RELATIONSHIPS BETWEEN PLANT FOLKLORE AND ANTITUMOR ACTIVITY: AN HISTORICAL REVIEW[1]

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ABSTRACT

The National Cancer Institute's (NCI) record of plants that have shown significant inhibitory effect in experimental tumor systems (active plants), 1960–1974, was compared with species and genera in references on medicinal folklore, including poisonous plants, to determine whether their percentages of active plants were significantly greater than those screened at random (10.4%). The percent active species in medicinal and/or poisonous references in general were found to be 1.4 to 2.6 times greater, while the number and different kinds of medicinal uses appear related to geographical data of species that also indicate medicinal plants were screened more thoroughly because of their widespread occurrence. The best correlation is seen with poisonous plants, including medicinal plants that suggest a moderate to strong therapeutic effect; their percentages of active species were nearly three (29.3%, anthelmintics) to four times (45.7%, arrow and homicidal poisons) greater than plants screened at random. Selection of plants based strictly on use in folk medicine would probably benefit new (start-up) screening programs, whereas in the long-term, it appears more cost effective to systematically screen the broadest diversity of plants readily available since the common medicinal species would be collected irregardless. A systematic collection strategy could give emphasis to genera that have not been exhaustively studied, especially to species with medicinal uses that indicate toxicity or are considered poisonous.

RESUMEN

El registro de plantas del National Cancer Institute (NCI) 1960–1974, que han mostrado un efecto inhibidor significativo en sistemas tumorales experimentales (plantas activas), se compararon con géneros y especies que aparecen en referencias de medicina popular, incluyendo plantas venenosas, para determinar en que medida los porcentajes de plantas activas eran significativamente más altas que las investigadas al azar (10.4%). El porcentaje de especies activas referenciadas como medicinales y/o venenosas en general se encontró que era de 1.4 a 2.6 veces mayor, mientras que el número y diferentes tipos de usos medicinales parecen relacionados con datos geográficos de especies que también indican que las plantas medicinales fueron investigadas más minuciosamente debido a su amplia distribución. La mejor correlación se aprecia con las plantas venenosas, incluyendo las plantas

[1]A summary of the data in this paper was presented at the Society for Economic Botany Symposium on Plants And Cancer held in Baltimore, August 1975. An alternate paper was published in Cancer Treatment Reports in August 1976 (Spjut & Perdue, Vol. 50, 8:979–985). Left out were all data and discussion on Quisumbing's (1951) Medicinal Plants of The Philippines, reviews on genera with geographically disjunct uses of medicinal species, and activity according to the tumor systems employed.

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medicinales que parecen tener un efecto terapéutico de moderado a fuerte; los porcentajes de especies activas fue de cerca de tres (29.3%, antihelmínticos) a cuatro veces (45.7%, venenos para flechas y homicidios) mayor que las plantas investigadas al azar. La selección de plantas basada estrictamente en el uso en medicina popular probablemente sería beneficiosa para los nuevos programas de investigación, mientras que a largo término, parece tener un costo efectivo mayor la investigación sistemática de una diversidad de plantas fácilmente disponibles ya que las especies medicinales comunes pueden colectarse en cualquier parte. Una estrategia de colecta sistemática pondría énfasis en géneros que no hayan sido estudiados exhaustivamente, y especialmente en especies con usos medicinales que indiquen toxicidad o que se consideren venenosas.

INTRODUCTION

The USDA Agricultural Research Service (ARS) was a major supplier of plant samples for the National Cancer Institute (NCI) Cancer Chemotherapy Screening Program from 1960–1982. The objective of this program was to identify novel chemical structures produced by plants that would be useful in treatment of cancer. Two major discoveries of novel anticancer drugs from this period were taxol (Wani et al. 1971), isolated from stem-bark of *Taxus brevifolia* Nutt. (Taxaceae), initially collected in Washington, August 1962, followed discovery of confirmed antitumor activity in KB Cell Culture (KB), July 1964 (NCI CPAM, 1977), and camptothecin (Wall et al. 1966), isolated from *Camptotheca acuminata* Decne. (Nyssaceae), based on fruit samples collected in September 1961 from a USDA Plant Introduction Station in Chico, California, and reported to have confirmed antitumor activity in L-1210 Leukemia (LE), July 1962 (NCI CPAM 1977). Semi-synthetic derivatives of compounds from both species are currently employed to treat various cancers (Cragg et al. 1996). The commercial development of these anticancer drugs, however, did not occur until the 1990s. In 1986, the NCI re-developed its biodiversity screening program of natural products (Boyd 1992; Cragg et al. 1996; Newman et al. 2003); however, the acquisition of plant samples for the NCI screen was suspended in 2004.

In August 1975, a symposium on "Plants and Cancer" was held in Baltimore, MD at the Annual Meeting of the Society for Economic Botany. The contributors included many scientists actively involved in the NCI search of new anticancer drugs from plant products who had agreed, in advance, to providing a research contribution. My assigned study was "Plant Folklore: A Tool for Predicting Sources of Antitumor Activity? Other contributed papers were "Procurement of Plant Materials for Antitumor Screening" (Perdue 1976), "Preparation of Plant Extracts for Antitumor Screening" (Statz & Coon 1976), "Bioassay of Plant Extracts for Anticancer Activity" (Abbott 1976), "Isolation and Chemical Characterization of Antitumor Agents from Plants" (Wall et al. 1976), "Types of Anticancer Agents Isolated from Plants" (Hartwell 1976), "Distribution of Anticancer Activity in Higher Plants" (Barclay & Perdue 1976), "Novel Plant-Derived Tumor Inhibitors and Their Mechanisms of Action" (Kupchan 1976), "Pharmacology of Antitumor Agents from Higher Plants" (Sieber et al. 1976),

and "Plant Products in Cancer Chemotherapy" (Carter 1976). These and others were published collectively in Cancer Treatment Reports, edited by Robert E. Perdue, Jr., and Jonathan L. Hartwell (Vol. 60, No. 8, 1976).

Upon investigating the relationships between antitumor activity and plant folklore, I felt that plants used in folklore were not going to lead to discovery of novel compounds any more than a systematic sampling of the world's plant diversity based on taxonomy, the approach that had been in practice 14 years. Therefore, in order to show this, the most common medicinal uses of plants, and also poisonous plants, would need to be investigated. During the course of the study, the results on the NCI active species found in literature on medicinal and poisonous plants, in comparisons to those screened at random, raised more questions than could be answered, including the one originally proposed. The Spjut and Perdue (1976) paper excluded much data in another manuscript that had been completed and peer reviewed.

After nearly 30 years, the unpublished data still seem relevant to present day studies in ethnobotany and pharmacology, particularly the relationship between antitumor activity and folklore indicating plant toxicity; therefore, this paper will focus on that relationship, including also data from Spjut and Perdue (1976). Another important relationship involves the multiple uses for a large number of widely distributed species; their impact on the apparent correlation between antitumor activity and medicinal folklore will be discussed. Additionally, Spjut (1985) reviewed the random screen methodology in detail with reference to unpublished data on The Philippine medicinal plants; these data will be presented in this publication.

MATERIALS AND METHODS

Literature Surveys.—This paper deals with data compiled from literature and the NCI plant screening program prior to 1977. Folklore and plants in this study were limited to literary sources for evaluating medicinal uses and poisonous effects of higher plants in man and animals. Included are plants believed to have medicinal or poisonous properties, and the scientific literature dealing with active chemical agents in confirmed poisonous and medicinal plants. Botanical data and the references cited, including the nomenclature of plants, are not updated since this paper was prepared and last reviewed in July 1976; however, in regard to pharmacological data on compounds that were isolated, more recent references are provided.

Eight compendia on medicinal and poisonous plants were employed to identify which of their genera and species were active in the NCI program: Hardin & Arena (1974), Hartwell (1967–1971), Kingsbury (1964), Krochmal & Krochmal (1973), Quisumbing (1951), Train et al. (1957), Webb (1948), and Weiner (1972). One of these, Quisumbing (1951), was further utilized to determine whether a specific medicinal use was more closely correlated with antitumor

activity. Because antitumor activity appeared to correlate with a wide variety of medicinal uses, additional data from Quisumbing (1951) were compiled and analyzed in regard to multiple uses of plants as related to their geographical distribution. Additionally, we (Spjut & Perdue 1976) prepared our own compilation on plants used as (1) anthelmintics, (2) fish poisons, and (3) arrow, ordeal and homicidal poisons to determine whether there was a correlation between antitumor activity and plant toxicity in contrast to medicinal plants in general.

Active species.—An active species is defined as one represented by one or more extracts having shown a significant inhibitory effect in any tumor system used in the NCI preliminary screen; these were primarily KB Cell Culture (human epidermoid carcinoma of the nasopharynx, KB, 1960–1982), P-388 Leukemia (PS, 1968–82), Lewis Lung Carcinoma (LL, 1962–66), Walker Carcinoma 256 (WA, 1966–69), Sarcoma 180 (SA, 1956–62), Adenocarcinoma 755 (CA, 1956–62) and L-1210 Leukemia (LE, 1956–71) (Abbott 1976; Geran et al. 1972; Hartwell 1976; Suffness & Douros 1979). The NCI provided a print-out of their active species for this study; additionally, another printout indicating tumor systems for the confirmed active species was consulted (NCI CPAM 1977).

Active agents have included a broad spectrum of compounds (Hartwell 1976), some of which were precluded from further screening (e.g., tannins, phytosterols) by changes made in the extraction procedure and tumor assays (Hartwell 1976); thus, the NCI screen evolved to become more selective in identifying active candidates for drug development by eliminating classes of compounds not considered useful for treating cancer (Hartwell & Abbott 1969). During the 1960s, tannins—in aqueous extracts from a wide variety of plants—were frequently active in WA, but also in CA, LL and SA tumors; a total of 164 species, representing 7.7% of all active species (2,127) in this study were tannin actives (Barclay & Perdue1976; Hartwell 1976). Later, tannins were extracted out before testing, while tumors insensitive to tannins were subsequently employed (Hartwell 1976). Consequently, many variables are represented in the definition of an active species, such as differences in extraction procedures, quantity and kind of tumor systems employed, parameters that define activity from testing extracts, and whether specific plant parts screened correspond to those employed in folklore. Nevertheless, it is felt that all plants regarded active by the NCI from 1960–1976 are valid for making comparisons with folk uses of plants.

