An Analysis of Cytotoxic Botanical Formulations Used in the Traditional Medicine of Ancient Persia as Abortifacients †

ARTICLE *in* JOURNAL OF NATURAL PRODUCTS · SEPTEMBER 2004

Impact Factor: 3.8 · DOI: 10.1021/np049953r · Source: PubMed

Reviews

An Analysis of Cytotoxic Botanical Formulations Used in the Traditional Medicine of Ancient Persia as Abortifacients†

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Received January 23, 2004

We report here an analysis of plants used by traditional healers of ancient Persia to induce abortions. Six herbal formulations that contain 39 different species from 21 plant families with their vernacular names, English names, amounts used, and their methods of preparation are reported. Our initial objective of this ethnobotanical analysis was to evaluate the validity and the efficacy of the plants used by (1) comparing other reported uses of these plants in traditional medicine, (2) investigating the medical and pharmacological literature on the medicinal properties of the plant species used, and (3) investigating the reported cytotoxic effects of compounds prevalent in these plants. Previous phytochemical analyses have shown that a number of plant species are rich in coumarin compounds that have potential antineoplastic or cytotoxic activities. Our results indicate a correlation between the reported use of these plants as abortifacients and their cytotoxic (antineoplastic) effects. In addition, we discuss the process in which this ethnobotanical investigation led to the discovery of dicoumarol (a coumarin anticoagulant) as a potential chemotherapeutic agent.

1. Introduction

From the beginning of civilization, man has experimented with higher plants in an attempt to find remedies against various illnesses and diseases. Through trial and error, early mankind has found medicinal properties in the seeds, barks, and roots of certain plants. Until the early 20th century, the main source of medicines consisted of drug preparations obtained primarily from terrestrial plant and vegetable sources. Natural products, as crude plant extracts, have been used for thousands of years, and many of these ancient formulations have been recorded in ancient literature.[1] There is over 4000 years of recorded history of botanical medicines from China, the Middle East, South America, Europe, and Mexico. The first available records, dated from about 2600 B.C., were found from Mesopotamian clay tablets (from modern day Iraq, Iran, and part of Syria) written in cuneiform that contained approximately 1000 different plant-derived formulations. These include oils of cedar, poppy juice, myrrh, juniper, mandrake, saffron, and licorice, all of which are still used today for the treatment of various ailments.[2,3]

The use of plants in Egyptian, Asian, Indian, African, and south-central American traditional medicine has been extensively documented in Western scientific literature;[4] however, there have been very few documents written on the study of Persian medicinal plants or research into the scientific validation of ancient Persian medicinal formulations. There exist many privately held documents and books written on the subject of traditional Persian botanical medicines, representing the long history of botanical medicine in Iran. However, only a few of these works have been published or translated. Written medicinal history of ancient Persia is usually traced to Abu Ali Al-Hussain ibn Abdullah Ebn-e Sina (known in the West as Avicenna) (980−1037 A.D.). The Persian pharmacist, physician, philosopher, and poet contributed greatly to the sciences of pharmacy and medicine through *Canon Medicinae*. Avicenna's work, which is regarded as a doctrine of all Greco-Roman medicine, accumulated the existing medical information of his time in addition to incorporating his own scientific knowledge and rationalizations regarding medicinal plants and drugs.[5] It was the *Canon* that provoked Latin scholars to call him the "Prince of Physicians", and this work was among the central texts in all the European Universities from the 13th to the 18th centuries.[6,7] The *Canon* is believed to have had a great influence in the development of modern medicine; for many years, it served as the most complete discourse on medical plants and herbs containing medicinal formulations from Greek, Arabian, Indian, and Persian cultures.

