Natural Product Extracts of Plant and Marine Origin Having Antileukemia Potential. The NCI Experience[⊥]

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While effective treatments exist for acute lymphocytic leukemia (ALL), particularly in the case of children, and for chronic mylogenous leukemia (CML), more efficacious treatments for other forms of acute and chronic forms of the disease are still needed. The National Cancer Institute has tested over 90 000 extracts of terrestrial plants and marine plants and invertebrates in its human cancer one-dose/60-cell-line prescreen, and the results for plants and marine organisms meeting criteria established for activity against selected leukemia cell lines are presented. Taxonomic data are limited to family and genus in the case of plants, and phylum for marine organisms, and those groups of organisms exhibiting significant activity (so-called "hot" families and genera) are discussed. The "hot" terrestrial plant families Myrsinaceae and Sapindaceae have not been studied to any extent and appear to merit special attention, although leukemia cell line selectivity is also noted for other families.

Introduction

A recent analysis of natural products as sources of new drugs over the period 1981−2002 indicates that 67% of the 877 small-molecule new chemical entities (NCEs) are formally synthetic, but 16.4% correspond to synthetic molecules containing pharmacophores derived directly from natural products. Furthermore, 12% are actually modeled on a natural product inhibitor of the molecular target of interest, or mimic (i.e., competitively inhibit) the endogenous substrate of the active site, such as ATP.[1] Thus, over 60% of the NCEs can be related to natural products in one way or another. In addition, in a detailed analysis of the 99 compounds constituting the 150 most prescribed drugs in 1993, according to the National Prescription Audit of the United States, approximately 55% were either natural products or had structures based on natural product pharmacophores.[2] These statistics clearly demonstrate the importance and potential of Nature as a primary source for drug discovery and development.

In the area of cancer chemotherapy, some 67% of the effective drugs may be traced to natural origin, and many of these are comprehensively reviewed in the recent volume *Anticancer Agents from Natural Products*.[3] These include plant-derived agents, such as the vinca alkaloids vinblastine and vincristine, isolated from the Madagascar periwinkle, *Catharanthus roseus*;[4] paclitaxel (Taxol), originally isolated from the bark of the Pacific yew tree from the Pacific Northwest, *Taxus brevifolia*, and the analogue, docetaxel;[5] etoposide and teniposide, derived semisynthetically from epipodophyllotoxin, an epimer of podophyllotoxin, isolated from roots of *Podophyllum* species;[6] and camptothecin, isolated from the bark of *Camptotheca acuminata*, a precursor to the semisynthethetic drugs topotecan (Hycamptin) and irinotecan (Camptosar).[7]

Three plant-derived drugs currently in clinical trials, either alone or in combination with other drugs, are homoharringtonine, isolated from *Cephalotaus harringtonia*,[8] flavopiridol, a synthetic compound based on rohutikine from *Dysoxylum binectariferum*,[9] a plant native to India, and combretastin A4 as its phosphate prodrug, originally isolated from the southern African plant C*ombretum caffrum.*[10]

Widely used anticancer drugs of microbial origin include multiple anthracyclines,[11] the actinomycins,[12] bleomycins,[13] and mitomycins,[14] while both natural and derivatized forms of the ansamycins,[15] staurosporines,[16] and epothilones[17] are currently in clinical trials. Ansamitocins, related to maytansanoids originally isolated from plant sources but undoubtedly of microbial origin,[18] and enediynes, such as calicheamicin,[19] have been developed as drugs targeted to specific tumors through conjugation to appropriate monoclonal antibodies; Mylotarg (gemtuzumab ozogamicin; calicheamicin conjugated to the antibody hP67.6) is the first antibody-targeted agent approved by the FDA and is used for the treatment of patients with relapsed acute myelogenous leukemia (AML).[19] A similar strategy was adopted using conjugates of the potently cytotoxic CC1065 analogues with polyamides that recognized particular DNA sequences.[20]

Although no formal anticancer drugs sourced from the marine environment have as yet been approved for commercial use, there are significant numbers of agents in clinical trials. These include aplidine from the Mediterranean tunicate *Aplidium albicans*;[21] bryostatin from the bryozoan *Bugula neritina*, from the Gulf of California;[22] discodermolide, isolated from the Caribbean deep water sponge *Discodermia dissoluta*;[23] dolastatin 10, isolated from the Indian Ocean nudibranch *Dolabella auricularia*;[24] and ecteinascidin 743, from the tunicate *Ecteinascidia turbinata*, collected initially in the Caribbean.[21]

Clinical Treatment of Leukemias. Acute leukemias may be fatal within months if untreated. Treatment of acute lymphoblastic leukemia (ALL), in which lymphoid cell lines are affected, involves induction of remission using iv administered vincristine and oral administration of corticosteroids (prednisone or prednisolone). In the case of children, 90% show remissions, with 50% remission in the case of adults; addition of asparaginase and daunorubicin may achieve better remission rates and longer remissions.[25] Most children achieving initial remission receive CNS therapy (cranial irradiation and intrathecal methotrexate or cytarabine) to prevent relapse with meningeal involvement. Complete remission is generally followed by consolidation or intensification therapy at 5 and 20 weeks using cytarabine, etoposide, thioguanine, and daunorubicin and subsequent maintenance therapy for 2 to 3 years using mercaptopurine, methotrexate, vincristine, and prednisolone.[25]

Acute non-lymphoblastic leukemias (ANLL), in which myeloid cell lines are affected [acute myeloid or Myelogenous leukemias (AML)], are more common among elderly patients, making intensive chemotherapy more difficult to apply. Most treatment regimens involve cytarabine and an anthracycline, such as daunorubicin or idarubicin.[25] Subsequent consolidation therapy, although

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less common than for ALL, may involve use of daunorubicin and high-dose cytarabine, and maintenance therapy is not as effective. Due to the poorer prognosis, bone marrow transplantation is more widely accepted as a treatment than for ALL.[25]

Chronic leukemias usually occur in older patients. Chronic lymphocytic leukemia (CLL) accounts for about 30% of all leukemias in the West, but is rare in the Far East. Low-risk patients may survive over 10 years without treatment, and cytotoxic therapy is not generally recommended. For higher risk groups, chlorambucil is most widely used, and response rates vary from 40 to 70%.[25] No established therapies exist for those patients failing initial treatment.

Chronic myeloid leukemia (CML) is relatively rare and usually occurs in older patients. In over 90% of the cases, CML is associated with the presence of an abnormal chromosome (the Philadelphia chromosome) in blood cells, and the median survival time is about 5 to 6 years.[25] Palliative therapies have involved use of bisulfan or hydroxyurea, and in some cases cytarabine or, under experimental conditions, homoharringtonine has shown some benefit. Interferon alpha has led to response rates of 70−80%,[25] but more recently the protein kinase inhibitor Gleevec has been heralded as a breakthrough in the treatment of CML.[26]

Agents in Clinical Trials. Several hundred trials are in progress for the treatment of acute lymphoblastic and myelogenous leukemias. Many involve the use of agents such as cytarabine, cladrabine, fludarabine, and decitabine in combination with anthracyclines, cyclophosphamide, melphalan, methotrexate, and mitoxantrone, and frequently combining with biological agents (e.g., Alemtuzumab, Epratuzumab, Rituximab), radiation therapy, and stem cell (e.g., allogenic peripheral blood stem cell) or bone marrow transplantations. Other agents being studied include arsenic trioxide, carboplatin, docetaxel, etoposide, flavopiridol, 17-*N*-allylamino-17-demethoxygeldanamycin (17-AAG), homoharringtonine, pentostatin, temozolomide, thalidomide, and topotecan (either alone or in combination), but this list is by no means exhaustive. Reference to http://www.cancer.gov/Search/SearchClinicalTrialsAdvanced.aspx gives a listing of the trials in progress (search "Type of Cancer" using the pull-down menu for the various leukemias).

