also the Peroxisomes Proliferating Activated Receptor-γ (PPAR-γ) and is partial cannabinoid (CB) receptor agonist [11,36]; [http://integrity.prous.com/].

LLL-2011 (Amigra) in *Phase III*: It is a botanical drug being developed by Lupin as a nasal spray for prophylaxis of migraine. Lupin has received regulatory approval in India to conduct clinical trials in 10 centres. In Phase II clinical trial it was found to be safe and well tolerated with good efficacy data [37]; [http://www.lupinworld.com/].

Lobeline in *Phase I*: It is a pyridine alkaloid isolated from *Lobelia inflata* (Campanulaceae), which has been used for centuries as an emetic and respiratory stimulant and, more recently, as a smoking cessation agent. Yaupon Therapeutics and NIH are evaluating Lobeline for methamphetamine addiction. Preclinical studies have suggested that lobeline has utility in helping to treat attention deficit hyperactivity disorder (ADHD) [11]; [http://www.yauponterapeutics.com/].

M6G in *Phase III*: It is morphine 6-glucuronide a metabolite of morphine, the naturally occurring alkaloid in the opium poppy (*Papaver somniferum*). M6G is being developed by CeNeS Pharmaceuticals plc for post-operative pain following surgical procedure and has shown promising results comparable to morphine. It has superior side effect profile in terms of reduced liability to induce nausea, vomiting and respiratory depression. It has higher efficacy and low affinity on μ-opioid receptor than morphine. The U.S. FDA has approved the IND application for the clinical development of M6G. CeNeS is currently completing the protocol design of the first U.S. Phase III trial [38]; [http://www.cenes.com/index.htm].

NGX-4010 in *Phase III & II*: It is an application of a pure, high-concentration of synthetic trans-capsaicin developed by NeurogesX and is directly applied via a rapid-delivery dermal application system. Currently it is being studied in Phase III trials in post-herpetic neuralgia (PHN) and neuropathic pain related to HIV-associated neuropathy. Phase II trials are also underway for neuropathic pain related to peripheral diabetic neuropathy. The local anaesthetic effect results from continuous activation of the TRPV1 receptor, a ligand-gated ion channel activated by agonists such as capsaicin. NeurogesX plans to complete a confirmatory Phase III trial in PHN in the second half of 2007 [http://pharmalicensing.com, http://www.neurogesx.com/ngx_4010].

P58 (*PYM-50028*, *Cogane*™) in *Phase II*: It is a plant-derived compound obtained from a traditional Asian 'tonic' that has been found beneficial to those with dementia. This novel non-peptide is being developed by Phytopharm for the treatment of Parkinson's disease and AD type dementia. Cogane™ reverses the changes in area of the brain involved in Parkinson's disease by inducing the production of neurotrophic factors. These growth factors promote the growth and connectivity of neurones and reverse the atrophy of this area of the brain. In addition, this restores the learning and memory ability in Alzheimer's disease models and thereby offers the potential to reverse the symptoms of Alzheimer's disease [http://www.phytopharm.co.uk, http://integrity.prous.com/].

Phenserine (*Phenserine tartrate*, *Posiphen*™) in *Phase III*/*Phase I*: It is a third generation derivative of phytostigmine isolated from *Physostigma venenosum* (Leguminosae) being developed by Axonyx to treat mild-to-moderate Alzheimer's disease (AD). It is a reversible acetylcholinestrase (AChE) inhibitor and also reduces the production of beta amyloid precursor protein (β-APP). Because of this dual mechanism of action, Phenserine has the potential to improve memory as well as to slow AD progression. Posiphen is an antiamyloidogenic agent in Phase I clinical trials at TorreyPines for the treatment of AD and was recently acquired through a reverse merger with Axonyx [http://www.centerwatch.com, http://integrity.prous.com/]; [11].

RU 47213 in *Phase II*: It is a pro-drug based on arecoline, an alkaloid found in *Areca catechu* L. (Palmae) under development for treatment of AD by Sanofi-aventis, whose carbamate function is hydrolyzed *in vivo* to form the tetrahydropyridine oxime RU

35963, a muscarinic M1 agonist. After oral administration, RU 47213 seems superior to arecoline in terms of potency, central selectivity and duration of action, and is also active in animal models of cognition, without eliciting significant cholinergic side effects [39].