The period of Avicenna influence (9th to 13th century) was considered the golden age of Islamic medicine. Persian medicine not only combined and accumulated knowledge of the different medical traditions of Chinese, Indian, Egyptian, and Greek cultures[8] but also introduced new botanical formulations and knowledge to various other cultures. For example, during the Song dynasty (960−1129 A.D.), Islamic traders introduced foreign drugs to the Chinese, making important contributions to Chinese medicine, and with the Mongolian invasion of Europe, Islamic influences traveled as far west as Spain. Ancient Iranian medicine became the foundation of medical practice in 13th century Europe and eventually became the most significant and advanced medicine in the medieval world.[8,9]

Although ancient Persian medicine had a significant impact on the development of medicine, it lacks the attention of modern Western scientific literature and research. Instead, the traditional medicinal therapy of

† Dedicated to the late Dr. D. John Faulkner (Scripps) and the late Dr. Paul J. Scheuer (Hawaii) for their pioneering work on bioactive marine natural products.

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10.1021/np049953r CCC: $27.50
Published on Web 05/18/2004

China, India, South America, and Africa is increasingly a focus of attention as potential sources of new plant-derived drugs. For example, the compositions and efficacy of various Chinese herbs and plants have recently attracted much attention by Western science and have been subjected to modern methods of experimentation and screening assays.[10] In contrast, only few published reports or written texts[11−14] about Iranian medicinal plants are available in Western or Iranian literature. Furthermore, the majority of the medicinal plants from Iran have not been studied chemically or pharmacologically in detail.

It is evident that ethnomedical analysis substantially increases the probability of finding bioactive plants relative to a random extract screening approach.[15,16] Ethnobotanical investigations can also provide a basis for discovering novel structures or formulations with therapeutic benefit.[16,17] The advantage of the ethnopharmacological information is that the extensive published literature may allow for some rationalization with respect to the biological potential or efficacy of a reputed use.[16] The present study was undertaken to evaluate the pertinence of the cytotoxic activity of the botanicals in previously undocumented Persian traditional medicines used to induce abortions. We report our findings here, including the rationale for a hypothesis that led to the discovery of a compound with a unique mechanism of action that came as a direct result from this literature investigation.

2. Methodology

Six ancient medicinal formulations representing combinations of 39 different species from 21 plant families used to induce abortions in ancient Persia (ca. 1000 A.D.) were obtained from Seyedeh Nasrin Sohrab's personal archives of ancient Persian literature maintained in Tehran, Iran. This literature was an ancient unpublished pharmacopoeia written in Farsi. It detailed the nomenclature of the plants used in formulating the extracts and the quantities used. We have carried out an extensive literature analysis into the chemical components and biological activities of the plant species since 1997. An extensive literature analysis, including library and computer-based searches, into the chemical components and biological activities of the various plant species has been undertaken by us since 1997. Reported uses of the plant extracts were compared to published literature of traditional uses of plants from ancient cultures. A combination of ethnopharmacology and phytochemical data was used to establish correlations between reported activity and chemical composition and medical use.

Analysis of variance (ANOVA) was employed to test the statistical significance of the differences among the presence of coumarins from six different herbal formulations. Using the central limit theorem, we calculated two estimates of a population variance: (1) an estimate in which the square of the obtained means of the several samples is multiplied by n (the size of the samples); (2) an estimate that is calculated as the average (mean) of the obtained squares of the several samples. The statistic (F) is formed as the ratio of (1) over (2). If this ratio is sufficiently greater than 1, the observed differences among the obtained means are described as being statistically different, whereas values less than 1 are not significantly different.

3. Results and Discussion

The herbal mixtures from 39 plant species are presented in Table 1. The plant composition for the six formulations investigated are listed in alphabetical order of their scientific names in italics, followed by the local name used (Farsi), English name, plant family, amount used, and prescription for each remedy.