For the chronic leukemias, reference to the above-mentioned cancer website gives a listing of over a hundred trials and includes use of agents similar to those mentioned above. Other agents being studied include bryostatin, chlorambucil, hydroxyurea, and 12-*O*-tetradecanoylphorbol 13-acetate (TPA), and as with the acute leukemias, treatment often includes biological agents, radiation, and transplantation procedures.

Data Analysis. In this review we present a comprehensive evaluation and analysis of data obtained in the testing of more than 90 000 extracts of terrestrial plants and marine plants and invertebrates against the HL-60 and K-562 leukemia cell lines. A major portion of the data (1991−2000) was obtained using a prescreen based on the 60 human cancer cell line screen, which was performed at a nominal single dose of 100 μg mL^{-1} (85 000 assays), with the remainder being abstracted from data obtained from the five-dose, 60-cell-line screen performed in the 1989−1991 time frame. The six leukemia cell lines routinely used in the NCI 60-cell-line screen are CCRF-CEM, MOLT-4, RPMI-8226, SR, HL-60(TB), and K-562. The CCRF-CEM and MOLT-4 cell lines are acute lymphocytic leukemia cell lines consisting of T-cells, while the RPMI-8226 cell line, derived from a human myeloma, and the SR cell line, derived from pediatric immunoblasts, are B-cells. HL-60(TB) cells are derived from promyelocytic leukemia, and K-562 cells are derived from chronic myelogenous leukemia. Details of the screen have been published by Boyd.[27]

From 1989 to 1991, the NCI Developmental Therapeutics Program (DTP) tested approximately 8000 extracts in the five-dose, 60-cell-line format starting, in general, at a nominal dose of 100 μg mL^{-1}. To expedite the screening process, a one-dose, 60-cell-line prescreen, starting at a nominal 100 μg mL^{-1}, was instituted in 1991. Due to the apparent success in antileukemia drug development in the early NCI program (1960−1982), it was decided that activity observed solely against the leukemia lines would generally not be used as a criterion for selection of extracts for bioassay-guided isolation of potential active agents. As a consequence, a significant number of extracts solely possessing activity against leukemia lines were not studied further. Likewise, extracts showing activity against leukemia lines only in the single-dose prescreen were not advanced to the five-dose 60-cell-line screen.

To analyze the complete database on a uniform basis, a dataset was compiled encompassing all the leukemia test results from 1989 to early 2000 by combining the dataset from the early five-dose assays (1989−1991), using only data observed at the 100 μg mL^{-1} dose level (which amounted to approximately 5000 five-dose assays) and the ∼85 000 one-dose 60-cell-line dataset (1991−2000). Thus, the overall dataset analyzed was derived from approximately 90 000 extracts of marine invertebrates and algae and terrestrial plants.

In selecting "active" extracts for subsequent analysis, a very conservative criterion has been applied requiring that an extract demonstrate 50% or greater cytolytic activity against both the K-562 and the HL-60 leukemia cell lines at the 100 μg mL^{-1} level. We elected not to use data from the other cell lines because the CCRF-CEM and RPMI-8226 lines are generally too sensitive to cytolytic agents, and the Molt-4 and SR cell line data were not included in all the earlier assays.

In a significant number of cases, the collection contractor(s) provided multiple parts (e.g., bark, fruit, leaves, roots, stems, twigs, wood) from the same terrestrial plant specimen, and each part constituted a separate physical sample. In addition, each physical sample was extracted by an organic solvent (methanol−dichloromethane, 1:1) and water, thus producing two extracts per sample (see http://npsg.ncifcrf.gov/ for the extraction protocols). With this in mind, once the base dataset was established using uniform assay conditions, only one "active" extract per plant specimen has been counted, even though several extracts of different parts may have exhibited "activity". Thus in the limit case, even though 14 extracts from the same plant specimen (seven parts with two extracts per part) may have shown "activity", this has been recorded as a single "active" plant. Similarly, in the case of the marine-derived extracts, if both the organic and the aqueous samples were "active", only one organism has been counted.

In the subsequent discussion, to protect the rights of the Source Countries from which organisms (plants and marine invertebrates) have been collected, geographic areas have deliberately been defined by region rather than country names, and, in addition, the only taxonomic data given are phylum for the marine samples and family and genus for the terrestrial plant samples. In the performance of the collections through the qualified contractors listed below, the NCI agreed to abide by the terms of its Letter of Collection (LOC), which ensures confidentiality of specific results and collection data. Details of the LOC are available at http://ttb.nci.nih.gov/nploc.html.

Discussion

Between late 1986 and late 2004, the Natural Products Branch (NPB), a Branch of the NCI's Developmental Therapeutics Program (DTP/NCI), coordinated the collection of over 60 000 samples of higher plants (which as mentioned above often included multiple parts per single plant specimen) through contracts with Missouri Botanical Garden (tropical and subtropical regions of Africa and Madagascar), the University of Illinois at Chicago (Southeast Asia), New York Botanical Garden (Central and South America; 1986−1996), the Morton Arboretum (1996−2001), and World Botanical Associates (2001−2004) (in the continental United States and territories). Approximately 12 000 marine samples from the Caribbean and Indo-Pacific regions have been collected through contracts

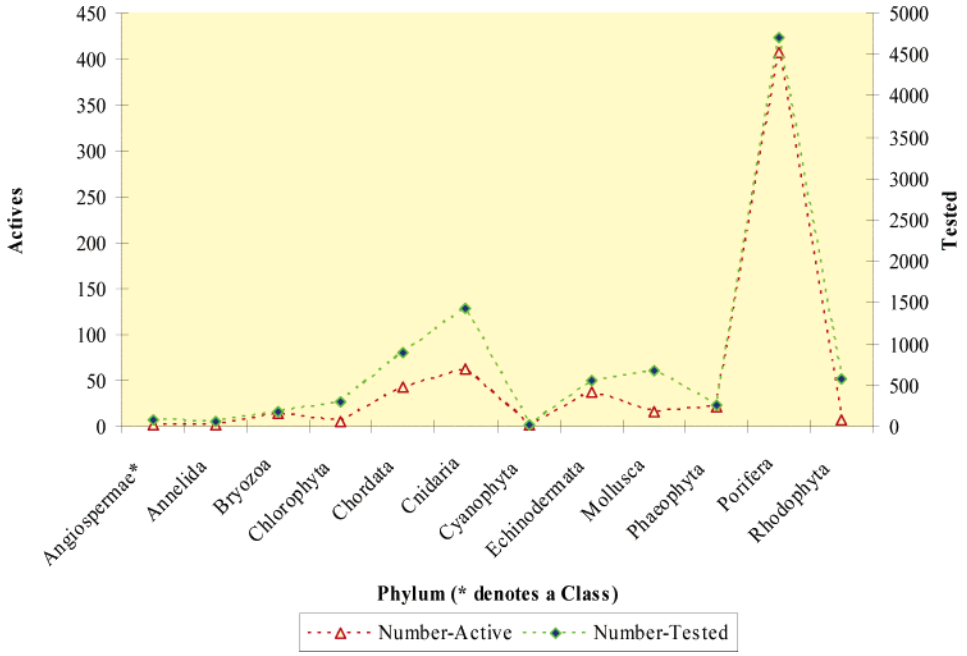

Figure 1. Number of antileukemia "active" and total number of marine organism phyla tested in the NCI human cancer one-dose/60-cell-line prescreen.