Comparisons between the NCI active species and those in the literature considered taxonomic synonyms and closely related species when known. For instance, the NCI active species, *Thalictrum polycarpum* (Torr.) S. Wats., based on a sample collected and identified by A.S. Barclay from southern California in 1962, was not found in the literature reviewed to have medicinal or poisonous reports; however, this species could be interpreted as a synonym of *T. fendleri* Engelm. (Munz 1959), one that was reportedly used in medicine by the Indian

Tribes of Nevada (Train et al. 1957). Based on taxonomy, *T. polycarpum* is considered a medicinal plant.

Active genus. Comparisons were also made at the genus level; however, the size of the genus varies—from just one species (e.g., *Camptotheca*) to more than 1,000 species (e.g., *Euphorbia*); Willis (1922) had determined that 47% of all genera are monotypic, 17% have two species, 8% have three species, and the remaining 28% have four or more species. An active genus is one with one or more active species. Because most genera have more than one species (53%), the percentages of active genera will be higher than active species. Also, when more than one species in an active genus is reportedly used medicinally and/or poisonous, the relationship between antitumor activity and folklore will appear closer, or lie between the percentages of active genera and active species.

Random Screen. The rationale of the NCI screen has been to regard any species as a potential source for novel anticancer drugs; thus, screening of plants has been considered random. In practice, however, collecting was not purely random. One reason is that it is not possible to collect every plant species encountered in the field, because the quantity of dry weight needed may not be practical to obtain. Another is that geographic sampling has not been uniform for political and economic reasons.

The number of genera and species screened and active in the NCI program was determined by A.S. Barclay for the symposium on "Plants and Cancer" at the Society for Economic Botany meeting in Baltimore, August 1975. His data accounted for all species and genera screened by the NCI—up to the end of 1974, taking into consideration synonyms and samples that the NCI acquired not only from the USDA, but from all contractors. His tabular summary is reproduced here, Table 1 (Barclay & Perdue 1976).

The percentages for active genera, 26.0, and species, 10.4, are the bases for making comparisons to those in folklore references; however, it must be kept in mind that the numbers for active species and genera are cumulative; i.e., they do not represent the actual frequency at which activity occurs. This is because some species have been screened more than once, or have included more plant parts than others, thus, have had more opportunity to show activity—also keeping in mind that the NCI screen has become more selective over time.

GENERAL SURVEYS

The NCI computer record of active plant species was compared with species and genera cited in indices or texts of eight compendia to determine which have shown antitumor activity (Table 2). With two exceptions, active species were 1.4 to 2.6 times more frequent in references on medicinal and/or poisonous plants than in plants screened at random, while results with active genera were more consistent—at nearly double that of the random screen.

The greater variation at the species level for medicinal plants is partly due

TABLE 1. NCI overall screening data for vascular plants (1960–1974).

	Number Screened	Number Active	% Active
Genera	4,716	1,225	26.0
Species	20,535	2,127	10.4

to many species not screened, in contrast to higher percentages of genera screened. For one reference, Quisumbing (1951), it was determined that 626 of the 855 species were tested; thus, instead of the 16.4% active of those recorded (855), 22.4% of those species actually screened (626) were active—nearly double that of the random screen.

In regard to the wide ranging values seen for poisonous plants, the lower percentage of 9.2% active species in Webb (1948) seems related to many species that are suspected to cause poisoning of livestock. When data from the same reference was restricted to species that were reported to be poisonous *and* also used medicinally, the percent active species was notably higher, 18.9%. These data suggest that plants, both poisonous *and* used medicinally, are more likely to show antitumor activity than those strictly used medicinally. Also, data from other references (Kingsbury 1964; Hardin & Arena 1974) had more plants confirmed to be poisonous, which in Hardin and Arena (1974) were restricted to those taken internally (Spjut & Perdue 1976). The higher percentages of active species (21.5%, 41.1%) and genera (56.4%, 66.4%) in these references on poisonous plants indicate that toxicity is a factor in the apparent correlation between antitumor activity and plants generally used in medicinal folklore.

Active Plants According to Number and Kinds of Medicinal Uses

Quisumbing (1951), in his *Medicinal Plants of the Philippines*, provided species indices for 116 different categories of therapeutic uses and for 111 different kinds of specific diseases, a total of 227 different medicinal applications from which 90 were selected on the basis of 19 or more species being listed to determine whether antitumor activity was more closely correlated with a particular therapeutic effect (Appendix I, 62 medicinal applications) or specific disease (Appendix II, 28 medicinal applications). What we found, however, was a broad correlation with all medicinal applications (Appendix I, II). This broad correlation appears related to a large number of widely distributed species for which many have probably been screened more than once by the NCI, while a correlation between antitumor activity and toxicity is also evident. These relationships will be made apparent in the data and discussion that follow.

Quisumbing (1951), in reporting on 855 species in 580 genera and 143 families of vascular plants in The Philippines, did not limit his review to medicinal uses within The Philippines. He also drew on literary sources outside The Philippines.

TABLE 2. Number and percent of active genera and active species for medicinal and poisonous plants in eight selected references.

Reference	Genera Listed	Genera active	% Genera active	Species Listed	Species active	% Species active
Medicinal Plants						
Krochmal (1973)	207	131	63.3	251	67	26.7
Quisumbing (1951)	580	271	46.7	855	140	16.4
Train et al. (1957)	142	77	54.2	214	32	15.0
Webb (1948)	398	228	57.3	529	87	16.5
Weiner (1972)	285	156	54.7	388	73	18.8
Poisonous Plants						
Hardin & Arena (1974)	113	75	66.4	141	58	41.1
Kingsbury (1964)	282	159	56.4	488	105	21.5
Webb (1948)	433	211	48.7	760	70	9.2
Poisonous Plants used Medicinally						
Webb (1948)	229	153	66.8	196	37	18.9
Plants Used Against Cancer						
Hartwell (1967–1971)	1,201 (1,033 tested)	480	46.5 (tested)	2,725 (1,815 tested)	314	17.3 (tested)

Thus, many plants not known to be used medicinally in The Philippines were included so long as the plant occurred there, a practice not uncommonly employed by many ethnobotanists in other geographic studies of medicinal plants. Nevertheless, the result is that there are many widespread species represented. This is evident in part by finding that 8% of all species in Quisumbing (1951) are endemic to The Philippines, based on geographical data he also provided; thus, 92% of the species in Quisumbing (1951) extend beyond The Philippines.

The distribution of endemic species according to the number of uses is shown in Figure 1. Among 110 species in Quisumbing (1951) listed for only one medicinal application, 25% were found to be endemic to The Philippines, followed by a sharp decline for those reported under multiple applications—15% for plants listed under two medicinal applications, 8% for three medicinal application—to none found under nine or more medicinal applications. It is certainly not surprising to find that narrower geographically distributed species have fewer medicinal reports.

However, the extent to which medicinal species are reported for many different uses is perhaps not fully realized by many ethnobotanists. The 808 species listed, among the 90 medicinal applications selected from Quisumbing (1951), accounted for a whopping, 5,843 species entries (meaning that many of the 808 species are used for more than one application), the distribution of which is shown in Figure 2. As an average, 50% of the species reported under any one

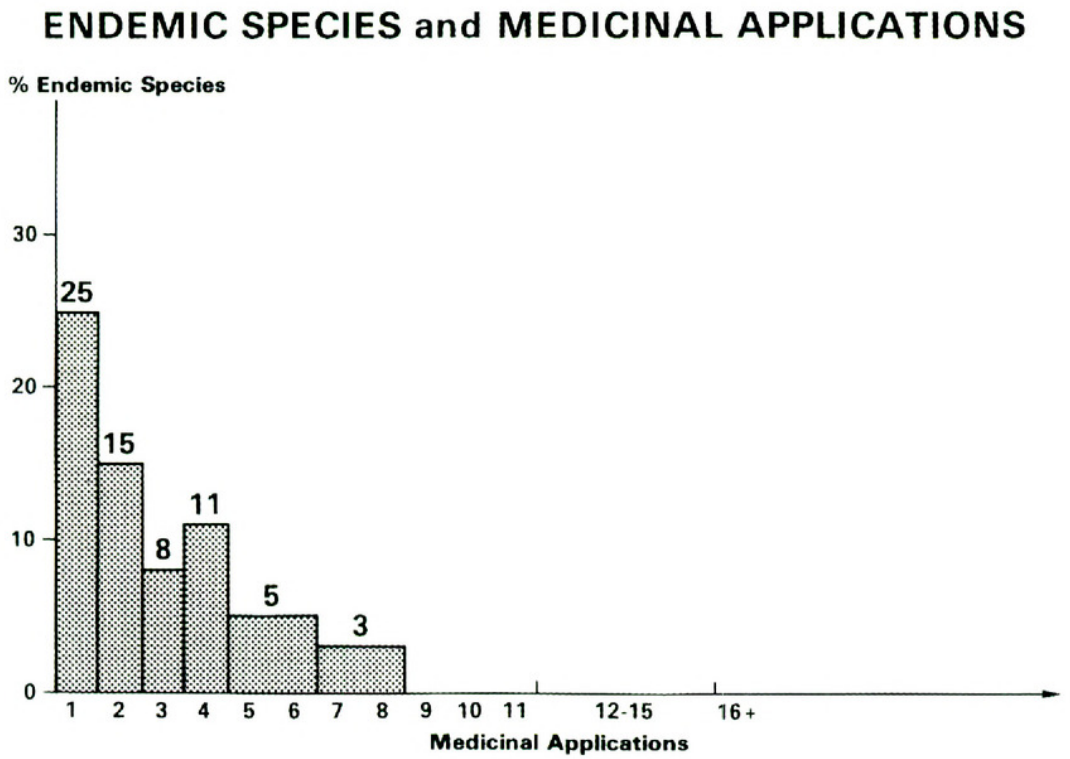

FIG. 1. Percent endemic species to The Philippines according to number of different medicinal applications based on 90 of 227 medicinal applications in Quisumbing (1951). The number of medicinal species for each number of uses is shown in Fig. 2. Of 110 species reportedly used for only one medicinal application, 25% were endemic to The Philippines; for species with two medicinal applications, 15% were endemic, etc., to no endemics for species reported to have nine or more medicinal applications. Geographical data are based on Quisumbing (1951).

medicinal application were also found under 11 or more other medicinal applications.

