JOURNAL OF AGRICULTURAL AND FOOD CHEMISTRY

REVIEW

pubs.acs.org/JAFC

Artemisia dracunculus L. (Tarragon): A Critical Review of Its Traditional Use, Chemical Composition, Pharmacology, and Safety

Dmitry Obolskiy,[†] Ivo Pischel,[†,‡] Bjoern Feistel,[§] Nikolay Glotov,[#] and Michael Heinrich*[,†,⊥]

[†]Center for Pharmacognosy and Phytotherapy, The School of Pharmacy (University of London), 29−39 Brunswick Square, London WC1N 1AX, United Kingdom

[‡]Phytolab GmbH & Company KG, Dutendorfer Strasse 5−7, 91487 Vestenbergsgreuth, Germany

[§]Finzelberg GmbH & Company KG, Koblenzer Strasse 48−56, 56626 Andernach, Germany

[#]Department of Pharmacology, I. M. Sechenov First Moscow State Medical University, 8 Trubetskaya Str., Moscow 119992, Russia

[⊥]Southern Cross Plant Science, Southern Cross University, Lismore, NSW 2480, Australia

ABSTRACT: *Artemisia dracunculus* L. (tarragon) has a long history of use as a spice and remedy. Two well-described "cultivars" (Russian and French) are used widely and differ in ploidy level, morphology, and chemistry. Key biologically active secondary metabolites are essential oils (0.15−3.1%), coumarins (>1%), flavonoids, and phenolcarbonic acids. In vivo studies mainly in rodents, particularly from Russian sources, highlight potential anti-inflammatory, hepatoprotective, and antihyperglycemic effects. Despite concerns about the toxic effects of two of its main constituents, estragole (up to 82%) and methyleugenol (up to 39%), no acute toxicity or mutagenic activity has been reported at doses relevant for human consumption. Water extracts of *A. dracunculus* contain very low amounts of estragole and methyleugenol and, therefore, are considered to pose a very limited risk. Overall, a stronger focus on clinical studies and precise taxonomic and phytochemical definition of the source material will be essential for future research efforts.

KEYWORDS: *Artemisia dracunculus* (tarragon, Asteraceae), essential oil, estragole, methyleugenol, antihyperglycemic, anti-inflammatory, hepatoprotective

INTRODUCTION

Artemisia dracunculus L. (tarragon) is a perennial herb in the Asteraceae (daisy) family, which has a long history of use in culinary traditions. It also possesses a wide range of health benefits and has therefore been widely used as a herbal medicine. The botany and chemical constituents are well described in the literature, the latter mainly focusing on its essential oil composition that determines its distinct flavor. Additionally, a wide range of secondary metabolites (flavonoids, phenylpropanoids, coumarins, etc.) are reported, determining *A. dracunculus* biological activities and its potential use as a source for plant-derived pharmaceutical chemical entities and complex extracts.

The goal of this paper is to review existing knowledge of *A. dracunculus*'s phytochemical composition, its uses in local medicine, and reported in vitro and in vivo pharmacological studies on plant-derived extracts and also to highlight the potential for developing evidence-based *A. dracunculus* preparations. Due to taxonomic ambiguities, an understanding of the source material used in reviewed studies is crucial.[8,10,16,17,21] Significant differences in phytochemical profile and pharmacological properties between different varieties occur.[12,13,71] French tarragon (sometimes called German tarragon) and Russian tarragon are the two main reported cultivars for this species. Whereas French tarragon is well described in the recognized Western scientific literature, considerable information on Russian tarragon is covered in Russian publications only. All available literature has been compared accordingly in this review.

The specific epithet *dracunculus* (Latin meaning "little dragon") is believed to describe its coiled, serpentine root and/or the shape of the leaves, which is reminiscent of a dragon's tongue.[1,2] Tarragon's common names include Tarkhun (Arabic, Russian), ai hao (Mandarin), estragoa (Dutch), dragon (Dutch, Swedish), estragon (French, German, Italian, Norwegian, Russian), tarragon (Hebrew), estragón (Spanish), targone (Italian), esutoragon (Japanese), and estragao (Portugese).

A. dracunculus is described in several well-recognized herbal reference texts from the 17th to the 19th centuries, where authors indicate the species' appearance, distribution, and, importantly, local and traditional medicinal uses. However, it is not included in earlier herbals. Gerard's *Herbal or General History of Plants*[3] makes reference to tarragon's culinary benefits and use as a spice in Europe, whereas Culpepper[4] highlights its application in urogenital system malfunctioning. In addition, Dragendorff,[5] in his synopsis about medicinal herbs, describes *A. dracunculus* as a middle European spice plant containing estragole-rich essential oil with antiscurvy (antiscorbutic), antiarthritic, and other health benefits.

A. dracunculus's distribution spans over western North America, eastern and central Europe, and most of temperate Asia.[6] The species is widely cultivated across the world, mainly in southern Europe, Russia, and the United States.[8,23,28,57]

Received: June 8, 2011
Revised: September 22, 2011
Accepted: September 24, 2011

Table 1. Synonyms Used for the Main Tarragon Cultivars

synonyms		
French tarragon	Russian tarragon	ref
A. dracunculus f. *dracunculus* L.	*A. dracunculus* f. *redowskii hort*	17
French Tarragon German Tarragon	(described as cultivars)	8
A. dracunculus var. *sativa* Besser	*A. dracunculus* var. *dracunculus*	10
A. dracunculus (authors not specified)	*A. dracunculoides* (authors not specified)	7
A. dracunculus var. *sativa* (authors not specified)	*A. dracunculus* var. *dracunculus* (authors not specified)	21
(not stated)	*A. dracunculus var. pratorum* Krasch. *A. dracunculus* var. *turkestanica* Krasch. Krasc *A. dracunculus* var. *pilosa* Krasch. *A. dracunculus* var. *humilis* Kryl. *A. dracunculus* var. *Redovskyi Ldb*	16
Artemisia aromatica A. Nelson *A. dracunculina* S. Watson *A. dracunculoides* Pursh *A. dracunculoides* subsp. *dracunculina* (S. Watson) H. M. Hall & Clements; *A. glauca* Pallas ex Willdenow *A. glauca* var. *megacephala* B. Boivin		22[a]
Artemisia redowskyi Ledeb *Oligosporus condimentarius* Cass. *Oligosporus dracunculus* L. Polj. *Artemisia inodora* Willd.		95[a]
Artemisia dracunculus L.	*Artemisia dracunculus*, numerous varieties	106

[a] In case of references 22 and 95 no distinction between Russian or French origin is made.

TAXONOMY AND KARYOTYPES

A. dracunculus is characterized by a wide range of morphological and phytochemical variability, which is associated with different geographical origins of the samples studied. Additionally, polyploidy is notably common, and reported cytotypes differ in external morphology, anatomy, fertility, and phytochemical constituents and also differ cytogenetically.[6−9] Thus, the existing literature lacks a common approach to the species' taxonomic classification, with some authors classifying French tarragon and Russian tarragon as subspecies, varieties, or even species (Table 1).