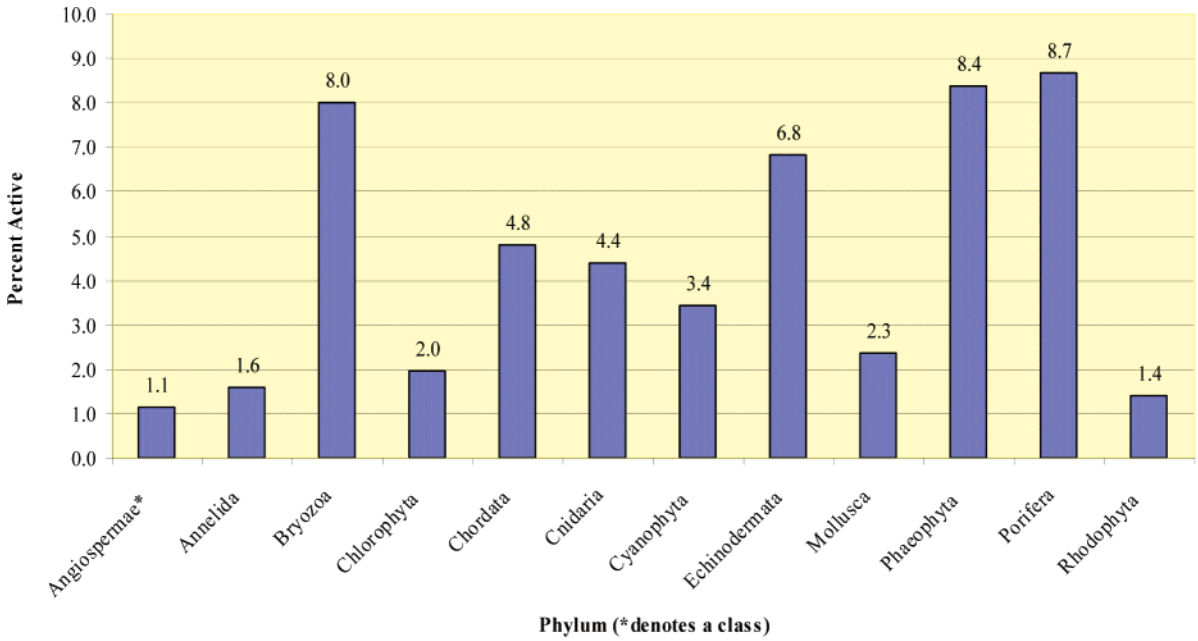

Figure 2. Number of antileukemia "active" marine specimens from marine organism phyla expressed as a percentage of the total number tested.

with SeaPharm and Harbor Branch Oceanographic Institute (1986−1989), the Australian Institute of Marine Science (1987−1991), the University of Canterbury, New Zealand (1987−1990), and Coral Reef Research Foundation (1992−present). Cancer cell line screening data represented by over 943 000 assays of individual extracts have been recorded, and from these, 1296 individual organisms of marine and terrestrial origin have been designated as "active" by reason of their strong cytolytic activity against the HL60 and K562 cell lines.

It should be noted that in the years after 2000 a prescreen comprising the MCF-7 breast, NCI-H460 lung, and SF-268 CNS human cancer cell lines run at a nominal concentration of 100 μg mL^{-1} replaced the 60-cell-line single-dose prescreen. Although a large number of extracts have been tested in this three-cell-line prescreen, the data are not applicable to the present discussion.

In Vitro "Active" Antileukemic Extracts from Marine Invertebrates and Plants. A total of 620 active organisms of marine origin, representing 12 phyla (in the case of the mangrove plants, these are listed under Angiospermae, a class, and denoted by an asterisk against the name, rather than under the true phylum, Tracheophyta) were selected as "active" from a total of 9945 individual organisms tested. The data are summarized in Figure 1, where for ease of visualization, the points have been connected, but no graphical connotations should be drawn, and in Figure 2, the percentage "hits" are given with the actual percentages shown adjacent to the bars.

Among the 620 "actives", 407 (8.7%) belong to the phylum Porifera (sponges), which is generally a major source of bioactive metabolites, although currently there are a number of compounds that though isolated from members of this phylum, are probably

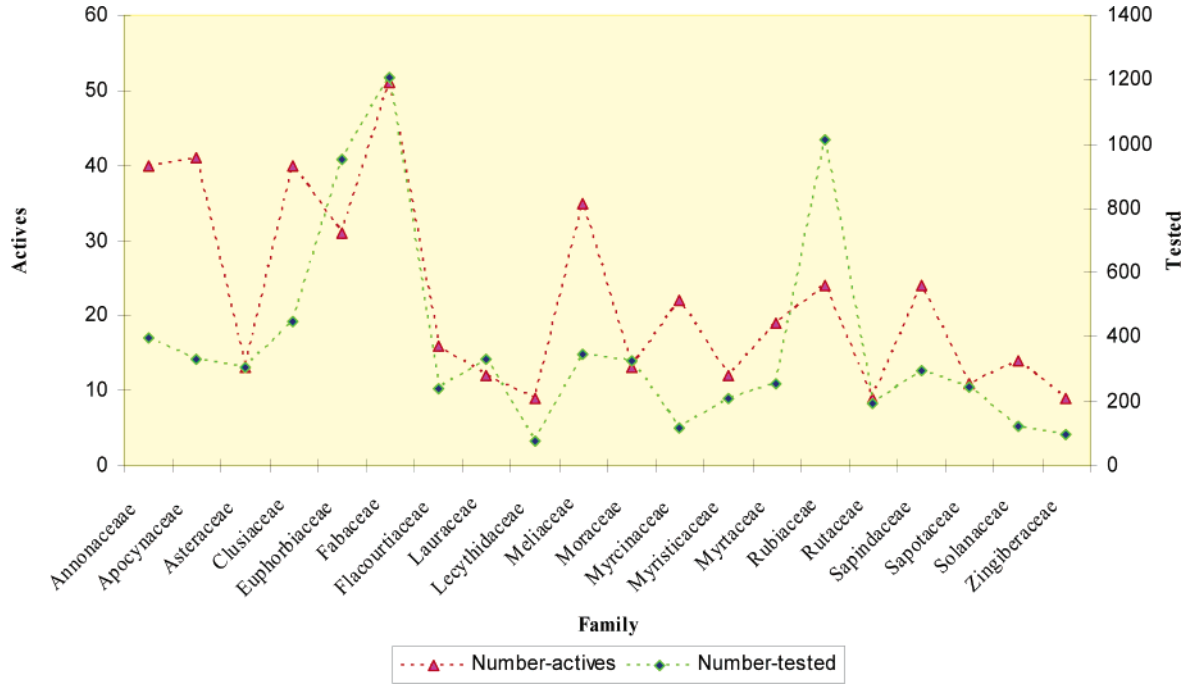

Figure 3. Number of antileukemia "active" and total number of plant specimens from selected terrestrial plant families tested in the NCI human cancer cell line one-dose/60-cell-line prescreen.

produced from interactions by the host sponge and microbes either within or associated with the nominal producer. Irrespective of the actual source(s), significant anticancer leads from this phylum include discodermolide[23] and the hemiasterlin derivatives.[28] This represents an initial "hit rate" of ca. 8% and is comparable to those found with the phyla Phaeophyta (brown algae, 8.4%), Bryozoa ("moss animals", 8.0%), and then by the Echinodermata ("starfish", 6.8%). However, the total numbers tested in these latter phyla were considerably less than those for the Porifera, reflecting perhaps an initial bias in these earlier collections from prior knowledge of nominally "active" phyla. Perhaps the most notable discovery from these phyla are the bryostatins from the Bryozoan *Bugula neritina*, which are still in clinical trials as components of combined therapies, usually in conjunction with cytolytic agents.[22] It should be noted that the bryostatins were initially developed using a murine leukemia model and, in fact, required a six-day assay in the 60-cell-line screen to show the significant effects on human leukemia lines, rather than the usual two-day assay.