3.1. Persian Botanicals as Abortifacients. 3.1.1. Traditional Uses. Twenty-four of the 39 plant species appearing in the Persian literature were also found in traditional medicines of other cultures for use as abortifacients and emmenagoges. Emmenagogues are defined as remedies that induce menstruation, which, in appropriate doses, are known to act as abortifacients. These same plant uses were found in *Aloe vera, Anthemis tinctoria, Apium graveolens, Aquilegia vulgaris, Artemisia absinthium, Cinnamomum camphora, Citrullus colocynthis, Commiphora myrrha, Coriandrum sativum, Costus speciosus, Crocus sativus, Cucumis melo, Ferula assa-foetida, Juniperus sabina, Lactuca sativa, Marrubium vulgare, Mentha pulegium, Paeonia officinalis, Phaseolus vulgaris, Pimpinella anisum, Punica granatum, Rubia tinctorum, Ruta graveolens*, and *Santolina chamaecyparissus*.[18−21] The most widely used plant species by various cultures were rue (*Ruta graveolens*), savin oil (*Juniperus sabina*), pennyroyal (*Mentha pulegium*), and *Ferula assafoetida*. Interestingly, *Ferula* species were ingested by ancient Greek women, apparently to limit births, and are currently used as an abortifacient by practitioners of folk medicine in central Asia.[3] In many cases abortion was believed to be a secondary effect of the woman poisoning her body with large quantities of toxic plants.

3.1.2. Experimental Toxicology. Nine plants have been experimentally studied and demonstrate abortifacient or antifertility activity. These include *Apium graveolens* (extracts were found effective in causing contraction of the gravid and virginal uterus),[22] *Crocus sativus* (various extracts stimulated uteri of guinea pigs, rabbits, and dogs),[23] *Coriandrum sativum* (aqueous extracts of seeds at doses of 250−500 mg/kg produced a dose-dependent significant anti-implantation effect),[24] *Foeniculum vulgare* (a drug preparation containing fine powders of the plant seed administered orally at 500 mg/kg to rats inhibited implantation in 60% of pregnant rats and increased the percentage of fetal loss),[25] *Juniperus sabina* (tops of *J. sabina*, when taken orally in large doses, produced abortions followed by serious poisoning; analysis of an aborted fetus showed the presence of oil of sabine in the viscera of the fetus, which proves the permeability of the placenta to the poison;[26] in addition, when the essential oil was evaluated for its fetotoxic potential on mice, the oil induced an embryotoxic effect;[27] the abortifacient effect of *J. sabina* essential oil has been attributed to an implantation-inhibiting effect induced by sabinyl acetate),[28] *Paeonia officinalis* (a crude alcohol extract of the root produced uterine stimulation in the rat),[29] *Phaseolus vulgaris* (3 phytohemagglutinins isolated from *P. vulgaris* induced abortion in all pregnant mice tested in early pregnancy),[30] *Punica granatum* (methanolic extracts prevented implantation in 50% of rats[33] and inhibited pregnancy in 70−90% of rats),[32] and *Ruta graveolens* (ethanolic and benzene extracts inhibited pregnancy in 50−60% of rats).[32]

3.2. Persian Botanicals Used for the Treatment of Cancer. 3.2.1. Traditional Uses. An interesting observation made during the course of this investigation was that the majority of plant species used as abortifacients were also present in traditional medicines of other cultures for the treatment of cancer. These include *Aloe vera, Apium graveolens, Aquilegia vulgaris, Artemisia absinthium, Cinnamomum camphora, Citrullus colocynthis, Crocus sativus, Cucumis melo, Ferula assa-foetida, Foeniculum vulgare, Hyacinthus orientalis, Lactuca sativa, Mentha pulegium*,

Table 1. Six Abortifacient Botanical Formulations Obtained from Personal Archives in Iran

Species Name	Persian Name	Vernacular Name	Plant Family	Grams
1. *Aloe vera*	Sabrezard	Aloe vera	Aloeaceae	0.05
Artemisia absinthium	Afsetin	Absinthe	Asteraceae	0.1
Crocus sativus	Zafaran	Saffron	Iridaceae	0.1
Juniperus sabina	Abhal	Savine	Cupressaceae	0.05
Ruta graveolens	Sadab	Rue	Rutaceae	0.05