Variable levels of polyploidy have been reported, which appear to correlate with the divergent phytochemical profiles of different samples and, hence, inconsistencies in the taxonomic classifications. *A. dracunculus*, like the majority of *Artemisia* species, has a base chromosome number of $x = 9$, but it is also polyploid ($2n = 2x = 18$; $2n = 3x = 27$; $2n = 4x = 36$; $2n = 6x = 54$, $2n = 8x = 72$, $2n = 10x = 90$).[6,10,11] Different cytotypes of the species express divergent phytochemical profiles. Therefore, knowledge of the origin of the source material is essential when the species' bioactivity or chemistry is studied. *A. dracunculus*'s diploid cytotype is widely distributed and can be found across Asia and North America, whereas wild tetraploids are found in Europe and Asia. In contrast, hexaploids appear to have a more restricted distribution in eastern Europe. Due to the complex distribution of *A. dracunculus* cytotypes, standardization of plant material becomes extremely important when medicinal applications are investigated.[6,10]

From a systematic/taxonomic perspective two main "varieties" or "cultivars" are recognized, French tarragon and Russian or wild tarragon (Russian tarragon). French tarragon is believed to be a sterile tetraploid and has to be propagated clonally, whereas Russian tarragon characteristically has a range of cytotypes, which vary depending on the origin of the samples.[6,10] Both have been cultivated, and French tarragon is believed to have originated from Russian tarragon by means of selection.[7,12,13,15] It is noteworthy that botanical systematic textbooks of the USSR do not make reference to French tarragon but distinguish six varieties of *A. dracunculus*, distributed throughout the territory of the former Soviet Union.[15] Furthermore, other regional "varieties" (Italian, Polish, Iranian, American), distinguished by essential oil composition, are described in the literature.[17−20] Nonetheless, according to current botanical classification, *A. dracunculus* L. is not separated into subspecies.[23]

CULINARY USE

French tarragon has a cool, sweet, licorice-like aroma with slight bitter tones. Its taste is herbaceous, with anise- and basil-like notes, and it is considered to be more delicate than the Russian tarragon. Russian tarragon has larger leaves, lacks the anise-like taste, and is slightly bitter and harsh in flavor.

dx.doi.org/10.1021/jf202277w |J. Agric. Food Chem. XXXX, XXX, 000–000

Table 2. Constituents of *A. dracunculus*

class	compound	ref
flavonoids (flavones, flavanones, dihydroflavanols, chalcones)	5,6,7,8, 4′ -pentahydroxymethoflavone	1, 13, 46−48, 106
	estragoniside	
	7-*O*-β-D-glycopyranoside 5,7-dihydroxyflavavone	
	pinocembrin	
	7-*O*-β-D-glucopyranoside	
	luteolin	
	quercetin	
	rutin	
	kaempferol	
	annangenin	
	5,7-dihydroxyflavone	
	naringenin	
	3,5,4′ -trihydroxy-7-methoxyflavanone	
	3,5,4 -trihydroxy-7,3′-dimethoxyflavanone	
	2′,4′-dihydroxy-4-methoxydihydrochalcone	
	davidigenin	
	sakuranetin	
phenylpropanoids	chicoric acid	13,48,106
	hydroxybenzoic acid	
	(*E*)-2-hydroxy-4-methoxycinnamic	
	chlorogenic acid	
	caffeic acid	
	5-*O*-caffeoylquinic acid	
	4,5-di-*O*-caffeoylquinic acid	
chromones/coumarins	herniarine	1, 42, 49, 50, 52−54, 106
	(−)-(*R*)-2′-methoxydihydro-artemidin	
	(+)-(*S*,*R*)-epoxyartemidin	
	dracumerin	
	(+)-(*R*)-(*E*)-3′-hydroxyartemidin	
	capillarin isovalerate	
	7,8-methylenedioxy-6-methoxycoumarin	
	γ,γ-dimethylallyl ether of esculetin	
	scopoletin	
	scoparone	
	daphnetin methylene ether	
	daphnetin 7-methyl ether	
	artemidiol	
	4-hydroxycoumarin	
	artemidin	
	artemidinal	
	artemidinol	
	esculin	
	capillarin	
	8-hydroxycapillarin	
	8-hydroxyartemidin	
	6-demethoxycapillarisin	
alkamides	pellitorine	52
	neopellitorine A	
	neopellitorine B	

dx.doi.org/10.1021/jf202277w |*J. Agric. Food Chem.* XXXX, XXX, 000–000

Table 2. Continued

class	compound	ref
benzodiazepines[a]	delorazepame	44
	temazepame	

[a] Trace amounts claimed to be produced by the cell culture.

Fresh aerial parts are used whole, chopped, or minced, and when dried, tarragon is used whole, crushed, or ground. Sometimes the stems are included with the leaves. In Europe, *A. dracunculus* is popularly used to flavor many sauces, and it is a favorite herb in France and characterizes French Dijon mustard and sauces based on sour cream, eggs, and mayonnaise, such as tartar, béarnaise, and hollandaise. It is also used in cream soups, salads, omelets, and gravies. These sauces are often added to broiled, baked, or fried fish, meat, and chicken.[2]

Armenians use tarragon on vegetables and fish and meat dishes. In the United States it is used in vinegar, tartar sauce, eggs, chicken, and seafood. Cooking intensifies and changes its flavor, so it is usually added to a dish toward the end of cooking to retain its characteristic aroma and taste.[23] In Slovenia, *A. dracunculus* is used as a spice for a sweet pastry called potica.[24]

A. dracunculus is also used to flavor a popular sweet nonalcoholic drink in Azerbaijan, Armenia, Georgia, Estonia, Russia, and Ukraine that gained popularity in 1980s and is still well-known. This "Tarkhun" is based on a syrup made from *A. dracunculus*, but artificial coloring is commonly used in commercial drinks, determining its distinct green color.[25]

USE IN LOCAL AND TRADITIONAL MEDICINE

In traditional medicine *A. dracunculus* is commonly used to improve a malfunctioning digestive system by increasing appetite, to flush toxins from the body, and as a digestive stimulant, especially in cultures with a high consumption of (red) meat.[1,2] Arabic cultures have used *A. dracunculus* to treat insomnia and to dull the taste of medicines. Additionally, *A. dracunculus* has also been used as an anesthetic for aching teeth, sores, and cuts. *A. dracunculus* has been used widely in central Asia and Russia for the treatment of skin wounds, irritations, allergic rashes, and dermatitis.[26] In the traditional medicine of Azerbaijan tarragon was used as an antiepileptic, laxative, antispasmodic, and carminative remedy (an infusion made from a teaspoon of its twigs was consumed an hour before meals).[27,28] *A. dracunculus* has also been used in the traditional medicine in India, including Ladakh, the northern district of Jammu and Kashmir, where an extract of the whole herb was used as vermifuge and to treat various fevers.[29] Additionally, *A. dracunculus* has a long history of use by Native Americans. The Chippewa used the root as a gynecological aid to reduce excessive flow during the menstrual cycle and to aid in difficult labor. The leaves of *A. dracunculus* were chewed for heart palpitations, and the root was used to make a bath for strengthening children and in steambaths for strengthening elders. Similarly, the Shuswap used the plant as a gynecological aid during childbirth and also burned *A. dracunculus* to repel mosquitoes, whereas the Ramah Navajo made a lotion to aid in healing cuts.[30−32] *A. dracunculus* is also widely used as a herbal remedy in an extensive range of conditions in traditional medicine in the territory of the former Soviet Union. The main reported therapeutic uses are for the nervous (mitigative, antiepileptic), digestive (appetite stimulation, spasmolytic, laxative), and renal systems (diuretic action); for liver function (choleretic); and as anti-inflammatory (wound healing, antiulcer), anticancer, and antibacterial agents.[33−37]