THC-CBD (Dronabinol/cannabidiol, GW-1000-02, Sativex®) in *Phase III*: It is a cannabis (*Cannabis sativa*)-based pharmaceutical product containing delta 9-tetrahydrocannabinol (THC) and cannabidiol (CBD) in a 1:1 ratio and is being developed by GW Pharmaceuticals. It has been approved as adjunctive treatment for neuropathic pain and cancer pain with multiple sclerosis (MS) in U.K. and Canada. It is being investigated for the management of other MS symptoms, such as spasticity. They act on CB receptors that are involved in the control of spasticity where there is neurological damage. The most common adverse events (AEs) reported in trials were dizziness, sleepiness, fatigue, feeling of intoxication and a bad taste [http://www.gwpharm.-com/, http://www.clinicaltrial.gov].

ZT-1 (DEBIO-9902) in *Phase II*: It is a pro-drug of huperzine isolated from the club moss, *Huperzia serrata* (Lycopodiaceae). ZT-1 was originally synthesized by Zhu and co-workers at Shanghai Institute of Material Medica. It is being evaluated by Debiopharm for the treatment of AD. The dual mode of action of ZT-1, as a *N*-methyl-D-aspartate receptor antagonist and an AChE inhibitor, positions it as a third generation anti-Alzheimer's product by improving the general condition and cognitive functions of affected patients as well as having the potential of being a neuroprotectant [http://www.debiopharm.com/; [11].

Cardiovascular and metabolic disease applications

Cardiovascular and metabolic diseases have been major causes of death throughout the world and are an ever increasing disease area because of the modern life style. According to the WHO cardiovascular diseases are the leading causes of death, responsible for 30% of all deaths or 17.5 million deaths in 2005 [25]. According to the International Diabetes Federation, 41 million people in India have diabetes, and this is expected to increase to 75–100 million people by 2025. Thus, there is a need for new drugs in these categories in both the developed and developing worlds. Plant-based drugs have been a useful source of active compounds for these indications, including cardiac drugs like digoxin, sennosides, forskolin and α-glucosidase inhibitors such as miglitol, for type 2 diabetes mellitus. Those drugs currently in clinical trials for these indications are reported below.

P-57 (P-57AS3) in *Phase II*: This is a functional food product candidate based on an extract of the succulent plant *Hoodia gordonii* (Asclepiadaceae), which has been traditionally eaten by Kung people of Kalahari desert to avoid feelings of hunger and thirst during hunting. P-57, a steroid glycoside, and related compounds were isolated from *Hoodia gordonii* by the South African Council for scientific and Industrial Research (CSIR). P-57 contains a novel satiety stimulator that reduces calorie intake in overweight subjects and, at present, is being developed by Phytopharm and Unilever for the oral treatment of obesity. [http://www.phytopharm.co.uk/].

PMI-5011 in *Phase II*: This is a proprietary anti-diabetic botanical extract derived from *Artemisia dracunculus* L. It is currently going through human efficacy study in 30 patients with type 2 diabetes. The synergistically acting compounds in the extract are likely to be responsible for its pronounced anti-diabetic effects that include modulation of aldose reductase inhibitors, steroid 5α-reductase inhibitors, xanthine oxidase inhibitors, glucagon like peptide-1 (GLP-1) binding, increase in glucose muscle uptake and inhibition of phosphoenolpyruvate carboxykinase (PEPCK) activity [http://www.phytomedics.com/].

Inflammatory and related disease applications

Plant-based drugs and many herbal preparations alter immune function and have an amazing array of immunomodulatory effects attributed to them [40]. The salicyclic acid derivative, aspirin, has been a cornerstone for the treatment of inflammation-associated diseases, and many plant-based preparations have also been reported for their activity against immunological conditions [41].

Flavocoxid in *Phase I*: An extract derived from *Scutellaria baicalensis* (Lamiaceae) and *Acacia catechu* (Mimosaceae) is being developed for Osteoarthritis by National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), U.S.A. and Primus Pharmaceuticals. It has been shown to inhibit cyclooxygenase (COX)-1 and COX-2 as well as 5-lipooxygenase [http://www.clinicaltrial.gov].