*** The above ingredients are made into a pill. The patient takes 2-4 pills daily for 4-5 days.**

2. *Cinnamomum camphora*	Kafour	Camphor	Lauraceae	2
Commiphora myrrha	Marmaky	Myrrh	Burseraceae	10
Coriandrum sativum	Gheshniz	Coriander	Apiaceae	15
Lactuca sativa	Kahu	Lettuce seed	Asteraceae	50
Portulaca oleracea	Khorfeh	Purslane seed	Portulacaceae	50
Punica granatum	Anar	Pomegranate	Punicaceae	7
Rosa damascena	Gole sorkh	Damask rose	Rosaceae	7

*** The ingredients are made into a 10 gram pill. The patient is directed to ingest the pill with pomegranate juice**

3. *Commiphora myrrha*	Marmaky	Myrrh	Burseraceae	10
Costus speciosus	Ghest	Costus	Costaceae	7
Ferula assa-foetida	Angozeh	Asafoetida	Apiaceae	7
Ferula communis	Sak Bineh	Giant fennel	Apiaceae	7
Hyacinthus orientalis	Sonbol	Hyacinth	Hyacinthaceae	7
Lupinus termis	Baghela Mesri	Lupine	Fabacea	15
Mentha pulegium	Poneh	Pennyroyal	Lamiaceae	7
Origanum dictamnus	Poneh Vahshi	Marjoram	Lamiaceae	7
Rubia tinctorum	Ronas	Dyers madder	Rubiaceae	7
Ruta graveolens	Sadab	Common rue	Rutaceae	7

*** The ingredients are made into a powder and mixed with sowab juice to make a 5 gram pill**

4.Andropogon schoenanthus	Azhkar		Ranunculaceae	10
Anthemis tinctoria	Aghergharha	Yellow chamomile	Asteraceae	10
Apium graveolens	Karafs	Celery seed	Apiaceae	12
Aquilegia vulgaris	Ood	Columbine	Ranunculaceae	10
Costus speciosus	Ghest	Wild ginger	Costaceae	10
Foeniculum vulgare	Razianeh	Sweet fennel	Apiaceae	12
Marrubium vulgare	Frasion Abyaz	Horehound	Lamiaceae	15
Mentha pulegium	Poneh	Pennyroyal	Lamiaceae	12
Paeonia officinalis	Ood	Common peony	Paeoniaceae	10
Phaseolus vulgaris	Lobia sorkh	Kidney bean	Fabacea	30
Pimpinella anisum	Anison	Anise	Apiaceae	10
Origanum dictamnus	Poneh Vahshi	Marjoram	Lamiaceae	15
Rubia tinctorum	Ronas	Madder	Rubiaceae	20
Ruta graveolens	Sadab	Common rue	Rutaceae	12
Santolina chamaecyparissus	Gheisum	Lavender cotton	Asteraceae	15
Teucrium chamaedrys	Komaderios	Wall germander	Lamiaceae	10
Teucrium polium	Goehdeh	Golden germander	Lamiaceae	12
Trachyspermum copticum	Zinyan	Ajowan	Apiaceae	10

*** The ingredients are mixed in 2 L of water. The patient is directed to drink 250 ml.**

5. *Apium graveolens*	Karafs	Celery seed	Apiaceae	10
Artemisia absinthium	Afsentin	Absinthe	Asteraceae	15
Cucumis melo		Melon seed	Cucurbitaceae	10
Foeniculum vulgare	Razianeh	Fennel seed	Apiaceae	10
Juniperus sabina	Abhal	Savin	Cupressaceae	5
Pimpinella anisum	Anison	Aniseed	Apiaceae	10
Origanum dictamnus	Poneh Kohi	Marjoram	Lamiaceae	7
Pastinaca sativa	Havigh Sahra	Wild parsnip seed	Apiaceae	10
Ruta graveolens	Sadab	Common rue	Rutaceae	5
Valeriana officinalis	Sonbolotib	Garden valerian	Valerianaceae	7