MORPHOLOGY

A. dracunculus is a woody, perennial subshrub with stem heights ranging from 40 to 150 cm. Aerial stems arise from thick, horizontal rhizomes growing in clusters and singly. Leaves are alternate, 1.2−8.0 cm long and 1−6 mm wide. Basal leaves are cleft with one to three lobes. The inflorescence is a panicle with numerous flowers. The outer florets are pistillate and fertile, the central flowers are sterile, and the ovaries are abortive. The seeds are achenes. Seed size is approximately 1.5 mm in length[38−40]

MORPHOLOGICAL CHARACTERISTICS OF RUSSIAN AND FRENCH TARRAGONS

In general, Russian tarragon is taller than French tarragon and the leaves are usually more intensely green. The leaves of both are characterized by having secretory structures, glandular hairs, and secretory cavities that produce essential oils. This oil is extruded when the leaf is physically injured, even in very young leaves, through natural ruptures of the elevated hair cuticle.

A great similarity in the structure of the glandular hairs exists among different *A. dracunculus* "cultivars". All glandular hairs are biseriate, with a head consisting of several pairs of cells. The secretary substances of these hairs accumulate in a subcuticular space and are released with a cuticle rupture. In both French tarragon and Russian tarragon the glandular hairs are sparsely distributed and cannot be responsible for the large amount of essential oil extracted from the leaves. Therefore, the secretary cavities must be the main source of extracted essential oils. The observed differences in morphology of secretary structures of Russian tarragon and French tarragon are very minor, whereby the diverse compositions of essential oils of these two "cultivars" are understood to be linked to different biosynthesis mechanisms.[7,9]

BIOACTIVE CONSTITUENTS

The most important groups of biologically active secondary metabolites in *A. dracunculus* essential oil are coumarins, flavonoids, and phenolic acids. Most research attention has been directed to the composition of the essential oil, its dynamics, and variability.[19,40,41] However, a number of papers have addressed polyacetylene derivatives and flavonoids. Additionally, sesquiterpenoids, vitamins, and tanning substances have also been reported.[43−45] Reported bioactive constituents of *A. dracunculus* are outlined in Table 2, and the structures of the main representative compounds are shown in Figure 1.

Essential Oil. The composition of the essential oil is characterized by significant variation depending on the ecological niche occupied. Additionally, sample cytotype is vital in determining essential oil characteristics. Studies of the dynamics of

dx.doi.org/10.1021/jf202277w |J. Agric. Food Chem. XXXX, XXX, 000–000

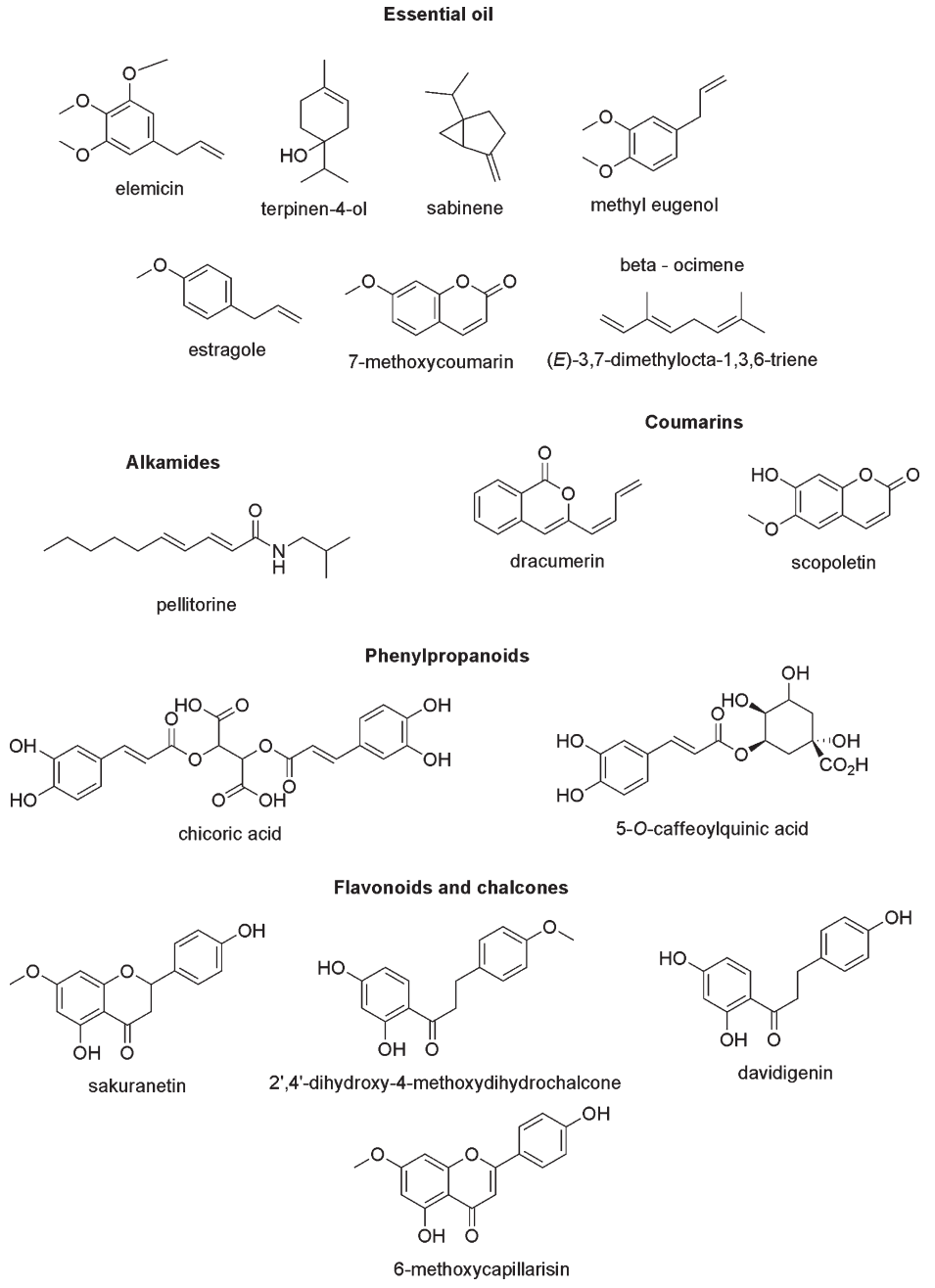

Figure 1. Representative constituents from *A. dracunculus*.

essential oil accumulation during ontogenesis showed that there are two peaks of oil content during the process of plant growth and development, at the beginning of budding and at the start of flowering.[1] Chemical "varieties" of the species have been identified in terms of the qualitative composition of the essential oil.