Other phyla, such as Cnideria (4.4%) and Chordata (4.8%), gave lower hit rates at the ca. 5% level, while the least productive phyla, in contrast to the Phaeophyta, were the Mollusca (2.3%), Chlorophyta (green algae, 2.0%), and Rhodophyta (red algae, 1.4%). Even though formally less productive, the phylum Chordata has yielded the promising agents aplidine (phase II clinical trials) and ecteinascidin 743 (approaching registration in the EU), isolated from the tunicates *Aplidium albicans* and *Ecteinascidia turbinata*, respectively, while another agent in phase I/II clinical trials, kahalahide F, has been isolated from the mollusk *Elysia rufescens*.[21] However, it is now known that this peptide is concentrated from the ingestion by the mollusk of an alga from the genus *Bryopsis*, although whether this is the actual producer is still under investigation.

Of interest, however, is that in the case of the Crustacea, where 149 separate organisms were tested as both organic and aqueous extracts, no "active" extracts/organisms were identified using our parameters for activity.

In Vitro "Active" Antileukemic Extracts from Terrestrial Plants. There are close to 70 000 records of plant extracts tested in the one-dose/60-cell-line screen when the data in the DTP Natural Product Extract database are examined. Following discussions with the plant collection contractors, it was estimated that an average of 2.5 plant part samples were collected for each plant specimen, and since two extracts are derived from each sample, this leads to an average of five extracts per single plant specimen. Thus conservatively, close to 14 000 (70 000/5) plant specimens have been screened.

Of the 242 plant families comprising the NCI collection, 95 contain samples whose extracts exhibit antileukemia "activity" based on the selection criteria mentioned above. An overview of some of the more significant findings is presented in Figure 3. Space limitation prevents the inclusion of families with eight or less active plants, but these 75 families, along with their active genera, are listed in footnote *d* of Table 1. The triangles indicate the number of individual discrete plants that tested as "active" within the designated families (numbers indicated on the left-hand axis), while the diamonds indicate the total numbers of discrete plants tested from the particular families (numbers indicated on the right-hand axis). The families are listed in alphabetical order along the horizontal axis, and in order to clarify the number of "actives" versus the total number tested for each of the families, all the triangles have been linked by a dashed line, as well as all the diamonds. It should be stressed, however, that these lines do not have any graphical significance. In Figure 4, the number of "active" plant specimens is expressed as a percentage of the total number tested, representing the so-called "hit rate", with that figure being adjacent to the column.

The largest number of plant specimens collected and tested were from the Fabaceae (1205), Rubiaceae (1015), and Euphorbiaceae (951). In the case of the Fabaceae, the number of "active" specimens recorded was 51, giving a "hit rate" of about 4.2%, while for the Rubiaceae and Euphorbiaceae, the "hit rates" were only 2.4% (24 "active" specimens) and 3.3% (31 "active" specimens), respectively. These rates are low compared to that observed for the Myrsinaceae (18.8%; 22 "actives"/117 tested) and the relatively high "hit rates" observed for the Annonaceae (10%; 40/399), Apocynaceae (12.3%; 41/333), Meliaceae (10.1%; 35/346), and Solonaceae (11.7%; 14/122). The Clusiaceae (8.9%; 40/449), Flacourtiaceae (6.6%; 16/241), Myrtaceae (7.4%; 19/256), and Sapindaceae (8.2%; 24/294) showed moderate rates of "activity".

Table 1 lists those families that contain14 or more individual plant specimens that were considered "active" (i.e., one or more

Table 1. Distribution of Leukemia Cell Line Active "Hot" Families and "Hot" Genera of Terrestrial Plant Origin[a,d]

family[b]	no. of genera in family	no. of genera collected	"active" genera (≥3 active plants)[c]	no. active	regions of collection of active plants
Annonaceae 40 (399)	128	69	*Annona*	6	Caribbean, South America, East Africa, South Africa
			Enicosanthum	5	Southeast Asia
			Mitrephora	4	Southeast Asia
			Polyalthia	6	Southeast Asia
			Xylopia	4	widespread
Apocynaceae 41 (333)	215	79	*Rauwolfia*	3	East Africa, South Africa, Caribbean
			Tabernaemontana	7	widespread
			Thevetia	3	East Africa, West Africa, Caribbean
Clusiaceae 40 (449)	47	26	*Calophyllum*	13	Southeast Asia, South Asia
			Clusia	3	Central America, South America
			Cratoxylum	4	Southeast Asia
			Garcinia	10	East Africa, West Africa
			Kayea	3	Southeast Asia
Euphorbiaceae 31 (951)	321	162	*Alchornea*	3	Central America, South America
			Croton	4	Southern Africa, Central America
			Glochidion	3	Southeast Asia
			Macaranga	6	Southeast Asia
Fabaceae (Leguminaceae) 51 (1205)	657	209	*Albizia*	14	East, Southern & Central Africa, Caribbean, Southeast Asia
			Cojoba	3	Central America, South America
			Entada	3	Central Africa, East Africa
			Inga	3	Central America, South America
			Piptadeniastrum	3	Central Africa, West Africa
Flacourtiaceae 16 (241)	89	46	*Casearia*	9	widespread
Meliaceae 35 (346)	51	36	*Aglaia*	6	Southeast Asia
			Chisocheton	7	Southeast Asia
			Dysoxylum	9	Southeast Asia
Myrsinaceae 22 (117)	37	16	*Ardisia*	4	Southeast Asia
			Conandrium	3	Southeast Asia
			Embelia	4	East Africa, Southeast Asia
			Maesa	7	East Africa, Southern Africa, Southeast Asia
Myrtaceae 19 (256)	120	53	*Eugenia*	6	South America, Southern Africa, Southeast Asia
			Syzygium	8	Southeast Asia, Central America, Southern Africa
Rubiaceae 24 (1015)	630	238	*Palicourea*	5	South America, Central America
			Psychotria	6	South America, West & Southern Africa, Caribbean
Sapindaceae 24 (294)	144	73	*Harpullia*	6	Southeast Asia
			Serjania	3	Central America
Solanaceae 14 (122)	90	41	*Cestrum*	4	Central America, South America, Caribbean
			Solanum	8	East Africa, South America