*** The seeds are smashed, placed in a bottle of water and stored in a high temperature room for 3 days. On day 4, the rest of the ingredients are added and given to the patient.**

6. *Apium graveolens*	Karafs	Celery seed	Apiaceae	NQ
Citrullus colocynthis	Hanzal	Colocynth	Cucurbitaceae	NQ
Physalis alkekengi	Kakoneh	Strawberry groundcherry	Solancaceae	NQ
Ziziphora teniur	Kakoti		Lamiaceae	NQ

The ingredients (not quantified; NQ) are boiled in a teapot.
The patient is directed to drink one soupspoon before each meal.

Table 2. Botanicals in Persian Traditional Medicine with Cytotoxic or Antineoplastic Activity

species name	reference(s)
Apium graveolens	33, 42
Citrullus colocynthis	43, 46, 119−120
Coriandrum sativum	34
Costus speciosus	49
Crocus sativus	51−54, 121−123
Cucumis melo	47
Foeniculum vulgare	35−36
Juniperus sabina	37, 114, 124
Origanum vulgare	125
Mentha pulegium	39
Pastinaca sativa	55
Phaseolus vulgaris	126
Physalis alkekengi	40
Punica granatum	35, 57
Ruta graveolens	41
Valeriana officinalis	127

Paeonia officinalis, Pastinaca sativa, Phaseolus vulgaris, Pimpinella anisum, Portulaca oleracea, Punica granatum, Rosa damascena, and *Ruta graveolens.*[18−21] This use is not unexpected since many contemporary pharmacological and toxicological studies have shown antineoplastic compounds are usually contraindicated in pregnant women because of cytotoxicity on fetal growth.

3.2.2. Experimental Pharmacology. Consistent with these findings, we determined that 16 of the 21 plants used traditionally for the treatment of cancer inhibit cell proliferation or mitigate tumor growth (Table 2). Water and lipid extracts of many of these plants have been experimentally studied and their cytotoxic activity demonstrated, including *Apium graveolens*. A hydrocarbon fraction was found active against A-549 lung carcinoma, MCF-7 breast carcinoma, and HT-29 colon adenocarcinoma (ED_{50} < 20−2 μg/mL).[33] *Coriandrum sativum* seed extracts have a protective role against the deleterious effects of lipid metabolism in 1,2-dimethylhydraxin (DMH)-induced colon carcinogenesis in rat.[34] Acetone extracts from *Foeniculum vulgare* have cytotoxic activity against murine leukemic (P88 and L1210) and human colon cancer cells in vitro (HRT-18, HT-29, and HCT-48).[35] In addition, aqueous extracts inhibited mouse L5178Y leukemia cells.[36] The hydro-alcoholic extracts of branches of *Juniperus sabina* showed inhibitory activities against MDA-MB-468.[37] *Punica granatum* seed oil effected 90% inhibition of proliferation of MCF-7 at 100 μg/mL. In addition, both aqueous and lipid fractions of fruits exerted multiple in vitro suppressive effects on human breast cancer cells.[38] Hot water extracts of pennyroyal (*Mentha pulegium*) at >2 μg/mL inhibited topoisomerase 1.[39] Aqueous extracts of *Physalis alkekengi* fruits were shown to have reproducible antineoplastic activity against Ehlich ascites carcinoma in mice.[40] Lipid extracts of *Ruta graveolens* showed significant cytotoxic effects in Yoshida ascites sarcoma cells.[41]