The contents of the essential oil are usually 0.15−3.1% in the aerial part, and the main components are nonterpenoid compounds: aromatic and acetylene compounds, isocoumarin derivatives, and fatty acids.[15,19,20,41,42,55−58] Notably, major components of the essential oil differ significantly depending on the origin of the material (Tables 3 and 4). Methyleugenol (up to 39%), estragol (up to 82%), elemicin (up to 57%), and terpinolene (up to 25%) are reported to be the prevalent constituents among various regional "varieties" (Tables 3 and 4).

The differences in essential oil composition between Russian tarragon and French tarragon have been reported by several authors. The major components of Russian tarragon are reported to be terpinen-4-ol, sabinene, and elemicin. Methyleugenol and estragole are usually present at about 10 and 3%, respectively. However, estragole is one of the predominant compounds in French tarragon essential oil, with up to 82% presence. Additionally, 7-methoxycoumarin and β-ocimene usually appear at about 10%. Importantly, the content of the main essential oil constituents depends heavily on harvesting time. It was shown that the quantity of estragole could rise more than twice compared to samples of Russian tarragon collected at the end of June or at the end of July. On the other hand, amounts of methyleugenol are normally higher at the beginning of summer.[106]

dx.doi.org/10.1021/jf202277w |J. Agric. Food Chem. XXXX, XXX, 000–000

Table 3. Reported Prevalent Constituents (>10%) of Essential Oil of *A. dracunculus*

origin of *A. dracunculus*	major essential oil constituents
Russian tarragon	**methyleugenol (up to 14%)**
	terpinen-4-ol (up to 41.34%)
	sabinene (up to 39%)
	elemicin (up to 57%)
	β-ocimene (up to 12%)
	estragole (up to 3.39%)
French tarragon	**estragole (up to 74%)**
	7-methoxy coumarin (up to 13%)
	β-ocimene (up to 10%)
	methyleugenol (up to 5%)
Georgia	**estragole (up to 82%)**
Canada	**methyleugenol (up to 35%)**
	terpinolene (up to 19.1%)
	estragole (up to 16.2%)
Denmark	**methyleugenol (up to 39%)**
	sabinene (up to 24.75%)
	elemicin (up to 10.37%)
United States	terpinolene (up to 25%)
	cis-ocimene (up to 22.2%)
Iran	α-*trans*-ocimene (up to 20%)
	limonene (up to 12%)
Cuba	**methyleugenol (up to 17%)**
Italy	*trans*-anethole (up to 53%)

Coumarins. *A. dracunculus* usually contains >1.0% coumarins, with maximal accumulation usually observed during the generative period, whereas the composition remains stable during this time. Coumarins identified include herniarin, coumarin, esculetin, esculin, capillarin, 8-hydroxycapillarin, artemidin, 8-hydroxyartemidin, artemidinol, and others.[1,50−52]

Peroxidase and Nitrogen Bases. Roots, stems, leaves, and inflorescences contain the enzyme peroxidase.[1] Although the exact mechanisms have yet to be elucidated, peroxidases are known to play a part in increasing a plant's defenses against pathogens. Correlational relationships were found between peroxidase activity and the maximal accumulation of phenol compounds. Peroxidase is able to manifest peroxidase activity (at pH 5.2) and oxidase activity (at pH 7.0−8.5).[1] Minimal conditions for the appearance of oxidase activity are the presence of two hydroxyl groups in the *ortho*-position and the absence of a carboxyl group as a substituent in the benzene ring.

The potential application of peroxidase isolated from *A. dracunculus* could be similar to that of horseradish peroxidase, which is used extensively in molecular biology for antibody detection and in immunohistochemistry for labeling of tissue sections. Additionally, peroxidase can be used in the treatment of industrial waste waters. Enzyme-catalyzed polymerization using horseradish peroxidase can remove phenols, which are important pollutants. Phenols are oxidized to phenoxy radicals, which convert to polymers and oligomers that are less toxic, and have been used in many manufacturing processes such as for adhesives, computer chips, car parts, and linings of drums and cans.

Some studies[44] have addressed nitrogen-containing substances in *A. dracunculus*, and an extract of tissue cultured cells was found to have positive influences on human brain benzodiazepine receptors. High-performance liquid chromatography separation of the extract produced benzodiazepine derivatives, which were identified as delorazepam and temazepam, the levels of which in the cellular tissues reached 0.1−0.2 μg/g of cell culture.[44] Nitrogenous bases were extracted from the aboveground parts of the plant: a previously studied compound, pellitorin, and two new compounds, neopellitorin A and neopellitorin B, were shown to possess insecticidal activity.[52]

BIOLOGICAL ACTIVITY AND PHARMACOLOGICAL PROPERTIES

Extracts and some individual compounds of *A. dracunculus* are reported to possess a wide range of pharmacological properties including antibacterial, antifungal, anti-inflammatory, antidiabetic, hepatoprotective, gastroprotective, and anticonvulsant activities. Aside from a number of in vitro experiments, a considerable number of in vivo studies have been conducted evaluating a wide spectrum of health benefits. Importantly, the antihyperglycemic action of extracts has been assessed extensively in animal models, and antidiabetic formulations and increased bioavailability have been developed.[13,60−63] An extensive number of pharmacological activities of Russian tarragon were explored in vivo and reported in Russian scientific literature, which is also summarized in the present review (Table 5).

IN VITRO PHARMACOLOGICAL ACTIVITIES OF TARRAGON

Antibacterial Activity. The antimicrobial activities of chloroform, acetone, and methanol as well as water extracts of *A. dracunculus* have been widely studied,[12,13,64,65] showing a wide variety of antimicrobial activity against pathogenic microorganisms, including inhibition of growth of *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Shigella* (RSHI), *Listeria monocytogenes*, *Staphylococcus epidermidis*, *Bacillus subtilis*, and others. Additionally, Kordali et al.[42] described the antibacterial potential of *A. dracunculus* essential oil against *Pseudomonas syringae glycinea* (RK-470), *Xanthomonas axanopodas* pv *vesicatoria*, *Brevibacterium casei*, *Proteus vulgaris*, and others. The bactericidal activity of water *A. dracunculus* extract on *Helicobacter pylori* was reported, highlighting the potential of *A. dracunculus* preparations as a treatment for gastroduodenal diseases, including gastric and duodenal ulcers.[65]

Antifungal Activity. *A. dracunculus* essential oil has been reported to possess moderate antifungal activity against a number of species including *Phythium ultimum*, *Sclerotinia sclerotiorum*, *Botrytis* sp., *Fusarium seminectum*, *Colletrotichum fragariae*, *Colletrotichum gloeosporioides*, and *Colletrotichum acutatum*.[42,54] This provides a basis for possibly developing *A. dracunculus* preparations for use against agricultural pathogenic fungi.