The extent of the widespread occurrence for many of the medicinal plants reported by Quisumbing (1951) is further evident by percent species screened according to the number of uses recorded, Figure 3, and the fact that relatively few species were actually collected from The Philippines. Some of the medicinal applications in the higher multiple use categories were combined to obtain a more equitable number of species for each category. The results show, as one might expect, a definite correlation between the number of uses and percent species screened, increasing from 45% for species with only one medicinal application, to 99% for those with 16 or more medicinal applications. Plants were procured largely from the United States, Australia, New Zealand, Fiji, Taiwan, India, Turkey, Ethiopia, Kenya, Tanzania, South Africa, Ghana, Mexico, Panama, Colombia, Brazil, and Peru. Small numbers of collections were also obtained from other countries; see also procurement map in Perdue (1976).

For the 90 selected medicinal applications from Quisumbing (1851), 626 species in 531 genera were found to have been screened of which 140 species

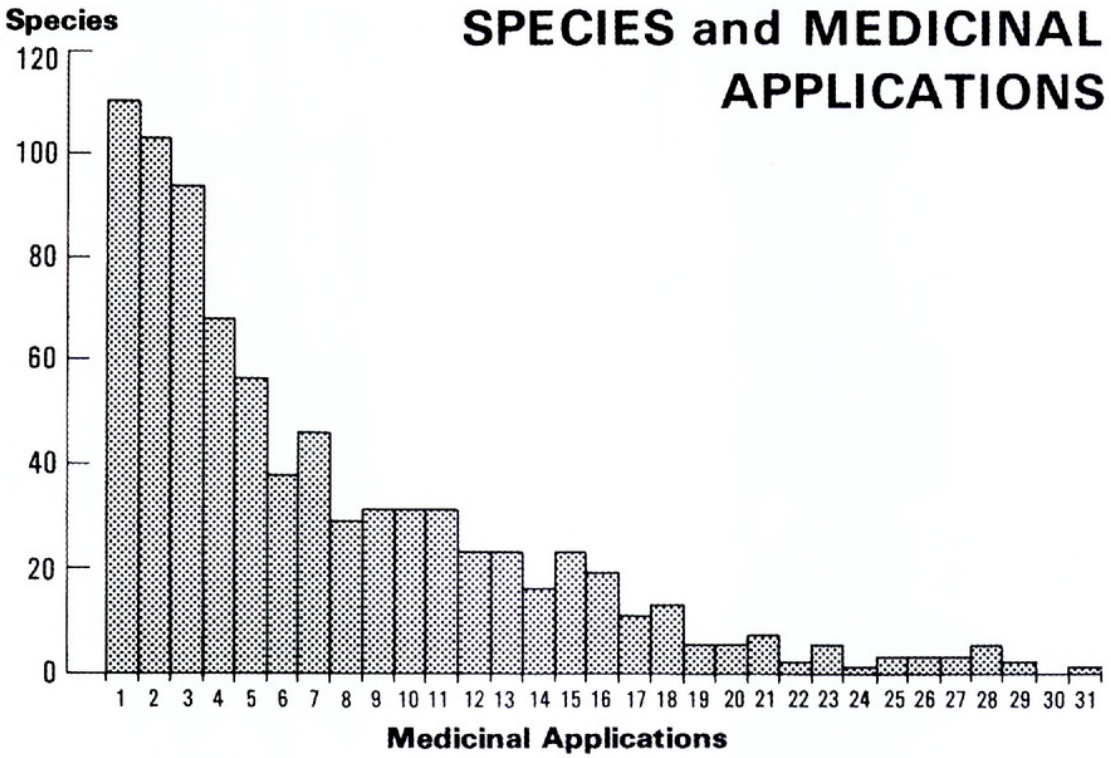

FIG. 2. A numerical distribution of species according to number of medicinal applications for a total of 90 different kinds of medicinal applications that included 808 species in Quisumbing (1951). The number of species for each number of medicinal applications decreases from 110 species used for just one purpose, to one species, *Artemisia vulgaris* L., cited under 31 different medicinal applications.

(22.4%) in 265 genera (49.7%) were active (Appendix III); additionally, 40% of the 140 active species were found to have 12 or more medicinal applications. One medicinal application with notably high percentages of active species and genera was plants used against hemorrhoids, 35.3% (24) of the 68 species and 72.1% of the 61 genera.

Are plants used for treatment of hemorrhoids more closely correlated with antitumor active plants than plants used for other purposes? Statistically, the distribution of active genera and species for the medicinal applications in Quisumbing (1951) might be expected to follow a bell-shaped curve distribution in which there will be higher than average as well as lower than average percentages of active species (and genera). The categories with higher percentages of active species would also be expected to have more widely distributed species based on data presented in Figures 1–3 and the absence of plant collections from The Philippines as already indicated. Indeed, among 68 species listed by Quisumbing (1951) for plants used against hemorrhoids, 75% (51) were reported for 11 or more other medicinal applications, which included 23 of the 24 active species. Therefore, it cannot be concluded that plants used for a particular remedy such as hemorrhoids are more likely to show antitumor activity than plants used for other purposes.

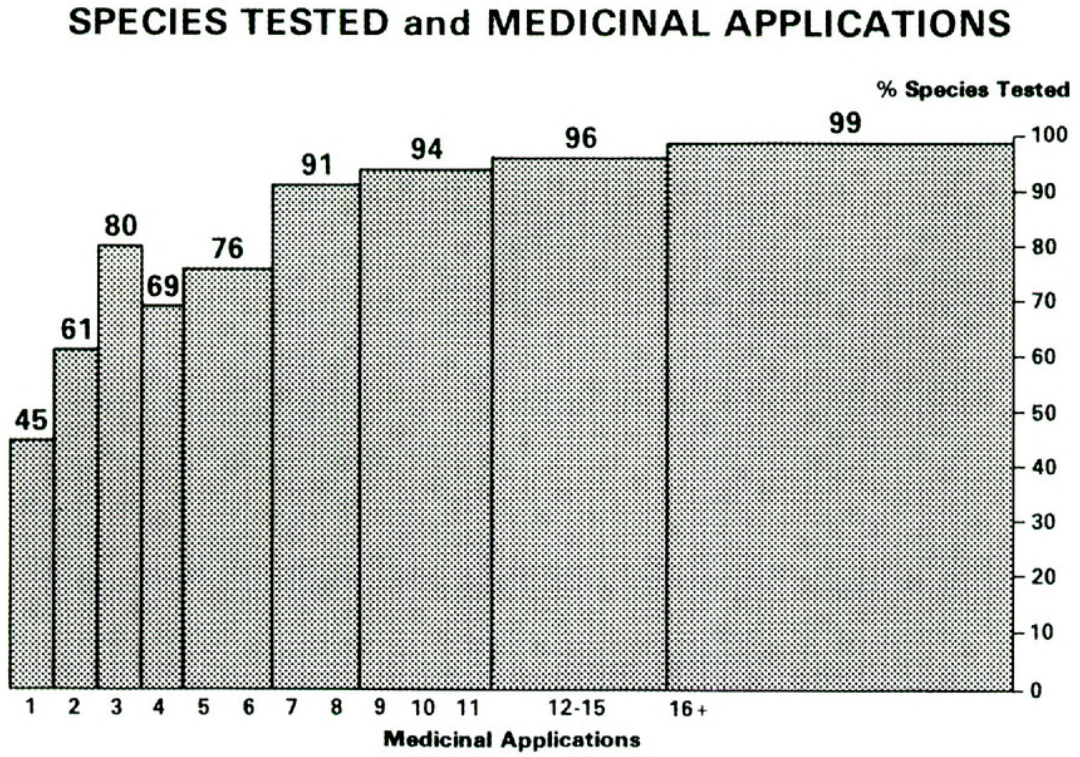

FIG. 3. Percent of species screened by the NCI for antitumor activity according to number of medicinal applications for 808 species listed in 90 of 227 different medicinal applications by Quisumbing (1951). The percent screened for each numerical category of medicinal uses of plants is shown to increase from 45% for species reported to have just one medicinal use to 99% screened for those reported for 16 or more different medicinal applications.

On the other hand, one might argue that the use of plants for many medicinal remedies by one or more cultures should constitute strong evidence for discovering biological activity. At the species level, however, cultural diffusion might exaggerate and multiply reports (Watson 1983), whereas medicinal reports based on disjunct occurrences of closely related species in genera may appear more valid, depending, however, on the size of the genus and number of medicinal species reported. The following six cases exemplify how folklore may appear in one case to have strong validity, while in other instances appears inconclusive.