[a] The term "hot family" refers to those families having more than 14 individual plants designated as active by the stated selection criteria, and "hot genera" refers to those genera containing three or more active plants. [b] The total number of active plants is listed next to each family name. The number in parentheses next to each family name refers to the total number of plants tested. [c] Only genera containing ≥3 active plants are listed herein. Those genera within the same family containing at least one but less than three active plants are listed in footnote *d*. [d] Genera containing at least one but less than three active plants are listed with the corresponding family in alphabetical order of family name (in bold). The number next to the family name designates the number of active plants found, and the number in parentheses indicates the total number of plants tested: **Actinidiaceae** 1 (45) *Saurauia*; **Alangiaceae** 1 (18) *Alangium*; **Alismataceae** 1 (1) *Sagittaria*; **Anacardiaceae** 7 (231) *Choerospondias*, *Koordersiodend*, *Lannea*, *Poupartia*, *Protorhus*, *Pseudospondias*, *Sorindeia*; **Ancistrocladaceae** 2 (11) *Ancistrocladus*; **Annonaceae** 40 (399) *Anaxagorea*, *Cleistopholis*, *Cyathocalyx*, *Cymbopetalum*, *Eupomatia*, *Goniothalamus*, *Guatteria*, *Isolona*, *Mezzettia*, *Miliusa*, *Monodora*, *Neouvaria*, *Oncodostigma*, *Rollinia*; **Apocynaceae** 31 (333) *Alstonia*, *Ancylobothrys*, *Bonafousia*, *Cabucala*, *Carvalhoa*, *Cerbera*, *Chilocarpus*, *Ervatamia*, *Holarrhena*, *Hunteria*, *Kopsia*, *Neisosperma*, *Strophanthus*, *Tonduzia*, *Voacanga*; **Aquifoliaceae** 2 (34) *Ilex*, *Sphenostemon*; **Araceae** 1 (47) *Philodendron*; **Araliaceae** 5 (155) *Arthrophyllum*, *Dendropanax*, *Didymopanax*, *Polyscias*, *Schefflera*; **Aristolochiaceae** 2 (11) *Aristolochia*; **Asclepiadaceae** 1 (36) *Parquetina*; **Asteraceae** 13 (303) *Baccharis*, *Bidens*, *Brachylaena*, *Inula*, *Melampodium*, *Montanoa*, *Pluchea*, *Senecio*, *Solidago*, *Tarchonanthus*, *Verbesina*, *Vernoniopsis*, *Zinnia*; **Betulaceae** 1 (7) *Alnus*; **Bignoniaceae** 1 (132) *Tynanthus*; **Bixaceae** 1 (22) *Bixa*; **Boraginaceae** 2 (90) *Cordia*, *Ptelocarpa*; **Burseraceae** 8 (227) *Canarium*, *Commiphora*, *Dacryodes*, *Protium*; **Canellaceae** 1 (4) *Warburgia*; **Caprifoliaceae** 1 (20) *Viburnum*; **Caricaceae** 1 (11) *Cylicomorpha*; **Chenopodiaceae** 1 (8) *Spirostachys*; **Chrysobalanaceae** 5 (90) *Atuna*, *Dactyladenia*, *Licania*, *Maranthes*, *Parinari*; **Clusiaceae** 40 (449) *Harungana*, *Mammea*, *Pentadesma*, *Tovomita*, *Tovomitopsis*; **Combretaceae** 7 (144) *Anogeissus*, *Bucida*, *Combretum*, *Conocarpus*, *Terminalia*; **Commelinaceae** 1 (14) *Palisota*; **Convolvulaceae** 6 (39) *Astripomoea*, *Erycibe*, *Ipomoea*, *Merremia*; **Cyperaceae** 1 (23) *Machaerina*; **Datiscaceae** 1 (4) *Octomeles*; **Didymelaceae** 1 (2) *Didymeles*; **Dilleniaceae** 2 (60) *Dillenia*, *Curatella*; **Dioscoreaceae** 1 (11) *Dioscorea*; **Dipterocarpaceae** 1 (100) *Shorea*; **Ebenaceae** 6 (152) *Diospyros*, *Euclea*; **Elaeocarpaceae** 4 (99) *Elaeocarpus*, *Sloanea*; ***Ericaceae*** 1 (71) *Philippia*; **Euphorbiaceae** 31 (951) *Amyrea*, *Antidesma*, *Aporusa*, *Bridelia*, *Chamaesyce*, *Cleistanthus*, *Homolanthus*, *Hyeronima*, *Margaritaria*, *Phyllanthus*, *Sapium*, *Securinega*, *Trewia*, *Uapaca*; **Fabaceae** 51 (1205) *Abarema*, *Acosmium*, *Adenanthera*, *Amblygonocarpus*, *Archidendron*, *Cassia*, *Chamaecrista*, *Clathrotropis*, *Dalbergia*, *Eriosema*, *Erythrina*, *Erythrophleum*, *Lonchocarpus*, *Lysiloma*, *Maniltoa*, *Milletia*, *Mundulea*, *Paraserianthes*, *Pentaclethra*, *Platymiscium*, *Platypodium*, *Prosopis*, *Psoralea*, *Senna*, *Xylia*; **Fagaceae** 7 (85) *Castanopsis*, *Lithocarpus*, *Quercus*; **Flacourtiaceae** 16 (241) *Bembicia*, *Laetia*, *Lindackeria*, *Scolopia*, *Zuelania*; **Gnetaceae** 1 (12) *Gnetum*; **Gonystylaceae** 1 (12) *Gonystylus*; **Hippocastanaceae** 1 (44) *Billia*; **Heliconiaceae** 1 (6) *Heliconia*; **Icacinaceae** 3 (81) *Icacina*, *Apodytes*, *Leptaulus*; **Iridaceae** 1 (5) *Crocosmia*; **Lauraceae** 12 (331) *Aniba*, *Beilschmiedea*, *Caryodaphnopsis*, *Cryptocarya*, *Dryadodaphne*, *Endlicheria*, *Gliricidia*, *Litsea*, *Pleurothyrium*; **Lecythidaceae** 9 (74) *Barringtonia*, *Eschweilera*, *Foetidia*, *Grias*, *Petersianthus*; **Loganiaceae** 2 (6) *Geniostoma*, *Norrisia*; **Loranthaceae** 1 (51) *Helixanthera*; **Magnoliaceae** 6 (32) *Kadsura*, *Liriodendron*, *Magnolia*, *Michelia*, *Talauma*; **Malpighiaceae** 1 (56) *Byrsonima*;

Footnote d for Table 1 continued:

Malvaceae 2 (57) *Thespesia*; **Marcgraviaceae** 3 (13) *Marcgravia*, *Marcgaviastrum*, *Souroubea*; **Melastomataceae** 8 (239) *Medinilla*, *Memecylon*, *Miconia*, *Miconiaorea*; **Meliaceae** 35 (346) *Cedrelopsis*, *Ekebergia*, *Entandrophragma*, *Gaurea*, *Malleastrum*, *Sandoricum*, *Trichilia*, *Turraea*, *Vavaea*, *Xylocarpus*; **Monimiaceae** 5 (59) *Glossocalyx*, *Siparuna*, *Steganthera*, *Xymalos*; **Moraceae** 13 (328) *Artocarpus*, *Ficus*, *Maclura*, *Malaisia*, *Parartocarpus*; **Myristicaceae** 12 (210) *Brochoneura*, *Endocomia*, *Horsfieldia*, *Knema*, *Myristica*, *Pycnanthus*; **Myrsinaceae** 22 (117) *Labisia*, *Monoporus*, *Myrsine*, *Rapanea*; **Myrtaceae** 19 (256) *Calyptranthes*, *Decaspermum*, *Eucalyptus*, *Melaleuca*, *Whiteodendron*; **Nepenthaceae** 1 (6) *Nepenthes*; **Olacaceae** 1 (150) *Diogoa*; **Onagraceae** 1 (4) *Ludwigia;* **Orchidaceae** 2 (3) *Bulbophyllum*, *Phaius*; **Pinaceae** 2 (14) *Pinus*; **Piperaceae** 4 (84) *Peperomia*, *Piper*, *Pothomorphe*; **Pittosporaceae** 6 (39) *Pittosporum*; **Polygalaceae** 5 (43) *Moutabea*, *Securidaca*, *Xanthophyllum*; **Polygonaceae** 1 (29) *Coccoloba*; **Proteaceae** 3 (48) *Faurea*, *Gevuina*, *Grevillea*; **Pteridophyta** 1 (41) *Nephelea*; **Rhamnaceae** 5 (87) *Alphitonia*, *Colubrina*, *Gouania*; **Rosaceae** 1 (72) *Polylepis*; **Rubiaceae** 24 (1015) *Bathysa*, *Chassalia*, *Coussarea*, *Enterospermum*, *Erithalis*, *Gardenia*, *Ixora*, *Mastixiodendron*, *Morinda*, *Randia*, *Rytigynia*, *Timonius*, *Tricalysia*; **Rutaceae** 9 (194) *Clausena*, *Euodia*, *Evodiella*, *Halfordia*, *Paramignya*, *Vepris*, *Zanthoxylum*; **Sabiaceae** 1 (5) *Meliosma*; **Santalaceae** 1 (21) *Osyris*; **Sapindaceae** 24 (294) *Allophylus*, *Arfeuillea*, *Chytranthus*, *Dodonaea*, *Eriocoelum*, *Haplocoelum*, *Lepidopetalum*, *Lepisanthes*, *Macphersonia*, *Majidea*, *Molinaea*, *Paullinia*, *Tina*, *Tristirops*is, *Zanha*; **Sapotaceae** 11 (244) *Breviea*, *Chrysophyllum*, *Manilkara*, *Palaquium*, *Payena*, *Planchonella*, *Pouteria*, *Tridesmostemon*; **Sarcolaenaceae** 2 (31) *Leptolaena*, *Sarcolaena*; **Simaroubaceae** 2 (51) *Cedronia*, *Simaruba*; **Solanaceae** 14 (122) *Datura*, *Vassobia*; **Sterculiaceae** 3 (186) *Sterculia*; **Styracaceae** 4 (7) *Styrax*; **Symplocaceae** 1 (31) *Symplocos*; **Theaceae** 8 (55) *Eurya*, *Ternstroemia*; **Tiliaceae** 2 (160) *Trichospermum*, *Grewia*; **Ulmaceae** 1 (70) *Trema*; **Velloziaceae** 1 (1) *Xerophyta*; **Verbenaceae** 4 (224) *Clerodendrum*, *Lantana*, *Vitex*; **Violaceae** 1 (42) *Leonia*; **Viscaceae** 1 (4) *Viscum*; **Winteraceae** 1 (13) *Zygogynum*; **Zingiberaceae** 9 (96) *Aframomum*, *Amomum*, *Boesenbergia*, *Hedychium*, *Hornstedtia*, *Plagiostachys*, *Pleuranthodium*, *Renealmia*, *Tapeinochilo.*