Antiplatelet Activity. Platelet hyperactivity is one of the most important factors responsible for arterial thrombosis and atherosclerosis. One important mechanism by which blood platelets

Table 4. Major Essential Oil Components (> 1% of Total Essential Oils) of *A. dracunculus*

compound	origin	amount (%)	ref
α-pinene	Iran	5.1	19
azarone	NS	40.36	59
	Russia	21.69	12
limonene	France	6.98	12
	NS	6.33	59
	Georgia	2.40	
terpinolene	Iran	12.4	19
	Turkey	3.1	42
	France	2.26	7
	Canada	1.1	20
	central Italy	7.26	58
	United States	25.4	18
phytol	Canada	19.1	20
	France	1.41	12
allo-ocimene	Iran	4.8	19
cis-ocimene	United States	22.2	18
cis-allo-ocimene	central Italy	10.61	58
	Russia	2.65	15
	central Italy	15.27	58
tetradecanoic acid	Russia	2.12	12
n- hexadecanoic acid	France	2.84	12
	Russia	9.51	12
trans-ocimene	France	7.74	12
	United States	7.0	18
α-*trans*-ocimene	central Italy	8.96	58
	Russia	2.99	15
	Iran	20.6	19
7-methoxycoumarin	France	12.38	12
3,4,7-trimethoxycoumarin	Russia	3.89	12
6,7-dimethoxycoumarin	France	7.32	12
	Russia	12.07	12
β-ocimene	France	5.66	12
	Turkey	9.6	42
trans-anethole	France	10.00	7
	USSR/Russia	12.65	7
	Canada	12.4	20
	Iran	21.2	19
(*Z*)-anethole	central Italy	53.37	58
	Turkey	81.0	42
hexadecenoic acid	Russia	2.89	12
9-octadecenoic acid	Russia	2.13	12
methyleugenol	Iran	2.2	19
	Georgia	1.24	106
	Denmark	39.35	106
	Russia	3.39	106
methylisoeugenol	United States	7.0	18
	Turkey	1.8	42
	USSR/Russia	6.27	7
	Canada	35.8	20
	Albania	∼9.0	55
	Cuba	17.61	57
	Russia	13.77	12
	France	4.84	12
	France	8.50	14
	Russia	14.72	14
	Russia	1.75	12
	Denmark	1.87	106
germacrene D	France	1.7	12
	Canada	1.4	20
germacrene D-4-ol	Georgia	*1.52*	106
	Denmark	*1.41*	106
squalene	Russia	8.60	12
	France	4.65	12
3,7-dimethyl-1,3,7-octatriene	NS	38.43	59
1-methoxy-4-(2-propenyl) benzene	NS	8.57	59
capillarin	Albania	∼4	55
spathulenol	France	1.16	12
estragole (*p*-allylanisole, methylchavicol)	Russia	2.74	15
	France	74.46	7
	Canada	16.2	20
	France	28.3	13
	France	68.80	14
	Georgia	82.06	
	Denmark	1.08	
α-chimachalene	Cuba	1.59	57
capillene (6-phenyl-2,4-hexadiyne)	United States	4.8	18

dx.doi.org/10.1021/jf202277w |*J. Agric. Food Chem.* XXXX, XXX, 000–000

Table 4. Continued

compound	origin	amount (%)	ref
elemicin	USSR/Russia	17.16	7
	Cuba	53.03	57
	Russia	27.33	15
	Russia	15.97	14
	Denmark	10.37	106
	Russia	57.21	106
geranyl acetate	USSR/Russia	1.47	7
sabinene	Russia	39.44	14
	Denmark	24.75	106
	Russia	14.28	106
methyl hexadecanoate	France	2.09	12
5-phenyl-1,3-pentadiyne	United States	11.7	18
(1-phenyl-2,4-pentadiyne)	Albania	~11.0	55
myrcene	USSR/Russia	2.69	7
α-phellandrene	United States	2.4	18
	Russia	1.77	13
β-phellandrene	United States	13.1	18
	Canada	3.4	20
γ-terpinene	France	8.89	7
	USSR/Russia	7.52	7
	Russia	1.85	14
terpinen-4-ol	Cuba	3.95	57
	Russia	7.15	14
	USSR/Russia	41.34	7
	Cuba	4.53	57
	Russia	30.10	15
	Denmark	1.80	106
	Russia	5.41	106
trans-sabinene hydrate	Cuba	2.43	57
terpineol	USSR/Russia	1.32	7
citronellyl formate	USSR/Russia	2.25	7
citronellol	Cuba	2.10	57
citronellyl acetate	Russia	2.77[a]	15
isoelemicin	Cuba	2.60	57
	Russia	6.48	12
	France	2.05	12
	Denmark	8.15	106

[a] Seed ripening phase.

perform their functions is adhesion to the injured vessel wall, which may be regarded as a crucial and complex step of hemostatic process. Shahriyary[66] showed the antiaggregatory potential of *A. dracunculus* leaves. The extract effectively inhibited platelet adhesion, aggregation, and protein expression induced by thrombin, which provides further scientific evidence for traditional use of this species in the treatment of thrombotic disorders.

IN VIVO PHARMACOLOGICAL ACTIVITIES OF TARRAGON

Anti-inflammatory Activity. Ethanol extracts of *A. dracunculus* were shown to possess considerable antiexudative activity.[12,68] Crude ethanol extracts (40 and 70%) of *A. dracunculus* reduced formalin and adrenalin edemas in rats up to 80%. A 70% ethanolic extract was shown to have potent anti-inflammatory action, stronger than that of phenylbutazone.

Hepatoprotective Activity. The hepatoprotective activity of tarragon crude ethanol extract was studied in animal models of subacute tetrachloromethane-induced hepatitis in rats. Considerable reduction of the necrosis area (by at least 30%) was observed in animals that were given 70% ethanol extract. Additionally, after introduction of *A. dracunculus* extracts in rats, segments of liver parenchyma contained more hepatocytes without any signs of dystrophy. It was concluded that *A. dracunculus* extracts strengthen cell membrane and enhance compensatory mechanisms of hepatocytes and, hence, increase resistance to stress factors.[12,68]

Antihyperglycemic Action. The antihyperglycemic activity of *A. dracunculus* was first described by Swanston-Flatt,[72] who reported that *A. dracunculus* significantly reduced hyperphagia and polydipsia in streptozotocin diabetic mice as well as enhanced body weight loss.[72] Interestingly, the authors noted the treatment did not significantly alter plasma glucose or insulin concentrations. Consequently, the ability of tarragon to reduce plasma glucose levels has been shown in a number of different in vitro and in vivo models.[45,62,67,73] In vivo tests showed that *A. dracunculus* preparations possess antihyperglycemic properties in models with exogenous glucose challenge (oral glucose tolerance test) and adrenaline-induced hyperglycemia as well as in toxin-induced diabetes models (alloxan- and streptozotocin-induced).[61,68]

In addition, an ethanolic extract of *A. dracunculus* (Tarralin) was studied extensively and shown to lower plasma glucose levels in KK-Aγ mice (genetic diabetes).[61] In vitro experiments concluded that Tarralin increases glucose takeover in muscles and enhances the activity of intracellular kinases, induced by insulin.[63] Additionally, it escalates the binding of incretin (GLP-1, glucagon-like peptide-1) with its receptor,[61] thus exhibiting insulin-mimetic activity. Moreover, Tarralin causes down-regulation of phosphoenolpyruvate carboxykinase (PEPCK) by reducing the amount of mRNA for this enzyme and also inhibits the activities of tyrosine phosphatase-1B (PTP-1B) and aldose reductase type 2 (ALR2).[45,61,67] The antidiabetic potential of the Tarralin extract has been associated with the presence of six compounds: 4,5-di-*O*-caffeoylquinic acid, davidigenin, 6-demethoxycapillarisin, 2′,4′-dihydroxy-4-methoxydihydrochalcone, 5-*O*- caffeoylquinic acid, and sakuranetin, found by activity-guided isolation.[10,45]

To summarize, the mechanism of the antidiabetic action of *A. dracunculus* is pleiotropic and is associated with increased glucose utilization in tissues by amplification of the endogenous insulin, suppression of gluconeogenesis (blockade of PEPCK), and possible cytoprotective action (blockade of ALR2).