1) *Brucea* (Simaroubaceae) is a small paleotropical genus of 6 species with *B. antidysenterica* in Africa and *B. javanica* (L.) Merr. in southeast Asia that have reportedly been used for treating skin diseases, dysentery, tapeworm, and cancer (Burkhill 1935; Chopra et al. 1956; Dalziel 1937; Hartwell 1967–1971; Quisumbing 1951; Watt & Breyer-Brandwijk 1962; Webb 1948). Anticancer activity has been identified in both species and one other, *B. guineensis* G. Don, found only in west tropical Africa without any reported use. The anticancer compound, bruceantin (Kupchan et al. 1973), isolated from *B. antidysenterica*, has undergone preclinical studies as a potential drug for cancer chemotherapy. It was found to be toxic in human application; however, derivatives of related

compounds are still being investigated for cancer chemotherapy (Cuendet & Pezzuto 2004; Mata-Greenwood et al. 2001).

2) *Colubrina* (Rhamnaceae) includes one widespread species, *C. asiatica* (L.) Brongn., eight species of spotty distribution in the Old World, one in India, three in Indonesia and four in Madagascar, plus about 22 species distributed in tropical and subtropical America (Johnston 1971). *Colubrina asiatica* has been used as an abortifacient and for treating skin diseases (Quisumbing 1951). Species of *Colubrina* in the West Indies and Mexico have been used as an anthelmintic and for treating dysentery and skin diseases (Standley 1922–1926). Anticancer activity has been identified in six New World species, but not in *C. asiatica*. An ansamacrolid, colubrinol (Wani et al. 1973), isolated from *C. texensis* (Torr. & Gray) A. Gray, is related to maytansine, which has undergone clinical studies for cancer chemotherapy as discussed below. *Colubrina californica*, a closely related species to *C. texensis*, has also shown similar activity, but no medicinal reports could be found for these species.

3) *Maytenus* (Celastraceae) is a large pantropical genus of 150 or more species with relatively few species reported for medicinal purposes. One species in South America, *Maytenus ilicifolia* Mart. Ex Reiss., has been employed for treating a variety of ailments such as peptic ulcers, dyspepsia, gastralgia, enteritis, cystitis, insomnia, nervousness, acne, hemorrhoids, dysentery, and cancer (Hartwell 1967–1971; Morton 1968). In Mexico, *M. phyllanthoides* Benth. has been employed as a remedy for scurvy and toothache (Standley 1922–1926), and *M. pseudocasearia* Reiss. has been used to treat dysentery (von Reis Altschul 1973). In East and South Africa, four or five species have been used medicinally as remedies for amoebic dysentery, diarrhea, colic, malaria, epilepsy, "madness," colds and cancer (Harington 1969; Watt & Breyer-Brandwijk 1962). Anticancer activity has been identified in 21 of 31 *Maytenus* species screened. An ansamacrolid, maytansine (Kupchan et al. 1972), isolated from several African species, underwent clinical trials for cancer chemotherapy. This was discontinued because of toxicity; however, there is renewed interest in derivatives of maytansinoids, which are less toxic (Bander et al. 2003; Larson et al. 1999).

4) *Ficus* (Moraceae) is a very large pantropical genus, ~800 species (Airy Shaw 1973), and many *Ficus* species are employed medicinally for a variety of purposes throughout the tropics. Seventeen species had shown antitumor activity; yet, none have yielded compounds for clinical studies.

5) *Fritillaria* (Liliaceae) has about 85 species distributed in temperate regions of the northern hemisphere (Airy Shaw 1973). In China, species of *Fritillaria* are used for a wide variety of ailments that include cancer (Hartwell 1967–1971; Steinmetz 1962). In Europe and the Himalayas of India, several species have been used against asthma and tuberculosis (Steinmetz 1962). The NCI has screened species from Southeast Asia, Europe, and the United States; none have shown activity.

6) *Thamnosma* (Rutaceae) is a small genus of ~8 species with a spotty distribution: southern Africa, Arabia, Socotra and the southwestern United States (Airy Shaw 1973). Africans have smoked plants of *T. africana* Engl. to relieve chest conditions (Watt & Breyer-Brandwijk 1962). A decoction of the stems of *T. montana* Torr. & Frem. has been used by Native American tribes of Nevada for colds and as a tonic (Train et al. 1957). Both species have been screened by the NCI; neither was active.

It is apparent from these six cases that an objective analysis is difficult. Subjectively, one might weigh small genera (*Brucea*) more than large genera (*Ficus*), similar medicinal uses as opposed to different uses—among different cultures, spotty distribution as seen for species of *Brucea* and *Thamnosma*, over continuous distribution as in the case of *Ficus*, and to the kinds of medicinal applications, especially cancer (e.g., *Brucea, Fritillaria, Maytenus*) as opposed to treating colds (e.g., *Thamnosma*). In *Ficus* it might appear significant that many species are used medicinally in folklore; however, of 174 species of *Ficus* screened by the NCI, only 9.8% were active, which is slightly less than that of the random screen (10.4%). In the case of *Fritillaria*, however, there is no correlation evident due to lack of activity.

PLANTS USED AGAINST CANCER

Hartwell (1967–1971) compiled a record of more than 3,000 species of plants reported in folklore for treating cancer and other symptomatic conditions such as warts and tumors. The vascular plants included 2,725 species representing 1,201 genera and 185 families. An estimated two-thirds of the species and 86% of the genera were screened for antitumor activity based on sampling of four families (Fabaceae, Liliaceae, Rubiaceae, Rutaceae; Spjut & Perdue 1976); it was not practical to compare all 2,725 species in Hartwell against the record of 20,225 species screened, as was done for the NCI record of 2,127 active species of which 314 active species were found in Hartwell (1967–1971). Thus, an extrapolated result is provided, indicating 17.3% active species and 46.5% active genera for those screened and used against cancer (Table 2).

The percentages of active species and active genera found in Hartwell's (1967–1971) record of plants used against cancer are comparable to that seen in the general references on medicinal plants (Table 2). It should be realized that the greater the number of species included in a study like that of Hartwell (1967–1971), the greater the number of species that will be represented with relatively narrower ranges in geographical distribution; thus, the impact of the more thoroughly screened, widely distributed species, will be less. The 1.7 fold increase in active species and the 1.8 fold increase in active genera over the random screen in Hartwell's (1967–1971) plants used against cancer is perhaps a more realistic assessment of the relationship between plants used in medicinal folklore and those that have shown antitumor activity in the NCI screen.

Relationships between Antitumor Activity and Medicinal Plants, Toxic Plants, and Poisonous Plants

General Surveys.—The percentages of active species in the general surveys (Table 2) indicated that poisonous plants, including those with medicinal uses, appear more likely to show antitumor activity than medicinal plants in general.

Antitumor activity among the different therapeutic uses (Appendix I) were also evaluated for evidence of a correlation with plant toxicity; for example, a plant used as an emetic will likely induce a stronger physiological reaction, which could also be more harmful if taken in excess, than a plant taken as a stimulant. In a further review of the 62 medicinal applications in Quisumbing (1951, Appendix I), ten were selected as representative of two therapeutic use categories: (1) five that represent a weak-to-moderate effect—stimulant, alterative, diaphoretic, aperient, and laxative—and (2) five that appear to exert a moderate-to strong physiological effect—purgative, cathartic, abortifacient, anthelmintic, and emetic. A comparison of the percentages of the active species in the two categories (Table 3) show that the percentages of active species are all higher in the moderate-to-strong category, suggesting, therefore, that plants with medicinal uses associated with possible toxic side affects are more likely to show antitumor activity than medicinal plants in general.

Plants Used as Anthelmintics.—Plants used as anthelmintics—those taken internally by humans for helminth infestations such as tapeworm, roundworm, guinea worm, elephantiasis and shistosomiasis—are included in Table 3 as an example of a medicinal application where one may expect a moderate to strong reaction in using a plant product that results in the expulsion or destruction of parasitic worms. Thus, from this perspective, the 30% active species of the 150 species listed in Quisumbing (1951) would appear to have a closer correlation with antitumor activity when compared to the 22.4% active species for all medicinal plants in that same reference, besides the less frequent active species among those therapeutic uses that imply a weaker physiological effect (Table 2, 3, Appendix I).

Nevertheless, an independent review of the literature was conducted to determine which species are reported as anthelmintics—because of Perdue's observation on such plants in Ethiopia that were also active in the NCI screen (Spjut & Perdue 1976). Recorded were 668 species in 457 genera and 128 families of which 482 species in 433 genera were screened. The active species, and the bioassay(s) in which they were active, are indicated in Appendix IV; a complete list of plants used as anthelmintics for this study with references to each species is available at www.worldbotanical.com. Of those tested, 29.3% of the species and 52.2% of the genera were active.

The 29.3% active for anthelmintic species is nearly three times that of the

TABLE 3. Antitumor activity as related to potency of therapeutic effect: selected medicinal applications from Quisumbing (1951).

	Therapeutic Use	Percent Active Species
Weak to Moderate in Effect		
	Stimulant	14.8
	Alterative	23.4
	Diaphoretic	23.1
	Aperient	22.5
	Laxative	20.6
Moderate-To-Strong In Effect		
	Purgative	25.7
	Cathartic	25.9
	Abortifacient	27.9
	Anthelmintic	30.0
	Emetic	32.1

random screen, and is clearly higher than that seen in general references on medicinal plants (Table 1), in particular the 22.4% found for all Medicinal Plants of the Philippines (Quisumbing 1951). These data support the finding that medicinal plants with indication of toxic side effects, such as the case with anthelmintics, are more likely to show biological activity, than medicinal plants in general.

Plants Used as Fish and Arrow Poisons.—As with anthelmintics, we compiled separate lists for plants used as fish and arrow poisons that also included ordeal and homicidal poisons (Spjut & Perdue 1976). These data can be found at www.worldbotanical.com; in this publication, only the active species with reference to the tumor assay are listed, Appendix V, VI.

The results, presented in Table 4, show that the percent active species among those tested was 38.6% for plants used as fish poisons and 45.7% for plants used as arrow, homicidal and/or ordeal poisons.