extracts of the plant exhibited greater than 50% cytolytic activity against both the HL60 and K562 leukemia cells lines). The number of "active" plants is given with the family name, together with the total number of plants tested in parentheses (column 1). Thus, for the Annonaceae, 40 "active" plants were recorded out of 399 tested. Also listed are those genera that contained three or more "active" plants (column 4), which are five in the case of the Annonaceae (*Annona*, *Enicosanthum*, *Mitrephora*, *Polyalthia*, *Xylopia*). Those genera containing at least one and less than three "active" plants are listed in the table footnote *d* following the corresponding family names, which are given in alphabetical order; again, for the Annonaceae, 14 such genera are listed. Also listed in Table 1 is the number of genera in the family as reported in the *Plant-Book* (column 2)[29] and the number of genera collected to date in the NCI program (column 3).

The families and genera listed in Table 1 are designated as "hot", and the regions where they were predominantly collected are given in the right-hand column. Thus, for the "hot" genera in the Annonaceae family, the collection locations for the *Annona* and *Xylopia* genera are widespread, whereas the "active" *Enicosanthum*, *Mitrephora*, and *Polyathia* samples were collected only from Southeast Asia. The predominant regions of collection for the various "hot" genera are included to give an indication of possible "hotspots" for antitumor lead and drug discovery, but, as stated in the Data Analysis section above, the names of countries of collection and detailed taxonomic data are not provided in order to protect the rights of the Source Countries that have participated in the NCI collection program.

"Hot" Plant Families and Genera. A Chemistry Update. The families and genera listed in Table 1 are designated as "hot", and previous research related to the study of these families and genera has been analyzed on the basis of publications reported in the PubMed database (http://www.ncbi.nih.gov/entrez/query.fcgi) of the NIH National Library of Medicine, together with some information from other sources, though not from use of Scifinder, as we do not have access to this database.

As mentioned above, the highest number of "actives" was recorded for the Fabaceae (51/1205), but the highest "hit rate" was observed for the Myrsinaceae (18.8%; 22/117). Of the "hot" genera listed for the Myrsinaceae, antitumor activity has been reported for a benzoquinone isolated from *Ardisia crispa*[30] and for an alkylphenol from *Ardisia iwahigensis*,[31] and the potential of this genus as a source of biologically active compounds has recently been reviewed.[32]

While antibacterial triterpenoids and benzoquinones (embelin) have been isolated from *Embelia* species,[33,34] a search of PubMed

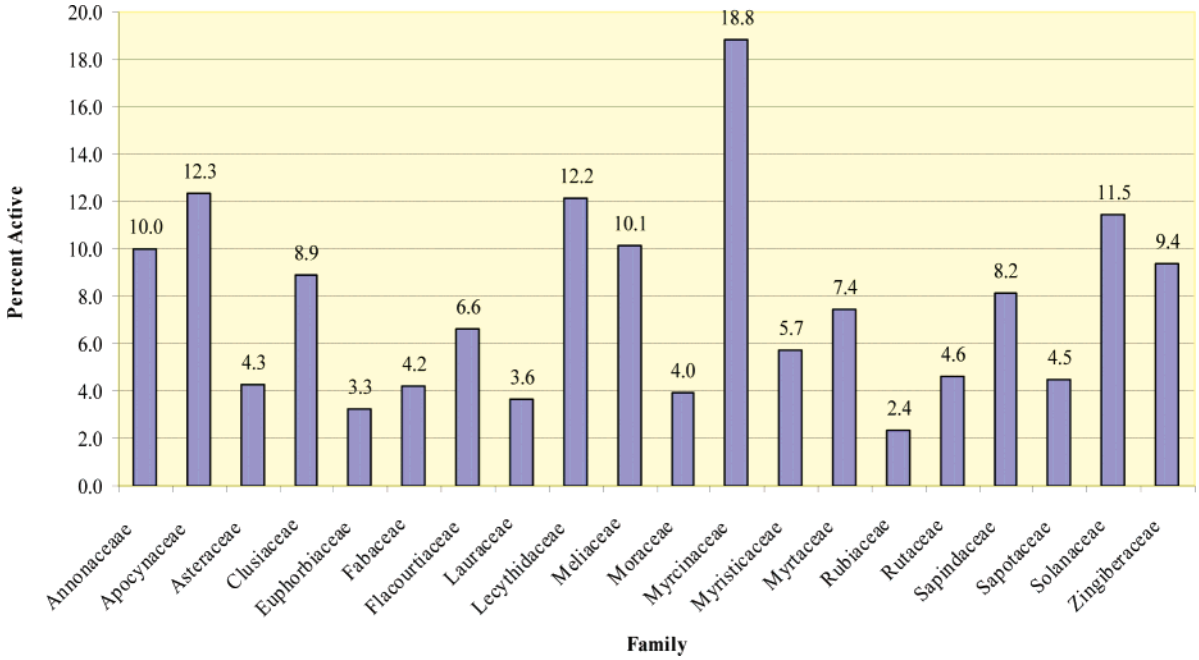

Figure 4. Number of antileukemia "active" plant specimens from selected terrestrial plant families expressed as a percentage of the total number tested.

failed to give any references to cancer-related activities for this genus, and the same applied to the genus *Conandrium*. The isolation of cytotoxic alkylated benzoquinones has been reported from *Maesa lanceolata*,[35] while other diverse biological activities, including antileishmanial and virucidal, have been reported for triterpenoid saponins from *Maesa* species.[36,37] It is clear from the antileukemia data reported herein that this family and its constituent genera merit closer examination as a source of potential antitumor leads.