Hypolipidaemic Action. Diabetes mellitus is characterized by violation of all types of metabolism including carbohydrate, fat (dyslipidemia, atherosclerosis, obesity), and protein (predominance of catabolism over synthesis) as well as mineral, water, and salt misbalances. Activation of lipid peroxidation plays a major role in the pathogenesis of atherosclerosis. Additionally, increases in the concentrations of atherogenic lipoproteins and vascular endothelial damage are also significant factors. Furthermore, hyperlipoproteinemia leads to a number of liver disorders. Consequently, hepatoprotective, hypoglycemic, antiplatelet, and antioxidant properties of *A. dracunculus* make the species promising for use as a hypolipoproteinemic and antiatherosclerotic agent. To date, there is only one paper describing the ability of the aqueous extract of *A. dracunculus* to reduce total cholesterol and triglyceride plasma, and we believe this topic deserves increased attention.[70]

Antioxidant Activity. The ability of *A. dracunculus* extracts to reduce accumulation of malonic aldehyde and sialic acid suggests an ability to suppress lipid peroxidation, indicating antioxidant activity.[20,68] Additionally, components of *A. dracunculus* essential oil were shown to exhibit moderate in vitro radical scavenging activity.[42,72] Unfortunately, the specific mechanism of action remains unclear and usually falls within the common approach of antioxidant potential of complex mixtures of phenolic compounds. Therefore, there is an apparent need for further assay-guided fractionation experiments in the search for individual active compounds.

With the properties described above taken into account, further investigations of the species' nootropic, neuroprotective, and anti-ischemic potential as well as influence on exercise performance would be of important scientific interest.

Antihypoxic Activity. Crude ethanolic extracts of *A. dracunculus* also prolonged the life-span and decreased mortality rates in acute hypobaric anoxia in rats, supporting an antihypoxic activity of *A. dracunculus*.[12] Interestingly, *A. dracunculus*'s water extracts did not possess such effects.

Effects on the Gastrointestinal Tract. *Stomach.* Gastroprotective properties were shown to be one of the most prominent effects of *A. dracunculus* in vivo.[12] *A. dracunculus* ethanolic extracts effectively prevented ulcerogenic effects of phenylbutazone in rats. Additionally, Shamsudinov[68] reported the ability of water extracts to increase secretion of gastric juice. Whereas *A. dracunculus* extracts might increase gastric secretion by a reflex mechanism, the gastoprotective action is unlikely to be associated with coating or antacid effects and most probably is due to activation of protective factors (such as mucin and bicarbonate production), astringent properties, or anti-*Helicobacter* activity.[65]

Liver. Shamsudinov [68] reported the ability of a dried extract and infusion to significantly lower the activity of hepatic transaminases (γ-glutamyl transferase, aspartate aminotransferase, alanine aminotransferase) in experimental subacute hepatitis induced by tetrachloromethane.[68] In the same experimental model reproduced by Aglarova, injections of *A. dracunculus* extracts resulted in decreasing dystrophic changes in hepatocytes as well as lowering of the quantity and size of necrotic zones, which were examined in hepatic histological sections.[12] The above-mentioned preparations stimulate cholepoiesis and bile secretion in anuran amphibians. Taking into account the safety of the components of its essential oil, which has recently been reported,[75] preparations of this species might be used as effective hepatoprotectors, and we believe that comparing *A. dracunculus* with the other herbal remedies with proven hepatoprotector activities would be scientifically beneficial.

Neurotropic Activity. *Psychosedative.* Supilnikova[13] reported the ability of *A. dracunculus* extract to prolong thiopental-induced sleep in rats.[13] However, the dose−effect relationship was of the inverse type, and thus challenges the results of the experiment (50 mg/kg, duration of sleep +62%; 100 mg/kg, duration of sleep +37%). Injections of water−alcohol extracts of the species in exploratory behavioral tests (open field and hole-board tests) resulted in improved orientation, increased emotional lability, and lowered exploratory behavior.[12] Kavvadias[44] reported the presence of benzodiazepines (delorazepam and temazepam) in extracts of cultured callus cells of *A. dracunculus* in amounts of 0.1−0.2 μg/g of cell culture.[44] Although the claim that the cell culture is able to produce benzodiazepines needs to be verified independently, these compounds cannot be responsible for the sedative properties of *A. dracunculus* as the concentrations of benzodiazepines are too low. Additionally, the origin of benzodiazepines in samples of the mentioned study remains unclear.

Analgesic. The ability of French tarragon extract to prolong latency periods of nociceptive response and to reduce the number of writhes induced by intraperitoneal (ip) injection of 3% acetic acid (10 mL/kg) supports its effectiveness against visceral pain.[12] The author hypothesized antagonism to calcitonin gene related peptide (CGRP) as the possible mechanism of action of the extract. Thus, the extract of *A. dracunculus* acted as a peripheral analgesic.

Anticonvulsant. Sayyah[19] examined the ability of *A. dracunculus* essential oil to prevent seizures induced by maximal electroshock and pentylenetetrazole.[19] Moderate anticonvulsant activity was shown. However, in the reported study the median effective dose (ED_{50}) to obtain anticonvulsant effect was shown to be only twice lower than the median lethal dose (LD_{50}), which challenges the potential toxicity of its essential oil when used as an anticonvulsant.

SAFETY

The safety of medicinal and spice plants and of their preparations deserves increased scientific attention. One of the main conditions for use of herbal preparations in medicinal conditions is the absence of such risks as mutagenicity, carcinogenicity, and teratogenicity. In general, such products need to have minimal toxicity and side effects. Generally, the vast majority of herbal remedies are recognized as safe, and individual hypersensitivity is usually considered as the most common but controllable risk. However, for those individual compounds exhibiting toxic effects in laboratory animals, the question of possible negative effects in humans remains open. In the case of *A. dracunculus* some compounds have come under scrutiny, most importantly, estragole and methyleugenol.

Individual Compounds. *Estragole (Methylchavicol).* Estragole (1-methoxy-4-allylbenzene) is one of the main components of the essential oil of *A. dracunculus*.[76] Estragole is usually the dominant constituent, particularly in French tarragon. This compound possesses beneficial physiological effects and, consequently, determines pharmacological effects of this species and its preparations. On the other hand, it has been reported that estragole is associated with the development of malignant tumors in rodents. This was the basis for the recommendations of the Scientific Committee on Food (SCF) of the European Union to restrict the use of this substance,[77] but the potential of estragole to induce carcinogenesis in humans remains unclear.