Plants used as poisons are obviously more toxic than those generally used for medicinal purposes, which are not employed for lethal purposes, but still can be deadly if taken in excess. One might also expect fish poisons to be somewhat less harmful than arrow poisons, because fish poisons are used to capture fish for consumption in which the fish are often only stunned, whereas arrow poisons are intended to kill. Data on antitumor activity that correlates with these differences (Table 4) are seen as another example of a correlation between plant toxicity and antitumor activity.

The correlation that is evident between poisonous plants and antitumor activity led to further evaluation in regard to the type of tumor activity, because activity in poisonous plants was suspected as largely occurring in the KB Cell Culture, a bioassay that is sensitive to cytotoxic agents (Hartwell 1976).

TABLE 4. Antitumor activity in poisonous plants.

Poisons	Genera tested	%Genera active	Species tested	%Species tested active
Fish	158	65.8	145	38.6
Arrow, Ordeal, & Homicidal	60	75.0	70	45.7

Data in Appendix III, IV, V, and VI, which indicate tumor system of activity with their percentages of active species and genera, confirmed this. These data are summarized in Table 5. The percentages of KB active species were found to be 6.7% for medicinal plants in The Philippines (Quisumbing 1951), 11.4% for anthelmintics, 20.7% for fish poisons, and 30.0% for arrow poisons, in contrast, for example, to activity in the WA assay that was 8.5%, 8.3%, 8.3%, and 7.1%, respectively. Clearly, there is correlation between antitumor activity and plant toxicity based on the KB assay and folklore data.

DISCUSSION AND CONCLUSIONS

Selective approaches to screening plants for antitumor activity have been conducted previously by taxonomy (Belkin & Fitzgerald 1953b), by taxonomy and medicinal use such as anti-malarial plants in the Amaryllidaceae (Fitzgerald et al.1958), and by specific medicinal or poisonous applications such as plants used as cathartics, diuretics and pesticides (Belkin et al.1952a; Belkin & Fitzgerald 1952b, 1953c). These and other similar experimental studies were limited to screening against Sarcoma 37. It is interesting to note that in the case with plants used as cathartics, nearly half of the species tested were active. This might be compared to another study by the same authors using the same bioassay in screening "miscellaneous plants" in which they found only 14% active (Belkin & Fitzgerald 1953a); a comparison that is analogous to the "random screen" in the present study.

One important discovery relating to these investigations came from the medicinal use of a root extract of May-apple, *Podophyllum peltatum* L. (Berberidaceae), known as "podophyllin." Hartwell (1960, 1976) indicated he had investigated podophyllin and samples of May-apple because of their use against cancer by practitioners in the United States and by the Penobscot Indians of Maine. Records for such use were found to date back to 1849; additionally, in Louisiana May-apple was used to treat venereal warts or as an "escharotic," dating back to 1845 (Hartwell 1960). Podophyllotoxin and two peltatins were isolated and found to be highly active in Sarcoma 37 (Hartwell & Shear 1947). Hartwell (1976) commented that the development of podophyllotoxin as a potential drug was complicated by toxicity, but also indicated "there is reason to hope that chemical derivatives may be developed which with will eliminate this disadvantage." "Etoposide" and "teniposide" are semi-synthetic derivatives

TABLE 5. Comparison of general and specific folk uses of plants with percentages of active species according to antitumor assay.

Folklore Use	KB	PS	WA	LL	SA
Medicinal Uses in General (Quisumbing 1951)	6.7	8.2	8.5	1.1	3.5
Anthelmintics	11.4	9.5	8.3	2.1	5.6
Fish Poisons	20.7	9.7	8.3	4.1	8.9
Arrow & Homicidal Poisons	30.0	18.6	7.1	1.4	1.4

currently in use as drugs to treat small-cell lung cancers, testicular cancer, carcinoma, and lymphomas (Moraes et al. 2002). Their development, known also as "VM-26" and "VP-213," came from 4'demethylpodophyllotoxin that was found in a Himalayan species, *Podophyllum hexandrum* Royle (Hartwell 1976).

Advocates of promoting folklore as the tool for discovery of biologically active compounds must recognize that there are a large number of widely distributed species that are frequently reported for use in medicines, and have already been chemically investigated. Examples of these, which have shown antitumor activity, are candlenut (*Aleurites molucanna* [L.] Willd.), custard apples (*Annona reticulata* L., *A. squamosa* L.), star fruit (*Averrhoa carambola* L.), cabbage (*Brassica olearacea*), paradise-flower (*Caesalpinia pulcherrima* [L.] Sw.), Indian laurel (*Calophyllum inophyllum* L.), safflower (*Carthamus tinctoris* L.), Madagascar periwinkle (*Catharanthus roseus* [L.] G. Don), coconut (*Cocos nucifera* L.), coffee (*Coffea arabica* L.), taro (*Colocasia esculenta* [L.] Schott), sunflower (*Helianthus annuus* L.), Indian heliotrope (*Heliotropium indicum* L.), beach morning glory (*Ipomoea pes capre* [L.] R. Br.), mango (*Mangifera indica* L.), China-berry (*Melia azedarach* L.), oleander (*Nerium oleander* L.), avocado (*Persea americana* Mill.), peach (*Prunus persica* L.), pomegranate (*Punica granatum* L.), bracken fern (*Pteridium aquilinum* [L.] Kuhn), mangrove (*Rhizophora mangle* L.), castor bean (*Ricinus communis* L.), nightshade (*Solanum nigrum* L.), teak (*Tectona grandis* L. f.), yellow oleander (*Thevetia peruviana* [Pers.] K. Schum.) (Tables 1 and 2 in Spjut 1985; Buckingham 1993–2005; USDA 1980), and most other species in Quisumbing (1951) that were found to be active in the NCI screen (Appendix III).

Uses for many of these active species date back to the early domestication of plants (Zohary & Spiegel-Roy 1975), a time when there was lack of concern for intellectual property rights or ownership that, for the most part, has evolved only since the last decade (Lesser 1997). Hartwell (1960) noted that cancer remedies can be found as early as 1500 B.C. in the Ebers papyrus of Egypt, that "plant remedies for cancer are described in ancient Chinese and Hindu medical writings," that "the record continues unabated through the Graeco-Roman period and the Christian and Arabian-Middle Ages to modern times," and that "the

roster of the hundreds of medical, pharmacological and botanical works recommending herbal treatments for cancer reads like a summary of the great names in the history of medicine." I have further suggested that the various uses for many of the widespread species (e.g., Appendix III) are the result of cultural diffusion; thus, any indigenous ownership claim(s) for a particular use for a particular plant remedy cannot be easily substantiated. Cultural diffusion may also explain many medicinal uses for a species within a relatively narrow geographic area, as evident with plants used by Indian Tribes of Nevada (Train et al. 1957).

Although the occurrence of anticancer activity among plants used as folklore remedies, when compared with that for plants tested at random, suggests that folklore could be a useful tool for predicting sources of anticancer activity, there are also costs that have to be taken into consideration in trying to selectively pursue such plants (Hartwell 1976). A field team can randomly collect as many as 60 (-100) samples in a day from 10–30 species (Perdue & Hartwell 1969), whereas a more selective approach, as I have experienced with recollections of active plants, would yield only 1–2 samples per day. Thus, a random field collection could generate 1–3 new active leads each day, whereas it would require 2–3 days to obtain a similar result in a selective approach. It might be added that this folklore study was based on reports in literature. Obtaining such information directly in the field would cost even more. On the other hand, it is also evident from the data presented in this study that many of the alleged medicinal species would be collected in a random (biodiversity prospecting) screening program—because of their widespread occurrence. Furthermore, a biodiversity (random) type of approach undertaken systematically is not only less expensive, but will also yield novel compounds from plants not reported in folk literature (e.g., camptothecin from *Camptotheca acuminata*, Perdue et al. 1970), and provide a scientific foundation for identifying chemotaxonomic, ecological and other relationships of pharmacological value. Random collections can also include medicinal and/or poisonous plants in the collection strategy, the focus of which might be on genera that are clearly indigenous or endemic to a collection area, and would likely yield novel compounds.

The NCI screen involves more than just identifying leads such as the 2,127 active species reviewed in this study; other steps in drug development include isolating and identifying the active compounds, pharmacological evaluation of the active compounds, and clinical evaluation for treating cancer in three phases (Goldin et al. 1974). Criteria for clinical consideration during the 1970s had included activity in a panel of tumor systems such as the L-1210 Leukemia, KB Cell Culture, P-388 Leukemia, new Lewis Lung tumor, and B16 Melanoma (Goldin et al. 1974; Hartwell 1976). Compounds from only ~1% of the 2,127 active species had reached clinical evaluation—Table 1 in Hartwell (1976). Seventeen of 21 genera in Hartwell (1976, Table 1) were identified as having less of

a taxonomic relationship to each other among the compounds of clinical interest (*Acer, Brucea, Camptotheca, Caesalpinia, Cephaelis, Cephalotaxus, Colchicum, Fagara, Heliotropium, Holacantha, Maytenus, Ochrosia, Stereospermum, Taxus, Thalictrum, Tripterygium, Tylophora*). With exception to *Camptotheca* and *Holacantha*, these genera were found to have species reported in the literature as poisonous. *Holacantha*, a genus of two species, has a very limited distribution in southwestern North America, thus, the lack of medicinal reports for this genus is not unexpected, although a closely related genus, *Castela*, includes species used in folk medicine (Standley 1922–1926). Similarly, *Camptotheca*, a monotypic genus of limited distribution in China, lacks reports on medicinal use except for one general reference on a herbarium specimen "drug plant" *F. A. McClure 6546* at AA (Perdue et al. 1970). Of the remaining genera, all except *Cephalotaxus, Ochrosia, Tripterygium* and *Tylophora* have species reportedly used against cancer or cancer like symptoms (Hartwell 1967–1971).