Relatively high "hit rates" were observed for the Annonaceae (10%; 40/399), Apocynaceae (12.3%; 41/333), Meliaceae (10.1%; 35/346), and Solanaceae (11.7%; 14/122). The so-called annonaceous acetogenins undoubtedly account for the high number of "actives" observed in the Annonaceae; these acetogenins often show potent cytotoxicity, and progress in this area has been reviewed by McLaughlin et al.[38] In the case of the Apocynaceae (12.3%; 41/333), the high number of "actives" may in part be attributed to the frequent occurrence of indole alkaloids as major antitumor active constituents in many of the genera. Notable examples are the highly effective anticancer drugs vinblastine and vincristine, isolated from *Catharanthus roseus*. Recent examples include ajmaline and yohimbine analogues and derivatives isolated from *Rauwolfia serpentina*[39] and three new indole alkaloids together with 12 known analogues isolated from *Tabernaemontana calcarea*.[40] In the case of the "hot" genus *Thevetia*, active cardenolides have been isolated from *Thevetia ahouia*.[41]

The "hot" genera in the *Meliaceae* have yielded benzofurans and terpenoids as active constituents. Notable discoveries from the genus *Aglaia* have been the potent rocaglate derivatives, silvestrol and episilvestrol, in addition to other rocaglate analogues and new baccharane-type triterpenoids.[42−47] Further investigations of these rocaglate derivatives have demonstrated that this class of molecules may well be cytostatic rather than cytotoxic agents with activities involving inhibition of NF-κB activation in T-cells (rocaglamides).[48−50] Recently, Greger's group in Vienna have reported[51] that one of these metabolites, aglaiastatin, inhibited growth and induced apoptosis of HT29/H11 colorectal carcinoma cells at nanomolar levels, with a 1000-fold higher concentration being required to affect normal intestinal cell lines. The limonoid trichilin B has been isolated as the active constituent from *Aglaia elliptica* (unpublished; NCI Molecular Targets Development Program, http://home.ncifcrf.gov/mtdp/compounds/692266.html). A search of PubMed gave no cancer-related references to the genus *Chisocheton*, whereas reports of the isolation of cytotoxic and antitumor active di- and triterpenoid constituents have been published for the other Meliaceae "hot" genus, *Dysoxylum*.[52−54] The Solanaceae family is notable as a source of steroidal glycosides and alkaloids, and a range of steroidal glycosides have been isolated as cytotoxic constituents from *Cestrum nocturnum*, one of the two "hot" genera listed in Table 1.[55] The other "hot" genus, *Solanum*, is a rich source of steroidal alkaloids[56−58] and glycosides,[59,60] with reported cytotoxicity and cancer-related activity, and the spiro cyclopentylcyclohexenone solavetivone, isolated from *Solanum indicum*, has been reported to be weakly cytotoxic to OVCAR-3 cancer cells.[61]

Moderately "active" families include the Clusiaceae (8.9%; 40/449), Flacourtiaceae (6.6%; 16/241), Myrtaceae (7.4%; 19/256), and Sapindaceae (8.2%; 24/294). While the Clusiaceae "hot" genera *Calophyllum* and *Garcinia* have been sources of anti-HIV agents in the NCI program (see the calanolides and guttiferones at http://home.ncifcrf.gov/mtdp/name_sor.html), the extracts of samples collected from these genera have also shown in vitro antileukemic activity, as reported in Table 1. The NCI has not pursued these as anticancer leads, but antileukemic activity has been reported for coumarins isolated from *Calophyllum brasiliense*,[62,63] while several prenylated benzophenones[64−67] and a prenylated depsidone[68] have been isolated as active constituents from *Garcinia* species. Prenylated benzophenones isolated from *Clusia* species and propolis derived from *Clusia* species have also been associated with cytotoxic activity.[69,70] No cancer-related references were found in PubMed for the genus *Cratoxylum*, while cytotoxic coumarins have been isolated from *Kayea assamica*.[71]

In the family Flacourtiaceae, clerodane diterpenoids have been reported as the cytotoxic constituents from *Casearia* species,[72−74] while the same genus was found to be the most promising in a screening study of Australian Flacourtiaceae for cytotoxicity and other bioactivities.[75] Clerodane diterpenoids were also isolated as the cytotoxic constituents of *Laetia corymbulosa* (see Table 1 footnote *d*).[76] Activity against the leukemia HL-60 cell line by extracts of *Eugenia* species, one of the "hot" genera of the family Myrtaceae, has been attributed to eugenol in the case of *E. caryophyllata*[77] and hydrolyzable tannins in the case of *E. jambos*.[78] While numerous bioactivities, including antimicrobial,[79] antiplasmodial,[80] and cytotoxicity,[80] have been reported for extracts of *Syzygium* species, little research appears to have been reported thus far on the isolation of active agents. Antibacterial triterpenes have been isolated from *Syzygium guineense*,[81] and immunomodulatory effects have been reported for flavanoids isolated from *S. samarangense*.[82]

A similar situation exists for the two "hot" genera of the Sapindaceae, *Harpullia* and *Serjania*, with no reports of cancer-related activity for these two genera in PubMed, although hemolytic activity has been reported for the acylated triterpenoid saponins isolated from *Harpullia austro-caledonica*.[83] Of the Sapindaceae genera listed in footnote *d* to Table 1 (genera having at least one or two antileukemic plant extracts), there are no reports in PubMed related to cytotoxicity or cancer-related activity; however, two genera not listed are reported to yield cytotoxic compounds. Thus, the isolation of a novel cytotoxic and antibacterial long-chain fatty alcohol glycoside has been reported from the bark of *Cupania glabra*,[84] and very weak cytotoxicity has been observed with saponins isolated from *Nephelium maingayi*.[85] The genus *Dodonea* has been evaluated for antimicrobial and anti-inflammatory activities[86] and has yielded a novel clerodane diterpenoid and flavonoids.[87] Although a farnesyl glycoside has been isolated from *Lepisanthes rubiginosa*, no activity was reported.[88] In contrast, the genus *Paullinia* is associated with various biological activities; in particular, extracts of *Paullinia cupana*, commonly known as guarana, have been reported to show antibacterial and antioxidant activities[89] and chemopreventive effects against *N*-nitrosodiethylamine-induced lesions in mice[90] and ethanol- and indomethacin-induced gastric lesions.[91] Several *Paullinia* species contain purine alkaloids (e.g., caffeine), which are used as marker compounds in chemotaxonomic studies and may be associated with some of the biological observed effects,[92] and flavone glycosides have been isolated from *P. pinnata*, a plant used in African traditional medicine for the treatment of malaria, although no biological activities of the compounds were reported.[93] Finally, while there are no reports of cancer-related activity for the genus *Zanha*, saponins having antiphospholipase A_2 activity have been isolated from an anti-inflammatory extract of *Zanha africana* root bark.[94] It is evident that the Sapindaceae, like the Myrsinaceae, merits further study as a source of potential antitumor leads.