The ability of estragole to cause genotoxicity and, thus, to be carcinogenic was first described by Drinkwater[78] and then followed

Table 5. Reported Pharmacological Activities of Tarragon Preparations

preparation, compound	tarragon origin	effect	model	dose tested	ref
		In Vitro			
antibacterial activity					
crude ethanol extract	Russian tarragon	growth inhibition of *Staphylococcus aureus* (strain P-109)	disc diffusion method	0.01 mL per disk	13
crude ethanolic extract	Russian tarragon	growth inhibition of *Staphylococcus aureus*, actinomycetes, *Bacillus mesentericus*	serial dilution method	MIC 50−100 mg/mL	13
methanol extract diluted with 10 mL of distilled water	NS	zone inhibition against *Shigella* (RSHI), *Listeria monocytogenes* (ATCC 7644), *Pseudomonas aeruginosa* (ATCC 27853)	disc diffusion method	30 μL per disk	64
methanol extract diluted with 5 mLof distilled water	NS	zone inhibition against two different strains of *Escherichia coli* (RSHI, ATCC 25922), *Shigella* (RSHI), *Listeria monocytogenes* (ATCC 7644), and *Pseudomonas aeruginosa* (ATCC 27853)	disc diffusion method	30 μL per disk	64
chloroform extract	NS	inhibitory only toward *Pseudomonas aeruginosa* (ATCC 27853)	disc diffusion method	30 μL per disk	64
acetone extract	NS	inhibitory only toward *Pseudomonas aeruginosa* (ATCC 27853)	disc diffusion method	30 μL per disk	64
water extract	NS	bacteriostatic action against *Helicobacter pylori* (96.9% of colonies were inhibited)	viable colony count method	900 μL of extract for 60 min	65
crude ethanolic extract	French tarragon	inhibitory activity against *Staphylococcus aureus* (209-p), *Staphylococcus epidermidis* Wood-46, *Bacillus subtilis* L2, *Bacillus anthracoides*-1	disc diffusion method	not stated	12
essential oil	Turkish tarragon	moderate inhibitory activity against *Pseudomonas syringae glycinea* (RK-470), *Xanthomonas axanopodas* pv *vesicatoria*, *Brevibacterium casei*, *Proteus vulgaris* and others	disc diffusion method	600−1200 μg/disk	42
antifungal activity					
essential oil 5-phenyl-1,3-pentadiyne, capillarin, methyleugenol	NS	fungistatic against *Colletrotichum fragariae*, *Colletrotichum gloeosporioides*, and *Colletrotichum acutatum*	bioautography on silica gel TLC plates; microbioassay	NS	55
crude ethanolic extract	Russian tarragon	fungistatic against *microsporon* and *trychophyton*	serial agar dilution method	MIC 10000 and 5000 μg/mL	13

dx.doi.org/10.1021/jf202277w |J. Agric. Food Chem. XXXX, XXX, 000–000

Table 5. Continued

preparation, compound	tarragon origin	effect	model	dose tested	ref
essential oil	Turkish tarragon	moderate inhibitory activity against *Phythium ultimum*, *Sclerotinia sclerotiorum*, *Botyrtis* sp., *Fusarium seminectum*, etc.	contact assay; growth inhibition	20 μL of essential oil per plate	42
antiplatelet activity					
crude methanol extract	NS	lowers platelet adhesion to plate as well asr aggregation and secretion	turbidometry	50−200 μL/mL for 60 min	66
antidiabetic activity					
Tarralin (ethanolic extract)	Russian tarragon	increases the binding of GLP-1 to its receptor in dose-dependent manner	in vitro modulation of GLP binding	10000 and 100 μg/mL	61
Tarralin (ethanolic extract)	Russian tarragon	increases glucose uptake in dose-related manner in primary HSMC; enhances insulin-stimulated intracellular kinase activities (PI-3 kinase)	Western blotting	0.1−100 μg/mL	63
6-demethoxycapsillarisin 2′,4′-dihydroxy-4-methoxydihydrochalcone	Russian tarragon	down-regulation of the PEPCK gene expression in H4IIE hepatoma cells	Western blotting	100 μg/mL	67
total ethanolic extract, 6-demethoxycapillarisin, 2′,4′-dihydroxy-4-methoxydihidrochalcone 4,5-di-*O*-caffeoylquinic acid, davidigenin	Russian tarragon	ALR2 inhibitory activity; effect comparable to that of quercetin	in vitro enzyme assay	3.75 μg/mL	45
		In Vivo			
anti-inflammatory activity					
water extract	NS	shrinkage of edema	serotonin-induced paw edema in rats	2 or 5 mL/kg intragastrically	68
water extract	NS	shrinkage of edema	histamin-induced paw edema in rats	2 or 5 mL/kg intragastrically	68
water extract	NS	shrinkage of edema	formalin-induced paw edema in rats	5 mL/kg intragastrically	69
crude ethanolic extract	French tarragon	shrinkage of edema	formalin-induced paw edema in rats	12.5 mL/kg intragastrically, single-dose	12
crude ethanolic extract	French tarragon	lung weight reduction	adrenalin-induced pulmonary edema	12.5 mL/kg intragastrically, single-dose	12
hepatoprotective activity					
water extract	NS	lowers the activity of hepatic transaminases	subacute tetrachloromethane-induced hepatitis in rats	2 or 5 mL/kg intragastrically	68

dx.doi.org/10.1021/jf202277w |*J. Agric. Food Chem.* XXXX, XXX, 000–000

Table 5. Continued

preparation, compound	tarragon origin	effect	model	dose tested	ref
crude ethanolic extract	NS	lowers the activity of hepatic transaminases	subacute tetrachloromethane-induced hepatitis in rats	2 or 5 mL/kg intragastrically	68
crude ethanolic extract	French tarragon	decreases dystrophic changes in hepatocytes	subacute tetrachloromethane-induced hepatitis in rats	12.5 mL/kg intragastrically	12
choleretic action					
water extract	NS	increase in bile secretion	subacute tetrachloromethane-induced hepatitis in rats	2 or 5 mL/kg intragastrically	68
crude ethanolic extract	NS	increase in bile secretion	subacute tetrachloromethane-induced hepatitis in rats	50 mL/kg intragastrically	68
crude ethanolic extract	French tarragon	increase in weight and volume of gall bladder	anuran	25 mL/kg intragastrically	12
antihyperglycemic action					
80% ethanolic extract	Russian tarragon	hypoglycemic effect	high fat dietary induced obese C57BL/6J male mice)	50−500 mg/kg/day	62
2′,4′-dihydroxy-4-methoxydihydrochalcone	Russian tarragon	hypoglycemic effect comparable to that of metformin	high fat dietary induced obese C57BL/6J male mice	50−500 mg/kg bodyweight	62
Tarralin (ethanolic extract)	Russian tarragon	lowers glucose levels and decreases PEPCK mRNA expression	genetically diabetic KK-A^{y} mice	500 mg/kg/day intragastrically	61
Tarralin (ethanolic extract)	Russian tarragon	lowers glucose level; did not have effect on nondiabetic animals	streptozotocin-induced diabetic mice	500 mg/kg/day intragastrically	61
aqueous extract and subfractions	Russian tarragon	lowers glucose and raises insulin levels; no effect on DPP-IV inhibition in controlled, comparative study on hypoglycemic and insulinomimetic effect and dipeptidylpeptidase IV (DPP-IV) inhibition of different aqueous extract based preparations	fasted male Sprague−Dawley rats	6−60 mg/kg po	104
aqueous vs ethanolic extract	Russian tarragon vs French tarragon	lowers glucose and raises insulin levels; no effect on DPP-IV inhibition in controlled, comparative study on hypoglycemic and insulinomimetic effect and dipeptidylpeptidase IV (DPP-IV) inhibition of aqueous vs ethanolic extract of Russian vs French	fasted male Wistar and white Sprague−Dawley rats	6 mg/kg po without (basal) and with glucose challenge (2 g/kg ip after 30 min)	105
aqueous extract	Russian tarragon	slightly lowers the glucose load in response to a dextrose load in nondiabetic men	RCT; oral glucose tolerance test in 12 nondiabetic men	orally, 2 g in capsules	69