Grazax in *Phase III*: The standardized extract of the protein allergens obtained from the pollen of *Phleum pretense* (Poaceae) is being developed by ALK-Abelló (Sweden) for hay fever. It has been launched in Germany, Denmark, Norway, Sweden and the U.K. Clinical trials have shown that during the first allergy season, Grazax can reduce hay fever symptoms by 30% and reduce the need for symptomatic medication. Side effects include tingling or itching in the mouth. Phase III clinical trials are underway for use in the treatment of children aged 5–16 years with grass pollen induced rhinoconjunctivitis with or without asthma [42]; [http://www.alk-abello.com/].

Paxceed (micella Paclitaxel) in *Phase II*: An intravenous chemotherapy agent with anti-inflammatory and immunomodulatory properties is being developed by Angiotech Pharmaceuticals for RA. The active substance in Paxceed™, paclitaxel, has demonstrated its usefulness as an agent that stops growth of cells and blocks certain types of cell function associated with RA. Because of these effects, it is thought that Paxceed™ might alter the destructive course of RA. Another advantage is synergism rather than competition with recently developed anti-TNF therapies [http://www.centerwatch.com/, http://www.clinicaltrials.gov/, http://www.angiotech.com/].

PMI-001 in *Phase III*: An orally bioavailable and multi-mechanism botanical drug for auto-immune disease exerts its potent anti-inflammatory/immunosuppressant activities through unique and synergistic modes of action, including inhibition of IL-2, a-TNF, i-NOS, and COX-2 gene transcription. The Phase II trial showed halting joint erosion and joint space narrowing, and evidence of extremely rapid pain and inflammation reduction [http://www.phytomedics.com/].

PMI-005 Phase II completed: It is an anti-inflammatory botanical drug candidate being developed by Phytomedics for rheumatoid arthritis. PMI-005 is an orally bioavailable, small molecule gene-transcription inhibitor of a variety of pro-