The antineoplastic activities of certain plant extracts have been and can be attributed to a specific compound or class of compounds within the extract. Natural phthalides from celery seed (*Apium graveolens*) oil were active in tumor inhibition of benzo[*a*] pyrene-induced forestomach cancer in mice.[42] Fractions of the *Citrullus colocynthis* fruits demonstrated antineoplastic action on sarcoma-37.[43] This plant extract contains three antitumor ingredients: cucurbitacins B and E and the D-glucoside of beta-sitosterol.[44] Cucurbitacins B, D, E, and I are inhibitory to the growth of human colon, breast, lung, and central nervous system cancer cell lines with an IC_{50} < 0.4 μM.[45] In addition, cucurbitacin E has been identified with potent growth inhibitory activity in vitro against prostate carcinoma explants (IC_{50}, 7−50 nm). The compound caused marked disruption of the actin cytoskeleton, and the antiproliferative activity correlated directly with the disruption of the F-actin cytoskeleton.[46] Actin and actin-binding proteins have been implicated as critical intermediates in signal transduction pathways controlling cell division. The cucubitacins also disrupt the formation of the actin-derived contractile ring important for separation of cells during mitosis. Cucurbitacins A, B, C, D, and L were also isolated from the petroleum ether extracts of the dried rind of *Cucumis melo* fruits.[47]

Curcumin, extracted and isolated from rhizomes of *Costus speciousus*,[48] was found to inhibit the activation of nuclear factor κB (NF-κB), a transcription factor[49] that plays an essential role in several processes including inflammation, apoptosis, and cellular proliferation.[50] NFκ-B controls the transcription of genes that confer resistance to death-inducing signals.

A growing body of research has demonstrated that *Crocus sativus* (saffron) extract and its main constituents, the carotenoids, possess chemopreventative properties against cancer. Saffron obtained from the dried stigmas of the plant delayed ascites tumor growth and increased the life span of treated mice by 45−120% as compared to untreated controls.[51] The glycoconjugate extracts demonstrated cytotoxic activity against HeLa cells,[52] and long-term treatment with crocin, a glycosylated carotenoid from stigmas, enhanced survival in female rats with colon cancer without major toxic effects.[53] In addition, crocetin, an additional carotenoid isolated from saffron, caused a dose-dependent inhibition of nucleic acid and protein synthesis in HeLa, A549 (lung adenocarcinoma), and VA13 (SV-40 transformed fetal lung fibroblast) cells.[54]

Deoxypodophyllotoxin and beta-peltatin A, isolated from *Juniperus sabina* extracts, were active against P-388 murine leukemia, A-549 human lung carcinoma, and HT-29 colon carcinoma with IC_{50} values in the range 2.5−4 ng/mL.[55]

Pastinaca sativa coumarin fractions obtained from fruits inhibited HeLa-S3 cells at concentrations greater than 5 μg/mL. The proliferation inhibition was in the following order: osthol, xanthotoxol, isompimpinellin, bergapten, xanthotoxin, imperatorin, coumarin, umbelliferone, 4-hydroxycoumarin.[56] Coumestrol from *Punica granatum* seeds was reported to be inhibitory to breast cancer cell growth (10−50 μg/mL).[57]

3.3. Prevalence of Coumarin Compounds in Persian Formulations. A detailed literature analysis of the phytochemical composition of the plant species revealed an abundance of coumarin compounds in the majority of the plant extracts used in these herbal medicinal extracts. Coumarin (1,2-benzopyrone) is the simplest compound of a large class of naturally occurring phenolic substances made of fused benzene and α-pyrone rings.[58] The coumarins are widely distributed throughout the plant kingdom, but they are especially abundant in a few families, particularly the Apiaceae (Umbelliferae) and Rutaceae,[59] which represent 11 of the 39 plant extracts used in the herbal mixtures. Of the 39 plant species in these six herbal formulations, 15 are known to contain coumarin compounds (see Table 3).