It might be noted that nearly all active compounds in these plants were discovered from screening in the KB Cell Culture (Hartwell 1976). The correlation between anticancer activity and plant use indicative of toxicity might indicate that future screening of plant extracts could place more emphasis on bioassays that can detect cytotoxicity, such as the KB assay (Perdue 1982; Spjut & Perdue 1976); however, KB activity alone will not lead to development of a new anticancer drug, as evident for plants used as arrow poisons, in which 21% of the active species are strictly KB actives. Many of these plant poisons belong to genera in the Apocynaceae and Asclepiadaceae whose activity is largely due to cardenolides, steroid lactones that have not demonstrated much in vivo activity (Hartwell 1976, Table 15). Poisonous plants in two other families, Cucurbitaceae and Datiscaceae, have yielded only cucurbitacins, triterpenes that are toxic without in vivo activity (Hartwell 1976, Table 10; Cassady & Suffness 1980). Additionally, many other species of poisonous plants are in the Euphorbiaceae in which P-388 Leukemia activity was more frequent, but the compounds were largely phorbol esters (Suffness & Douros 1979). Such compounds are known to be tumor-promoting (Farnsworth et al. 1976), while also inactive in other antitumor assays (Suffness & Douros 1979; Cassady & Suffness 1980); however, one non-tumor promoting phorbol ester was found to have potential for treating AIDS (Gustafson et al. 1992).

Nevertheless, the extent to which plant genera include species reported in folklore to be poisonous, and also used in medicine, especially against cancer, certainly deserve further study. The potential for discovery of novel chemotherapeutic agents would appear greater when geographical evidence indicates similar uses in different cultures as earlier described for *Brucea* and *Maytenus*, while Hartwell (1967–1971) also mentioned that *Heliotropium indicum* and other species of this genus have been reported in folklore for treating cancer in scattered regions of the world. Thus, the relationship between anticancer activity and

folklore appears more meaningful and less coincidental when there is this kind of support from taxonomic and geographic data. Future screening might focus on genera that have yet to show activity. A good example is *Fritillaria*, a genus reportedly rich in alkaloids with highly toxic species that are used for medicinal purposes, including cancer (Steinmetz 1962).

One of the most useful drugs in the chemotherapy of acute childhood leukemia (and other cancers), is vincristine from the periwinkle, *Catharanthus roseus* (L.) G. Don., one of the many widely distributed species used in folk medicine. This discovery resulted not from a search for antitumor activity, but was incidental to a search for compounds with hypoglycemic activity. The plant was under investigation in two different laboratories because of its folk use as a remedy for diabetes (Carter 1976). These facts, and the apparent correlation in this paper between various uses of medicinal plants and antitumor activity, suggest that antitumor activity should be looked upon as just one kind of biological activity that probably correlates well with a broad spectrum of other kinds of biological activity.

There is a growing interest in natural products as food additives and as alternative medicines, partly promoted by an awareness and need for biodegradable natural products to replace synthetic chemical compounds that increasingly contaminate our environment (Jacobson 1989). Where new kinds of biological activity are sought, such screening programs can benefit not only by taking into consideration folkloric uses of plants, but also the massive amount of data generated by the NCI random screen, such as the many novel antitumor agents that have been reported. Therefore, one would hope that the NCI continue screening of natural products. The byproducts of this program are invaluable as many compounds, undoubtedly, will find use in other therapies if they cannot be used to treat cancer. A case in point is recollections of antitumor active plants from which small amounts were funneled to Martin Jacobson at another ARS laboratory in Beltsville, MD who apparently found good insecticidal activity in many of the NCI active plants, e.g., *Arnica chamissonis* Less. ssp. *foliosa* (Nutt.) Maquire (USDA ARS Medicinal Plant Resources correspondence; data recorded for requests of recollections by active species and geographical location; www.worldbotanical.com; see also Jacobson 1989).

Finally, there is one aspect of the folk medicine that cannot be compared with the NCI's random method of searching for potential anticancer drugs. In folk medicine, prescriptions may include a combination of two or more plants, and/or other substances. This is especially common in Chinese medicine (American Herbal Pharmacology Delegation 1975). The separate ingredients of a prescription may not show activity, but one may speculate on whether there is a synergistic effect with combined materials as often seen in drug combination therapies.

APPENDIX I.
ANTITUMOR ACTIVITY IN QUISUMBING (1951) PLANTS ACCORDING TO THERAPEUTIC PROPERTIES

Therapeutic Property	Number of Species Listed	Number of Species Active	% of Species Active	Number of Genera Listed	Number of Genera Active	% of Genera Active
Abortifacient	61	17	27.2	58	63	74.1
Alexipharmic	20	8	40.0	20	16	80.0
Alterative	47	11	23.4	45	27	60.0
Anthelmintic	150	45	30.0	132	88	66.6
Antiarthritic	25	5	20.0	22	16	72.7
Antiasthmatic	83	22	26.5	74	49	66.2
Antibechic	121	22	18.2	99	57	57.6
Antibilious	27	8	29.6	25	14	56.0
Antiblennorrhagic	110	28	25.5	98	53	53.5
Anticatarrhal	36	8	22.2	34	20	58.8
Anticephalagic	96	23	24.0	89	50	56.2
Anticolic	71	18	25.4	69	46	66.6
Antidiabetic	35	8	22.9	31	22	71.0
Antidiarrhoetic	156	39	25.0	136	85	62.5
Antidyspeptic	60	15	25.0	54	34	63.0
Antidysenteric	177	43	24.3	150	86	57.3
Antiherpetic	26	9	34.6	25	13	52.0
Antimalarial	50	13	32.5	37	25	67.6
Antinephritic	23	3	13.0	22	7	31.8
Antineuralgic	22	5	22.7	21	12	57.1
Antiodontalgic	56	15	26.8	51	33	64.7
Antipyrotic	29	5	17.2	29	18	62.1
Antirheumatic	167	40	24.0	140	80	57.1
Antiscabious	77	17	22.1	67	43	64.2
Antiscorbutic	38	10	26.3	35	19	54.3
Antiseptic	42	10	23.8	39	25	64.1
Antispasmodic	49	15	30.6	46	30	65.2
Antisyphilitic	37	10	27.0	34	18	52.9
Antivenomous	50	9	18.0	46	22	47.8
Aperient	40	9	22.5	38	19	50.0
Aperitive	27	7	25.9	25	14	56.0
Aphrodisiac	48	9	18.8	47	27	57.4
Astringent	174	42	24.1	156	94	60.3
Carminative	92	11	12.0	80	44	55.0
Cathartic	27	7	25.9	24	18	75.0
Demulcent	64	11	17.2	59	33	55.9
Depurative	39	10	25.6	36	21	58.3
Diaphoretic	91	21	23.1	85	50	58.8
Digestive	27	8	29.6	25	16	64.0
Diuretic	220	53	24.1	181	107	59.1
Emetic	78	25	32.1	74	52	70.3

APPENDIX I. (CONTINUED)

Therapeutic Property	Number of Species Listed	Number of Species Active	% of Species Active	Number of Genera Listed	Number of Genera Active	% of Genera Active
Emmenagogue	132	34	25.8	119	72	60.5
Emollient	77	22	28.6	69	42	60.9
Expectorant	54	11	20.4	50	32	64.0
Febrifuge	222	53	23.9	191	112	58.6
Galactagogue	26	7	26.9	23	14	60.9
Hemostatic	36	8	22.2	35	19	54.3
Laxative	63	13	20.6	62	36	58.1
Lithotriptic	27	4	14.8	27	15	55.6
Narcotic	24	6	25.0	20	13	65.6
Pectoral	40	14	35.0	39	27	69.2
Poultice	218	41	18.8	178	85	47.8
Purgative	105	27	25.7	85	59	69.4
Refrigerant	53	6	11.3	48	29	60.4
Rubefacient	38	13	34.2	35	24	68.6
Sedative	31	5	16.1	27	13	48.1
Stimulant	108	16	14.8	89	50	56.2
Stomachic	145	34	23.4	125	76	60.8
Tonic	176	32	18.2	155	84	54.2
Tonics (bitter)	34	10	29.4	33	23	69.7
Vesicant	22	5	22.7	19	13	68.4
Vulerary	82	13	15.9	76	35	46.1

APPENDIX II.
ANTICANCER ACTIVITY IN QUISUMBING (1951) PLANTS ACCORDING TO SPECIFIC DISEASES

Medicinal Use	Number of Species Listed	Number of Species Active	% of Species Active	Number of Genera Listed	Number of Genera Active	% of Genera Active
Abscess	22	7	31.8	22	17	77.3
Alopecia	26	5	19.2	26	13	50.0
Amenorrhoea	29	5	17.2	27	18	66.7
Anasarca	57	17	29.8	54	37	68.5
Aphthae	57	17	29.8	54	37	68.5
Bronchitis	39	8	20.5	36	22	61.1
Cholera	29	6	20.7	27	16	59.3
Constipation	30	10	33.3	28	19	67.9
Ears, Affections of	36	8	22.2	32	19	59.4
Eczema	24	10	41.7	22	16	72.7
Eyes, Affections of	40	9	22.5	39	22	56.4
Furuncles	65	16	24.6	63	37	58.7
Gingivitis	19	6	31.6	19	14	73.7

APPENDIX II. (CONTINUED)

Medicinal Use	Number of Species Listed	Number of Species Active	% of Species Active	Number of Genera Listed	Number of Genera Active	% of Genera Active
Hemoptysis	26	3	11.9	26	11	42.3
Hemorrhoids	68	24	35.3	61	44	72.1
Indigestion	20	4	20.0	19	13	68.4
Jaundice	32	10	31.3	31	18	58.1
Leprosy	34	9	26.5	34	18	52.9
Liver Diseases	43	10	23.3	39	21	53.8
Menorrhagia	23	4	17.4	22	17	77.3
Nervous Diseases	50	16	32.0	48	34	70.8
Ophthalmia	21	9	42.9	21	15	71.4
Skin Diseases	123	29	23.6	105	55	52.4
Throat Diseases	57	16	28.1	49	34	69.4
Tinea	37	12	32.4	30	19	63.3
Tuberculosis	47	10	21.3	44	25	56.8
Ulcers	120	26	21.7	113	65	57.5
Wounds	128	26	20.3	111	69	62.2