TABLE 2

Plant-based anticancer drugs in clinical trials

Name of analogue	Clinical status	Developer	Reference
(A) Paclitaxel/Taxol analogues; MOA[a]—antimiotic agent blocking cells in the metaphase [48]			
ABI-007 (suspension)	Phase III	American Biosciences	[49], http://www.abraxisbio.com/
BMS-188797	Phase II	Bristol–Myers Squibb	[http://www.bms.com/]
BMS-184476	Phase II	Bristol–Myers Squibb	[http://www.bms.com/]
BMS-275183	Phase I/II	Bristol–Myers Squibb	[http://www.bms.com/]
DHA-paclitaxel	Phase III	Luitpold	[http://www.luitpold.com]
DJ-927	Phase II	Daiichi–Sankyo	[http://www.sankyopharma.com/products/pipeline.html]
MAC-321 (TL-00139)	Phase II	Wyeth/Taxolog	[http://www.wyeth.com,www.taxolog.com]
MST-997 (TL-909)	Phase I	Wyeth/Taxolog	[http://www.wyeth.com,www.taxolog.com]
Ortataxel (IDN-5109, BAY-59-8862)	Phase II	Bayer/Indena	[11]
Paclitaxel poliglumex (Xyotav)	Phase III	Cell Therapeutics	[50], http://www.cticseattle.com/
PNU-166945 (Taxol-HMPA polymer)	Phase I	Pfizer	[49], http://www.pfizer.com/
RPR-116258A	Phase III	Sanofi-Aventis	[http://www.sanofi-aventis.com]
TPI-287	Phase II	Tapestry Pharmaceuticals	[51], http://www.tapestrypharma.com/
TXD-258 (XRP-6258, RPR-116258A)	Phase IIa	Sanofi–Aventis	[http://www.sanofi-aventis.com]
XRP_9881 (RPR-109881 A)	Phase III	Sanofi–Aventis	[11,49]
(B) Camptothecin-based analogues; MOA[a]—topoisomerase I inhibitor [52]			
9-amino camptothecin	Phase III	Pharmacia	[49]
BN-80927	Phase I	Ispen/Roche	[http://www.ipsen.com, http://www.roche.com]
Diflomotecan (BN-80915) 100	Phase II	Ipsen	[http://www.ipsen.com]
DRF-1042	Phase II	Dr Reddy	[http://www.drreddys.com]
Exatecan mesilate	Phase III	Daiichi Pharmaceuticals	[49], http://www.daiichipharm.co.jp/english/
Gimatecan (ST-1481)	Phase II	Novartis/Sigma-Tau	[11]
Irinotecan (Hycamp)	Phase IIb	Meditech's & Alchemia	[53]
Karenitecin® (BNP-1350)	Phase I/II	BioNumerik	[11]
LE-SN38	Phase I/II	Neo Pharm	[http://www.neopharm.com]
Lurtotecan	Phase II	Glaxo/Gilead science	[49]
NK012 (nanoparticle formulation)	Phase II	Nippon Kayaku	[54]
Oral topotecan (Hycamptin)	Phase III	GlaxoSmithKline	[55]
PG-Camptothecin	Phase II	Cell Therapeutics	[49], http://www.cticseattle.com/
Rubitecan (9-nitro camptothecin)	Phase III	SuperGen	[56]
Sphigosomal topotecan	To be launched in 2007	Inex pharmaceuticals	[57]
(C) Combrestatin analogues; MOA[a]—inhibitor of colchicine binding site [58]			
AVE-8062 (AC-7700)	Phase I	Sanofi-Aventis	[45]
AVE-8064	Phase I	Sanofis-Aventis	[49]
AVE-8063	Phase I	Sanofis-Aventis	[49]
CA4PO$_4$ (combrestatin A-4 phosphate)	Phase II	OXiGENE	[45]
(D) Podophyllotoxin analogues; MOA[a]—binding to topoisomerase II			
NK-611	Phase I	Nippon Kayaku	http://www.nipponkayaku.co.jp/english
Tafluposide 105	Phase I	Pierre Fabre	[11]
(E) Vinca alkaloids analogues; MOA[a]—microtubule destabilising agents and bind to tubulin heterodimers [59–61]			
Anhydrovinblastine (Hydravin™)	Phase II	Keryx	[11]
Venorelbine	Phase III	Novacea	[62]
Vincristine sulfate TCS (OncoTCS)/Marqibo	Phase III	Enzon Pharmaceuticals/Inex Pharmaceuticals/Hanna Biosciences	[55]
Vinflunine ditartrate (Javlor®)	Phase III	Pierre Fabre/Bristol–Myers Squibb	[11]

[a] MOA, mechanism of action.

TABLE 3

Other plant-based anticancer drugs in clinical trials

Name	Lead compound/plant	MOA[a]	Clinical status	Developer	Reference
Bruceantin	*Brucea antidysenterica*	Inhibit peptidyl transferase elongation reaction	Phase II	NCI[b]	[63], http://www.cancer.gov/search/resultsclinicaltrials
Dimethyl xanthene-9-one-4-acetic acid (DMXAA)	Flavone-8-acetic acid analogue	TNF-α induction	Phase II	Antisoma	[64], http://www.antisoma.co.uk/
Flavopiridol	Flavone based/*Amoora rohituka & Dysoxylum binecteriferum*	Interfering with CDK and there by blocking cell cycle progression	Phase III	Sanofi–Aventis, NCI[b]	[65], http://www.sanofi-aventis.com/
Homoharringtone (Ceflatonin®)	Homoharrington/*Cephalotaxus harringtonia*	Protein synthesis inhibition	Phase II	ChemGenex	[63], http://www.chemgenex.com
Ingenyl 3-angelate (PEP005)	Ingenol	Protien kinase C activation	Phase IIa	Peplin	[11], http://www.peplin.com
4-Ipomeanol	Furan derivative/*Ipomoea batatas*	DNA binding	Phase II	NCI[b]	[63], http://www.cancer.gov/
Kahalalide F	Alga (*Bryopsis sp.*)/Sea slug	Interferes with lysosome function	Phase I	PharmaMar	[66]
Kanglaite	*Coix lachryma-jobi*	Inhibits mitosis of tumour cells during G2/M phase	Phase II	Zhejiam kanglaite pharmceutical	[39]
Meisoindigo	Indirubin derivative/*Indigofera tinctoria*	Apoptosis by blocking Stat3 signaling	Phase III	Chinese Academy of Sciences	[67]
NM-3	Isocoumarin derivative	Inhibits VEGF expression, angiogenesis inhibitor	Phase I complete	ILEX oncology	[68]
Perillyl alcohol	Limonene analogue	Activate capase 3, apoptosis	Phase II completed	NCI[b]	http://www.cancer.gov/ltrials
PG490-88Na	Triptolide	T cell proliferation suppression, IL-2 expression & NFk-B activation	Phase I	Pharmagenesis	[http://integrity.prous.com/]
Phenoxodiol	Daidzein	NADH oxidase (tNOX) inhibition	Phase III/Phase I	Marshall Edwards/Novogen	http://www.cancer.gov/search/resultsclinicaltrial
Protopanaxadiol (PBD-2131, Pandimex™)	Protopanaxadiol	Caspase 3, 8 & 9 stimulant	Phase I	PanaGin	http://www.panagin.com
Roscovitine (CYC 202)	Olomucine/*Raphanus sativus*	CDK inhibitor	Phase II	Cyclacel	http://www.cyclacel.com
SAOB-0401 (Xenavex™)	Oleandrin/*Nerium oleander*	Inhibit fibroblast growth factor-2 (FGF-2), blocked tumour necrosis factor (TNF) induced NF-kB activation	Phase I/II	Shimoda-atlantic Oncology Biosciences	http://www.clinicaltrial.gov