More interesting is that one of the herbal mixtures contains *Ferula communis*, a plant species of the Mediterranean regions that contains coumarin anticoagulants (4-hydroxycoumarins) such as dicoumarol,[60] ferulenol (3-farnesyl-4-hydroxycoumarin), and ferprenin.[59,61,62] These

Table 3. Botanicals in Persian Traditional Medicines That Contain Coumarin Compounds

species name	reference(s)
Aquilegia vulgaris	128−130
Apium graveolens	130−133
Citrullus colocynthis	134
Coriandrum sativum	135
Ferula assa-foetida	136−138
Ferula communis	59−61, 139−142
Foeniculum vulgare	143−145
Juniperus sabina	146−147
Pastinaca sativa	148−150
Phaseolus vulgaris	151
Pimpinella anisum	152
Portulaca oleracea	153
Punica granatum	57, 154
Rubia tinctorum	155
Ruta graveolens	156−161

compounds induce internal hemorrhaging and have been shown to increase prothrombin time in sheep.[59,63] Rats that were administered extracts of the plant or the isolated 4-hydroxycoumarin compound developed hypothrombinemia with internal and external hemorrhages similar to warfarin poisoning.[64−66]

The coumarin anticoagulants, dicoumarol (a natural anticoagulant drug chemically designated as 3,3′-methylenebis[4-hydroxycoumarin]) and its synthetic derivative warfarin sodium (Coumadin), are contraindicated in women who are or may become pregnant because the drug crosses the placenta and may cause fetal hemorrhaging in utero. In addition, there have been reports of birth deformities in children born to mothers on coumarin anticoagulant therapy during pregnancy and spontaneous abortion and stillbirth are associated with its use.[67−69] Depending on the dosage, dicoumarol can serve as an anticoagulant or a means of inducing abortion.[70] In addition to *F. communis*, two additional plant species, *Crocus sativus* and *Marrubium vulgare*, have demonstrated remarkable inhibitory effects on blood coagulation.[71−73]

Analysis of variance (ANOVA) was employed to test the statistical significance of the differences among the presence of coumarins from the six different herbal formulations. The (F) ratio was less than 1 (F ratio = 0.6026), indicating that the observed mean incidence of coumarins in the different herbal formulations is similar and significant.

3.4. Anti-Cell Proliferative and Anticancer Properties of Coumarins. Subsequent analysis of scientific literature revealed numerous reports on the antiproliferative and antitumor activities of a variety of coumarin compounds. For example, both coumarin itself and 7-hydroxycoumarin have been reported to inhibit the proliferation of a number of human malignant cell lines in vitro[74−80] and have demonstrated activity against several types of animal tumors.[77,78,81−85] These compounds have also been reported in clinical trials to demonstrate activity against prostate cancer, malignant melanoma, and metastatic renal cell carcinoma.[86−91]

In addition, the coumarin anticoagulants have been shown to decrease metastases in experimental animals.[92,93] Warfarin sodium, largely replacing dicoumarol therapeutically as an anticoagulant, has been used for the treatment of a variety of cancers and has been shown to improve tumor response rates and survival in patients with several types of cancer.[94−100] These findings strongly support the possibility that coumarin anticoagulants have an antineoplastic effect, but this hypothesis remains controversial without a biochemical or pharmacological explanation.

3.5. Origin of Hypothesis: Coumarins Disrupt Spindle Microtubule Function. As a result of our extensive investigation of the ancient medicinal literature and of the recently published coumarin literature, we developed the hypothesis that certain coumarins may be antimitotic and elicit their antiproliferative activity via an interaction with microtubule spindle function. The rationale behind this theory began with several published reports on the antimitotic activity of coumarins in plant cells. Using root tips of *Allium cepa* as a model system, coumarin, 7-hydroxycoumarin, and 4-hydroxycoumarin were shown to inhibit mitosis.[101] Of particular interest, Podbielkowska et al.[102] found that 7-hydroxycoumarin disorganized microtubules in the mitotic spindle of these cells, leading to the random spreading of metaphase chromosomes. This action is similar to that of well-known antimitotic drugs, which inhibit mitosis by modifying spindle microtubule dynamics.[103,104] Despite considerable evidence that the coumarins demonstrated antimitotic activity in plants,[105] the possibility that these agents might affect mitosis by affecting spindle microtubule function had not been investigated.