APPENDIX III.
ANTITUMOR ACTIVE SPECIES IN QUISUMBING (1951) MEDICINAL PLANTS OF THE PHILIPPINES

Species	Tumors KB	PS	WA	LL	SA	CA	Other
Abrus precatorius L.	1	1					
Albizia procera (Roxb.) Benth.			1				
Aleurites molucanna (L.) Willd.		1					
Allamanda cathartica L.	1						
Alstonia scholaris (L.) R. Br.		1					
Amorphophallus paenoiifolius (Dennst.) Nicolson			1				
Anacardium occidentale L.			1				
Anamirta cocculus Wight & Arn.		1					
Anaxagorea luzonensis A. Gray		1					
Annona muricata L.	1						
Annona reticulata L.	1	1					
Annona squamosa L.	1						
Antiaris toxicaria (Rumph. ex Pers.) Lesch.	1	1					
Arcangelisia flava (L.) Merr.		1					
Argemone mexicana L.	1						
Asclepias curassavica L.	1			1			
Averrhoa bilimbi L.		1					
Averrhoa carambola L.			1				

APPENDIX III. (CONTINUED)

Species	Tumors						
	KB	PS	WA	LL	SA	CA	Other
Bacopa monniera (L.) Wettst.	1		1				
Barringtonia asiatica (L.) Kurz					1		
Bauhinia malabarica Roxb.			1				
Boerhavia diffusa L.			1	1			
Brassica olearacea L.			1				
Bryophyllum pinnatum Kurz	1						
Caesalpinia pulcherrima (L.) Sw.			1		1		D1
Calotropis gigantea (L.) Dryander ex Aiton f.	1		1				
Calophyllum inophyllum L.		1			1		
Canna indica L.		1					
Capsicum frutescens L.					1		
Cardiospermum halicababum L.			1				
Carthamus tinctorius L.		1				1	
Cassia alata L.					1		
Cassia occidentalis L.			1				
Cassia siamea Lam.		1					
Casuarina equisetifolia L.	1						
Catharanthus roseus (L.) G. Don		1					
Ceiba pentandra (L.) Gaertner				1	1		
Celastrus paniculata Willd.	1						
Celosia argentea L.			1		1		
Centella asiatica (L.) Urban			1				
Cerbera manghas L.	1						
Cestrum nocturnum L.	1						
Clausena excavate Burm. f.		1					
Clerodenrdon fragans R. Br.			1				
Cocos nucifera L.					1		
Coffea arabica L.			1				
Coix lachryma-jobi		1					
Coleus blumei Benth.		1					
Colocasia esculenta (L.) Schott.			1				
Corchorus olitorius L.	1						
Cordia dichotoma Forst.			1				
Crateva religiosa Forst. f.			1				
Crescentia cujete L. (Roxb.) R. Br. ex Lindley			1				
Cryptostegia grandiflora	1						
Cyperus rotundus L.					1		
Datura metel L.			1				
Derris trifoliate Lour.	1						
Diospyros discolor Willd.		1	1				
Dodonaea viscose (L.) Jacq.					1		
Dregea volubilis (L. f.) Benth. ex Hook. f.			1				
Duranta repens L.		1					

APPENDIX III. (CONTINUED)

Species	Tumors						
	KB	PS	WA	LL	SA	CA	Other
Elephantopus scaber L.			1		1		
Elephantopus mollis Kunth	1	1					
Entada phaseoloides (L.) Merr.			1				
Erythrina variegata L.		1	1				
Erythroxylum coca Lam.		1					
Flagellaria indica L.			1				
Gloriosa superba L.			1				
Grangea maderaspatana Poir.			1				
Graptophyllum pictum Griff.			1				
Hedychium coronarium Koenig.		1					
Helianthus annuus L.		1					
Hernandia ovigera L.	1						
Homonoia riparia Lour.			1				
Hyptis suaveolens (L.) Poit.	1	1					
Ipomoea pes-capre L.		1	1				
Ixora coccinea L.		1					
Jatropha curcas L.		1					
Jatropha gossypifolia L.		1			1		
Jussiaea erecta L.	1						
Justicia procumbens L.		1					
Kalanchoe laciniata (L.) DC.	1						
Lagerstroemia indica L.					1		
Lansium domesticum Correa			1				
Lantana camara L.			1				
Leucaena glauca L.		1					
Lonicera japonicum Thunb.					1		
Lunasia amara Blanco	1						
Mallotus philippensis (Lam.) Muell.-Arg.					1		
Mangifera indica L.					1		
Manilkara zapota (L.) D. Royle	1						
Melia azederach L.	1		1	1			
Melia dubia Cav.	1						
Merremia umbellata (L.) Hall. f.		1					
Mimusops elengi L.			1				
Mirabilis jalapa L.			1	1	1		
Morus nigra L.			1				
Muntingia calabina L.	1						
Nerium indicum Mill.	1		1		1	1	
Nopalea cochinellifera (L.) Salm-Dyck		1					
Oldenlandia corymbosa L.					1		
Paspalum scrobiculatum L.		1					
Passiflora foetida L.		1					
Pedilanthus tithymaloides (L.) Poit.	1						

APPENDIX III. (CONTINUED)

Species	Tumors KB	PS	WA	LL	SA	CA	Other
Persea americana Mill.		1					
Phragmites australis (Cav.) Trin. ex Steudel			1				
Physalis peruviana L.	1	1					
Pilea microphylla (L.) Liebm.		1					
Piper umbellatum L.	1						
Pithecellobium saman (Jacq.) Benth.		1					
Punica granatum L.	1						
Quassia amara L.	1	1					
Quisqualis indica L.			1				
Rhinacanthus nasutus Kurz	1						
Ricinus communis L.	1	1	1				
Rubia cordifolia L.			1				
Securinega virosa (Roxb. ex Willd.) Baillon			1				
Semecarpus cuneiformis Blanco	1		1	1			LE
Senecio scandens Buch. Ham.		1					
Setaria palmifolia (Koenig) Stapf		1					
Sida cordifolia L.		1					
Solanum nigrum L.			1	1	1		
Solanum verbascifolium L.					1		
Sonneratia acida L. f.			1				
Sphaeranthus africanus L.	1						
Streblus asper Lour.	1	1	1				
Tabernaemontana pandacaqui Lam.		1					
Tamarindus indicus L.			1				
Tectona grandis L.		1					
Tephrosia purpurea (L.) Pers.			1				
Terminalia catappa L.	1						
Theobroma cacao L.					1	1	
Thevetia peruviana (Pers.) Schumann	1	1					
Toddalia asiatica (L.) Lam.	1						
Toona calantas Merr. & Rolfe	1						
Trema orientalis (L.) Blume			1				
Trianthema portulacastrum L.			1				
Vernonia cinerea (L.) Less.			1				
Voacanga globosa (Blanco) Merr.		1					
Waltheria americana L.		1					
Total # Active: 140	42	51	53	7	22	3	
Screened: 626							
Percent Active: 22.4%	**6.71%**	**8.15%**	**8.47%**	**1.12%**	**3.51%**	**0.48%**	

APPENDIX IV.
PLANTS USED AS ANTHELMINTICS THAT HAVE SHOWN ANTITUMOR ACTIVITY

Species	Tumors						
	KB	PS	WA	LL	SA	CA	Other
Abrus precatorius L.	1	1					
Acacia sieberiana DC.		1					
Acokanthera oblongifolia (Hochst.) L. E. Codd	1						
Acokanthera oppositifolia (Lam.) L. E. Codd	1						
Afrormosia latiflora (Benth. Ex Baker) Harms		1					
Agrostemma githago L.			1				
Ailanthus altissima (Mill.) Swingle	1						
Alangium salviifolium (L. f.) Wangerin	1	1				1	
Aleurites molucanna (L.) Willd.		1					
Alstonia scholaris (L.) R. Br.		1					
Ambrosia artemisiifolia L.	1						
Anacardium occidentale L.			1				
Annona glabra L.	1						
Annona muricata L.	1						
Annona reticulata L.	1	1					
Annona senegalensis Pers.	1						
Annona squamosa L.	1						
Apocynum androsaemifolium L.	1						
Apocynum cannabinum L.	1		1				
Apodytes dimidiata R. Meyer ex Arn.		1					
Arcangelisia flava (L.) Merr.		1					
Aristolochia indica L.						1	
Argemone mexicana L.	1						
Asclepias curassavica L.	1			1			
Averrhoa carambola L.			1				
Azadirachta indica A. Juss.	1						
Barringtonia asiatica (L.) Kurz					1		
Bauhinia variegate L.			1				
Bersama abyssinica Fresen.	1	1	1	1			
Bocconia arborea S. Wats.	1						
Boerhavia diffusa L.			1	1			
Brassica olearacea L.			1				
Bridelia micrantha	1	1	1				
Brucea antidysenterica (Hochst.) Baillon	1	1					
Brucea javanica (L.) Merr.		1					
Calocarpum sapota (Jacq.) Merr.	1						

APPENDIX IV. (CONTINUED)