[a] MOA, mechanism of action.
[b] NCI, National Cancer Institute.

inflammatory cytokines including a-TNF, i-NOS, IL-1 beta and COX-2 [http://www.phytomedics.com/].

PYN17 in *Phase IIa:* A formulation of 1 European and 3 Chinese plants, which individually have been used to treat liver diseases in Asia and Europe, is being developed by Phynova as a treatment for the symptoms of Chronic Hepatitis C (CHC). PYN17 exhibited a range of pharmacological activities, including immuno-modulation, hepato-protection, and anti-inflammation. Clinical trials suggest that PYN17 could be developed both as a stand alone treatment and an adjunct treatment alongside established drugs for viral hepatitis, and other inflammatory liver diseases such as alcoholic cirrhosis and fatty livers associated with metabolic disorders [http://www.phynova.com/].

QS-21A and *QS-21B* in *Phase II and III*: The saponins derived from the South American tree, *Quillaja saponaria* (Rosaceae), have shown great promise as investigational adjuvants and are added to vaccines and other immunotherapies designed to enhance the body's immune response to the antigen contained within the treatment. QS-21 is an integral part of experimental vaccines being evaluated in Phase II and III trials for melanoma, malaria, HIV and other infectious diseases [11]; [http://www.clinicaltrials.gov/].

Oncological disease applications

Cancer is a complex disease that involves uncontrolled multiplication and spread (metastasis) of abnormal form of body's own cells. As per WHO 13% of world deaths, that is, about 7.6 million deaths accounted in 2005 are because of cancer, and this percentage is expected to increase in coming years [25]. Plant-derived compounds have played an important role in treatment of cancers, and some of the most promising and better drugs have come up from plant sources like Taxol® [43], Camptothecin [44], Combrestatin [45], Epipodophyllotoxin [46] and Vinca alkaloids (vinblastine, vincristine [47]. These drugs have also been the major source of new drug candidates for the treatment of cancers. Apart from this many other plant-derived compounds that are in clinical trials for cancers are tabulated in Tables 2 and 3.

Conclusion and future perspectives

The resurgence of plant-based drugs, as evident by the number of drugs in clinical trials, mainly for the treatment of cancer, immunological and CNS related diseases, is certainly exciting. There are many new plant-based drug candidates in active preclinical trials like Prostratin, CAPSOROLS and CCS. Inputs from traditional medical knowledge and using modern techniques to speed up the plant-based drug discovery have now made us to think beyond the only 10–15% of plant diversity that have been explored for their pharmaceutical purpose so far. Plants, the best combinatorial chemists, still wait for us to discover the hitherto hidden secrets of their healing properties to unburden mankind from dreaded diseases. Over 60 compounds are in the pipeline, as anticancer drugs alone, from plant sources. This is expected to remain an interesting disease area in the future as well. We must equip ourselves to screen a sizeable number of plants from our .27 million plant species, which can only be achieved by the concerted efforts exemplified by the NCI in recent years.

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