The clinical success of antimicrotubule drugs provides a rational motivation for the search for novel compounds that target mitotic spindle function. A variety of natural products are used as anticancer agents, their antimitotic activity being due to their interaction with microtubular protein. These compounds block cell division at mitosis by interfering with the function of the mitotic spindle. It is believed that the critical mechanism underlying successful chemotherapeutic use of antimitotic agents in humans is the kinetic stabilization of spindle microtubules at the metaphase/anaphase transition.[103,104] Plant-derived antimitotic drugs that interfere with the normal formation of mitotic spindles and cytoplasmic microtubules include cornigerine,[106] alkaloids such as colchicine,[107] vincristine and vinblastine,[108] and other drugs such as podophyllotoxin,[109] maytansine,[110] combretastatin,[111] and taxol.[112]

Most tubulin-disrupting drugs are contraindicated in pregnancy and cause fetal harm when administered to pregnant women. Interestingly, four of the plant species in the Persian formulations contain the well-known antimicrotuble agents podophyllotoxin or colchicine. Podophyllotoxin is the prototype for the structurally related group of anticancer agents known as the podophyllins. These compounds bind reversibly to tubulin and inhibit mitosis by inhibiting microtubule assembly.[109] Two semisynthetic derivatives of podophyllotoxin (etopside and teniposide) are currently available for the treatment of certain cancers. Podophyllotoxin was isolated from crude extracts of *Teucrium polium*, *Teucrium chamaedrys* (0.14%),[113] *Podophyllum emoddii*,[114] and *Podophyllum peltatum*.[115] In addition, podophyllotoxin was obtained in mesophyll cells of *Juniperus sabina* leaves.[116] Colchicine, a water-soluble alkaloid, also inhibits mitosis by inhibiting microtubule assembly and causes teratogenic birth defects in lab animals. Colchicine, formyldeacetylcolchicine, and demethylcolchicine have been isolated from *Crocus sativus*.[117]

Upon testing our hypothesis, we discovered that dicoumarol exerts its antiproliferative effects by stabilizing microtubule dynamics through a unique interaction with tubulin and microtubules. In addition, we have demonstrated that combinations of dicoumarol with taxol act synergistically to potentiate the inhibition of cell proliferation.[118] Taxol, a complex diterpene isolated from *Taxus brevifolia*, has a unique cytotoxic mechanism of action involving the stabilization of microtubules that leads to

mitotic arrest and is used to treat breast and ovarian cancer.[112] Our findings may support the idea that some botanicals in these Persian herbal formulations contain coumarins that stabilize microtubule dynamics that work to potentiate other microtubule-acting compounds, such as the podophyllotoxins or colchicine, to enhance their abortifacient or antineoplastic activity.

4. Conclusion

An impressive number of modern drugs have been isolated from plants, many based on their use in ancient medicine. History has demonstrated that botanicals from herbal remedies possess compounds with medicinal merit. Our systematic investigation into the chemical constituents, pharmacological actions, and toxicity of the botanicals from traditional Persian medicines proves their medicinal worth. The experimental literature gives scientific basis for the use of plant species as abortifacients and as antineoplastic agents. In addition, our scientific and literary examination of these Persian herbal remedies has led to the discovery of the antiproliferative mechanism of action of dicoumarol and other coumarin compounds.[118] These compounds could provide a new structural class for synthetic elaboration that could lead to improved antineoplastic drugs.

Acknowledgment. We especially thank the late Seyedeh Nasrin Sohrab for access from her personal archives to Persian Materia Medica that has allowed us to analyze and develop the conceptual aspects underlying our research. We also thank Amin Madari for his translation of the herbal formulations from the original Farsi, Les Wilson for his contributions to the tubulin-based experiments, and Bradley Buckley for his assistance in the statistical analysis.

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NP049953R