Species	Tumors						
	KB	PS	WA	LL	SA	CA	Other
Calophyllum inophyllum L.		1			1		
Calotropis gigantean (L.) Dryander ex Aiton f.	1	1					
Calotropis procera (Aiton) Dryander ex Aiton f.	1						
Canavalia cathartica Thouars		1					
Capparis deciduas (Florsk.) Edgew.			1				
Carissa edulis Vahl		1					
Cassia alata L.					1		
Cassia auriculata L.	1						
Cassia occidentalis L.			1				
Catharanthus roseus (L.) G. Don		1					
Celosia argentea L.			1		1		
Citrullus lanatus (Thunb.) Masf.	1						
Clausena anisata (Willd.) Hook. f. ex Benth.		1					
Clausena excavata Burm. f.		1					
Clerodendrum indicum (L.) O. Kuntze					1		
Clerodendrum phlomoides L. f.			1				
Cocos nucifera L.					1		
Coix lachryma-jobi L.		1					
Cordia dichotoma Forst.			1				
Cornus florida L.					1		
Croton macrostachyus Hutch. ex Del.		1		1	1		
Croton megalocarpus Hutch.		1					
Cyperus rotundus L.					1		
Cryptostegia grandiflora (Roxb.) R. Br. ex Lindley	1						
Cypripedium calceolus L.					1		
Datura metel L.			1				
Dichroa febrifuga Lour.	1						
Dicranopteris linearis (Burm. f.) Underw.			1				
Dodonaea viscosa Jacq.					1		
Dryopteris filix-mas (L.) Schott					1		
Ekebergia capensis Sparrm.	1						
Elephantopus scaber L.			1		1		
Embilia schimperi Vatke					1		
Entada phaseoloides (L.) Merr.			1				
Erythrina variegata L.		1	1				
Erythrophleum suaveolens (Guill. & Perr.) Brenan	1						

APPENDIX IV. (CONTINUED)

Species	Tumors						
	KB	PS	WA	LL	SA	CA	Other
Ficus sterrocarpa Diels			1				
Gloriosa superba L.			1				
Helenium autumnale L.	1	1					
Helenium hoopesii A. Gray			1				
Hippomane mancinella		1					
Holarrhena pubescens (Buch.-Ham.) Wall.	1	1					
Jatropha curcas L.		1					
Juglans nigra L.					1		
Juniperus communis L.	1	1					
Jussiaea suffruticosa L.	1						
Lansium domesticum Correa			1				
Liriodendron tulipifera L.	1						
Luffa echinata Roxb.			1				
Maesa lanceolata Forsk.	1			1			
Mallotus philippensis (Lam.) Muell.-Arg.					1		
Mangifera indica L.					1		
Maprounea africana Muell.-Arg.		1					
Maytenus senegalensis (Lam.) Exell	1	1					
Melia azederach L.	1		1	1			
Melia dubia Cav.	1						
Morus nigra L.			1				
Myrica cerifera L.			1				
Myrsine africana L.					1		
Nauclea latifolia Sm.		1					
Nicotiana glauca Grah.	1						
Pergularia daemia (Forsk.) Chiov.	1	1					
Persea americana L.		1					
Physalis peruviana L.	1	1					
Phytolacca americana L.			1				
Pilostigma thonningii (Schumach.) Milne-Redh.	1				1		
Pinus palustris Mill.			1		1		
Pinus taeda L.					1		
Piper umbellatum L.	1						
Plectranthus blumei (Bent.) Launert		1					
Plumeria rubra L.		1					
Podophyllum peltatum L.	1						
Prunus persica (L.) Batsch.			1				FV
Prunus virginiana L.		1					
Pteridium aquilinum (L.) Kuhn.					1		

APPENDIX IV. (CONTINUED)

Species	Tumors						
	KB	PS	WA	LL	SA	CA	Other
Punica granatum L.	1						
Quassia amara L.	1	1					
Quisqualis indica L.			1				
Rapanea pulchra Gilg & Schellenb.		1	1				
Rhizophora mangle L.					1		
Rhus typhina L.	1			1			
Salvia officinalis L.					1		
Securidaca longipedunculata Fresen.		1					
Semecarpus anacardium L.	1		1	1			LE
Solanum nigrum L.			1	1	1		
Sphaeranthus africanus L.	1						
Sphaeranthus indicus L.			1				
Strychnos henningsii Gilg		1					
Tagetes minuta L.				1			
Tamarindus indicus L.					1		
Tanacetum vulgare L.	1	1					
Tectona grandis L.		1					
Tephrosia purpurea (L.) Pers.			1				
Tephrosia vogelii Hook. f.	1						
Terminalia cattapa L.	1						
Thuja occidentalis L.	1						
Toddalia asiatica (L.) Lam.	1						
Trema orientalis (L.) Blume			1				
Trichilia emetica Vahl	1						
Typha domingensis Pers.		1					
Urtica dioica L.					1		
Vernonia amygdalina Del.			1				
Vernonia cinerea (L.) Less.			1				
Vernonia colorata (Willd.) Drake		1					
Ximenia caffra Sond.		1					
Total # Active: 141 Screened: 482	55	46	40	10	27	2	
Percent Active: 29.3%	**11.41%**	**9.54%**	**8.30%**	**2.07%**	**5.60%**	**0.41%**	

APPENDIX V.
ANTITUMOR ACTIVE PLANTS USED AS FISH POISONS

Species	Tumors						
	KB	PS	WA	LL	SA	CA	Other
Acacia albida Del.			1				
Acacia melanoxylon R. Br.	1				1		
Acacia pulchella R. Br.			1				
Acokanthera oppositifolia (Lam.) L.E. Codd	1						
Adenium obesum Balf. f.	1						
Aegiceras corniculatum (L.) Blanco			1				
Aesculus californica (Spach) Nutt.					1		
Agave americana L.	1			1	1		MS
Albizia procera (Roxb.) Benth.	1		1				
Anagallis arvensis L.					1		
Anamirta cocculus Wight. & Arn.		1					
Annona muricata L.	1						
Annona squamosa L.	1						
Asclepias curassavica	1			1			
Barringtonia asiatica (L.) Kurz					1		
Caesalpinia pulcherrima (L.) Sw.			1		1		D1
Calophyllum inophyllum L.		1			1		
Cassia alata L.					1		
Cerbera manghas L.	1						
Chlorogalum pomeridianum (DC.) Kunth.			1				
Cleistanthus collinus Benth.	1						
Croton sylvaticus L.	1	1					
Cucumis ficifolius A. Rich.	1						
Datisca glomerata (Presl.) Baillon	1						
Datura metel L.			1				
Derris trifoliata Lour.	1						
Diospyros maritima Blume		1					
Dodonaea viscosa Jacq.					1		
Eremocarpus setigerus (Hook.) Benth.		1					
Euphorbia esula L.		1			1		
Euphorbia hyberna L.				1			
Fagara macrophylla (Oliv.) Engl.	1						
Fluggea leucopyrus Willd.			1				
Gnidia kraussiana Meisn.		1					
Helenium autumnale L.	1	1					
Jatropha curcas L.		1					
Leucaena leucocephala (Lam.) Dewit.	1		1	1			

APPENDIX V. (CONTINUED)

Species	Tumors						
	KB	PS	WA	LL	SA	CA	Other
Lonchocarpus urucu Killip & Smith	1						
Mallotus philippensis (Lam.) Muell.-Arg.					1		
Melia azederach L.	1		1	1			
Millettia ferruginea (Hochst.) Bak.	1						
Mundulea sericea (Willd.) A. Chev.	1						
Pergularia daemia (Forsk.) Chiov.	1	1					
Persea americana Mill.		1					
Phyllanthus brasiliensis Muell.-Arg.		1					
Piscidia erythrina L.	1						
Pleiogynium solandri Engl.	1						
Sapindus saponaria L.	1						
Stephania abyssinica (Dillon & A. Rich.) Walp.	1			1			
Taxus baccata L.	1						
Tephrosia candida DC.	1						
Tephrosia purpurea (L.) Pers.			1				
Tephrosia vogelii Hook. f.	1						
Thevetia peruviana (Pers.) Schum.	1	1					
Verbascum phlomoides L.			1		1		
Voacanga globosa (Blanco) Merr.		1					
Total: 56 Active Species Screened: 145	30	14	12	6	12	0	2
Percent active: 38.6%	**20.69%**	**9.66%**	**8.28%**	**4.14%**	**8.28%**	**0.00%**	**1.38%**

APPENDIX VI.
ANTITUMOR ACTIVE PLANTS USED AS ARROW, HOMICIDAL, AND/OR ORDEAL POISONS

Species	Tumors						
	KB	PS	WA	LL	SA	CA	Other
Abrus precatorius L.	1	1					
Acokanthera longifolia Stapf	1	1					
Acokanthera oblongifolia (Hochst.) L.E. Codd	1						
Acokanthera oppositifolia (Lam.) L.E. Codd	1						
Acokanthera schimperi (A. DC.) Schweinf.	1						
Adenium obesum Balf. f.	1						
Amorphophallus campanulatus (Dennst.) Nicolson			1				
Antiaris toxicaria (Rumph. ex Pers.) Lesch.	1						
Boophone disticha Herb.		1					
Calophyllum inophyllum L		1			1		
Calotropis procera (Aiton) Dryander ex Aiton f.	1						
Canthium comprosoides F. Muell.			1	1			
Cassine crocea (Thunb.) Kuntze	1	1					
Cerbera mangas L.	1						
Cheiranthus cheri L.		1					
Derris trifoliata Lour.	1	1					
Erythrophleum africanum (Benth.) Harms	1		1				
Euphorbia candelabrum Tremaut ex Kotschy	1	1					
Fagara macrophylla (Oliv.) Engl.	1						
Gloriosa superba L.			1				
Hippomane mancinella L.		1					
Jatropha curcas L.		1					
Lansium domesticum Correa			1				
Lophopetalum javanicum (Thunb.) Kuntze		1					
Lunasia amara Blanco	1						
Parkia filicoidea Welw. ex Oliv.	1						
Rauvolfia mombasiana Stapf	1						
Securidaca longipenduculata Fresen.		1					
Strophanthus courmontii Franch.	1						
Strophanthus hispidus DC.	1						
Tephrosia vogelii Hook. f.	1						
Thevetia peruviana (Pers.)Schum.	1	1					
Total: 32 Active Species Screened: 70	21	13	5	1	1		
Percent active: 45.7%	**30.00%**		**18.57%**		**7.14%**	**1.43%**	**1.43%**

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