As mentioned above, the largest number of plant specimens collected and tested were from the Fabaceae (1205), Rubiaceae (1015), and Euphorbiaceae (951), but their "hit" rates, as shown in Figure 3, are the lowest compared to the other "hot" families (Fabaceae, 4.2%, 51/1205; Rubiaceae, 2.4%, 24/1015; Euphorbiaceae, 3.3%, 24/951). Cancer-promoting phorbol esters and related compounds are usually associated with the Euphorbiaceae,[95] and some also show some significant cytotoxicity, but other cytotoxic chemotypes have also been isolated from genera of this family. No cancer-related publications are recorded in PubMed for the "hot" genus *Alchornea*, although ellagic acid has been isolated as the active antiplasmodial constituent from *Alchornea cordifolia*.[96]

Clerodane[97] and labdane[98] diterpenoids have been reported to be the cytotoxic constituents of *Croton oblongifolius*, while cytotoxic lupane-type triterpenes have been isolated from *Glochidion sphaerogynum* and *G. eriocarpum*.[99] The schweinfurthins have been isolated as cytotoxic constituents of *Macaranga schweinfurthii*, representing the "hot" *Macaranga* genus.[100] Podophyllotoxin-like lignans are responsible for the cytotoxic activity of extracts of *Bridelia ferruginea* (see footnote *d* to Table 1).[101] A variety of compounds isolated from *Euphorbia* species have been reported to reverse multidrug resistance in mouse lymphoma cells, including cycloartanes[102] and driportlandin, a new scopoletin derivative from *E. portlandica*.[103] The jatrophane diterpenoids from various *Euphorbia* species have demonstrated effects against the P-glycoprotein complex in mouse and human tumor cell lines, with recent reports from Hohmann et al.,[104] Corea et al.,[105] Madureira et al.,[106] and Ferreira et al.[107,108] What is also of interest is that jatrophane esters, in particular jatrophane 1 isolated from samples of Corsican and Sardinianin *E. semiperfoliata*, are tubulin-stabilizing agents with a mechanism of action similar to that of paclitaxel.[109]

No cancer-related activity has been reported in PubMed for the "hot" genera *Cojoba* and *Piptadeniastrum* of the Fabaceae family. However, from the genus *Albizia*, antitumor triterpenoid saponins have been reported from *Albizia grandibracteata*[110] and *A. julibrissin*,[111] while the macrocyclic pithecolobine alkaloids isolated from *A. amara* have been shown to be cytotoxic and to interact with calf thymus DNA.[112] Triterpenoid saponins are also responsible for the cytotoxicity of extracts of the "hot" genus species *Entada pursaetha*,[113] as well as in the case of *Archidendron ellipticum* (see footnote *d* in Table 1).[114]

There are no records of cancer-related activity for the Rubiaceae "hot" genus *Palicourea*, but a number of compounds have been reported from species of the "hot" genus *Psychotria*. Some examples are the benzoquinolizidine alkaloids possessing antileishmanial and antimalarial activity in addition to cytotoxicity from *Psychotria klugii*,[115] the cytotoxic naphthoquinone from *P. rubra*,[116] and cytotoxic pyrrolidino-indole tetramers and pentamers from *P. forsteriana*.[117] Cytotoxic lupane triterpenoids have been isolated from *Coussarea paniculata*,[118] and antileukemic fractions have been reported from *Ixora coccinea* (see footnote *d* in Table 1).[119] In 1977, Jolad et al. reported the isolation and structures of two antitumor cyclic peptides, bouvardin and deoxybouvardin, from a well-known Mexican ethnobotanical plant, identified taxonomically as *Bouvardia ternifolia*, a member of the Rubiaceae known by a variety of names including "trompetilla" and "mirto".[120] Subsequently a number of bouvardin-like antitumor bicyclic hexapeptides have been reported from *Rubia* species, and in a number of cases, they have been synthesized and also used as scaffolds upon which to build other similar compounds.[121−125] From a mechanistic aspect, RA-VII (*O*-desmethyldeoxybouvardin) has been reported[126] to modulate the protein level of cyclin D1, and recently, it was reported that this compound alters the conformation of actin, causing G_2 arrest as a result of inhibition of cytokinesis.[127] Although these compounds are very potent, no reference can be found in PubMed to any clinical efficacy in human trials. This is similar to the lack of reported in vivo efficacy for other extremely potent actin inhibitors such as the jaspamides or cytochalasins, as their therapeutic indicies are close to unity. Other macrocyclic peptides have been isolated as in vitro active anti-HIV agents from *Chassalia parviflora*.[128] Finally, a cytotoxic tetrahydrotubulosine alkaloid was reported from *Pogonopus speciosus*, a Rubiaceae genus not listed in Table 1 (or its footnote *d*).[129]

There are several families recorded in Figures 3 and 4 that are not listed as "hot" families in Table 1, but nevertheless do contain a significant number of leukemia "active" plants. In the case of the Asteraceae (Compositae) (4.3%; 13/278), the observed activities may be due to the presence of sesquiterpene lactones that are common cytotoxic constituents of this family.[130] Similarly, in the family Lauraceae, cytotoxic constituents include flavonoids and α-pyrones from *Cryptocarya obovata*,[131] aporphine isoquinoline alkaloids from *Cassytha filiformis*[132] and *Lindera megaphylla*,[133] and butanolides (α,β-unsaturated-γ-lactones) from *Lindera communis*,[134] *Litsea acutivena*,[135] and *Machilus obovatifolia*.[136] In the family Lecythidaceae, the only report found in PubMed of cytotoxic constituents are a polysubstituted aryl benzoate, gustastatin, and betulinic acid isolated from *Gustavia hexapetala*.[137] Although acylated triterpenoid saponins have been isolated from *Foetidia africana*, no bioactivity was reported,[138] and triterpene saponins have been reported from *Barringtonia acutangulata*, a plant used in Australia as a fish poison.[139]

The genus *Artocarpus* of the family Moraceae is a rich source of cytotoxic prenylated flavones,[140−145] while cytotoxic triterpenes have been reported from *Ficus microcarpa*,[146] and xanthones from *Cudrania* species.[147−149] Interestingly, HIV-inhibitory prenylated xanthones have been isolated from *Maclura tinctoria*.[150]

There are no reports in PubMed of the isolation of constituents having significant cytoxicity from genera of the family Sapotaceae, although weak activity has been reported for 4-*O*-galloylchlorogenic acid, one of several polyphenolic antioxidants isolated from *Manilkara zapota*.[151] Polyphenolic antioxidants have also been reported from *Chrysophyllum cainito*,[152] while bioactive triterpenoid glycosides and saponins have been isolated from *Madhuca indica*[153] and *Tieghemella heckelii*.[154]

Several constituents having cancer-related activity have been isolated from genera of the family Zingiberaceae. 6-Gingerol, a major phenolic constituent of ginger, *Zingiber officinale*, has been reported to induce apoptosis in human leukemia HL-60 cells[155,156] and inhibit angiogenesis,[157] while curcumin from *Curcuma longa* has been reported to induce apoptotic effects in human breast cancer and mammary epithelial cells.[158] Panduratin A, an aryl cyclohexenyl ketone, from *Kaempferia pandurata*, shows similar effects in human colon cancer HT-29 cells.[159] Other cytotoxic constituents reported are labdane diterpenoids isolated from *Alpinia calcarata*[160] and *Renealmia alpinia*,[161] and a styryl cyclohexene isolated from *Zingiber cassumunar*.[162]

Selective Inhibition of Leukemia Cell Lines. While the majority of the "active" extracts did not exhibit selectivity for the leukemia cell line panel since they also showed varying levels of cytotoxicity against cancer cell lines in other disease panels (colon, CNS, breast, etc.), certain extracts demonstrated highly selective activity against the leukemia cell lines in the NCI 60 human cancer cell line screen. While detailed taxonomy cannot be provided for reasons stated earlier, these include extracts of plants belonging to the following plant genera (families in parentheses): *Millettia* (Fabaceae), *Quercus* (Fagaceae), *Sphenostemon* (Aquifoliaceae), and *Parinari* (Chrysobalanaceae); certain extracts of marine origin (Porifera) likewise showed selectivity for the leukemia cell lines. In the NCI experience, the K-562 CML cell line has proved to be particularly resistant to selective growth inhibition or cell kill, and extracts that demonstrate leukemia selectivity with an emphasis on inhibition of this particular line may well offer opportunities for the development of novel agents for the selective treatment of CML and ALL.

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