dx.doi.org/10.1021/jf202277w |J. Agric. Food Chem. XXXX, XXX, 000–000

Table 5. Continued

preparation, compound	tarragon origin	effect	model	dose tested	ref
hypolipidaemic effect					
water extract of leaves	NS	moderate reductions in the serum total cholesterol and triglyceride levels	high fat diet induced hyperlipidaemia in Wistar rats	1 mL intragastrically	70
antioxidant activity					
water extract	NS	reduces accumulation of malonic aldehyde and sialic acid	NS	2 or 5 mL/kg intragastrically	68
antihypoxic action					
crude ethanolic extract	French tarragon	life-span increase	acute hypobaric anoxia in rats	25 L/kg ip	12
gastroprotective activity					
crude ethanolic extract	French tarragon	reduces ulcerous destruction of gastric mucosa	phenylbutazone-induced ulcer in rats	12.5 mL/kg	12
water extract	NS	increases secretion of gastric juice	studied in rabbits	2 or 5 mL/kg intragastrically	68
diuretic action					
crude ethanolic extract	French tarragon	increases daily diuresis	studied in rodents	12.5 mL/kg	12
effects on nervous system					
essential oil	NS	anticonvulsant action	maximal electroshock in rats	ED_{50} = 0.84 mL/kg	19
essential oil	NS	anticonvulsant action	pentylenetetrazole induced seizures in rats	ED_{50} = 0.26 mL/kg	19
Tarralin (ethanolic extract)	Russian tarragon	treatment of neuropathic changes at early diabetic stages	physiological tests, tactile responses, plantar tests, Western blot	500 mg/kg, 7 weeks	71
crude ethanolic extract	Russian tarragon	prolongs sleep time	thiopental-induced sleep in rats	25, 50, or 100 mg/kg intragastrically	13
crude ethanolic extract	French tarragon	improves orientation and lowers exploratory behavior	open field and hole-board tests	12.5 mL/kg	12
analgesic activity					
crude ethanolic extract	French tarragon	prolongs latency period of nociceptive response and reduces the number of writhes	writhing test in mice induced by ip injection of 3% acetic acid	NS	12

dx.doi.org/10.1021/jf202277w |J. Agric. Food Chem. XXXX, XXX, 000–000

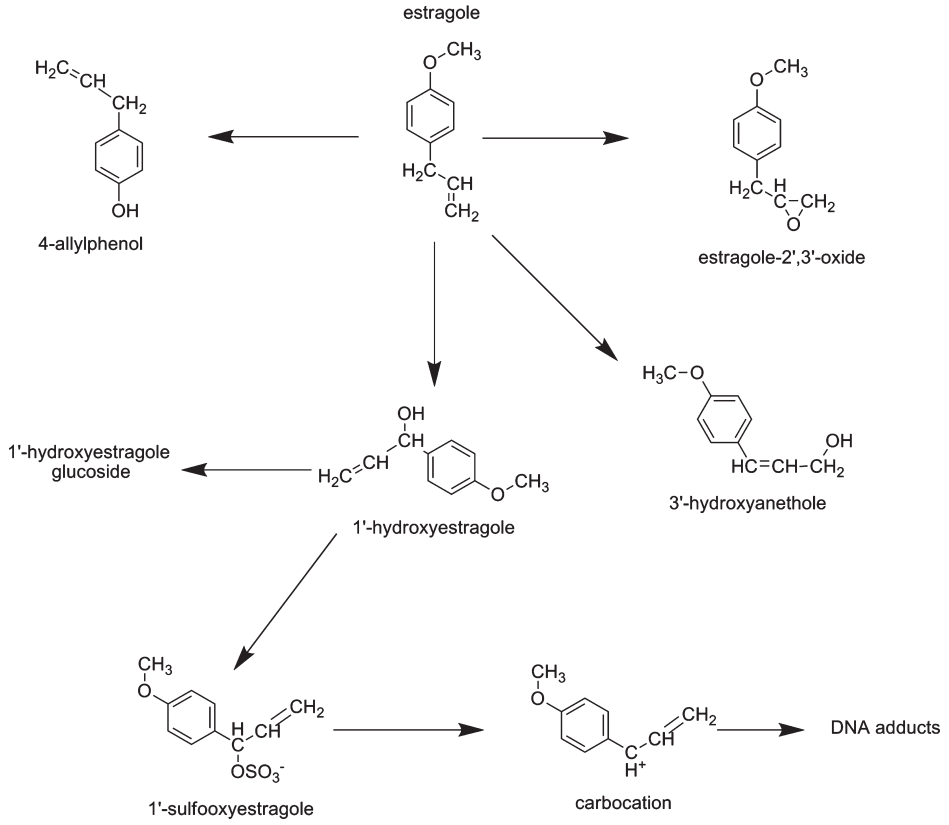

Figure 2. Metabolism of estragole (adapted from ref 91).

by numerous in vivo and in vitro studies.[74,76,79−90] It was found that estragole possesses tissue-, species-, and sex-specific carcinogenic effects.

According to recent evidence, estragole does not have a direct carcinogenic action. The essential factor for estragole's carcinogenicity is its metabolic activation, leading to the formation of unstable molecules and active radicals that form adducts with nucleic acids and thus damage DNA (genotoxic effect). Estragole metabolism (see Figure 2) is dose-dependent, and elevated doses of estragole increase its biotransformation, leading to the formation of mutagenic metabolites.[91]

The biotransformation of the same substances can differ in animals and in humans, which raises the question of whether the mutagenic metabolites of estragole are formed in humans. The results of the recent study by Punt,[75] which was dedicated to examining in vitro metabolic pathways of estragole in humans, demonstrate a significant prevalence of detoxification (oxidation) of 1′-hydroxyestragole compared to the reaction rate of its formation in 99% of the human population.[75] Thus, the probability of the formation of estragole metabolites that directly damage DNA is low. Consequently, in humans the risk of it acting as a carcinogen is extremely small.[93] This was also confirmed by Zeller et al. in their study of estragole metabolism in people consuming fennel tea.[92] Nevertheless, the available data cannot completely exclude the possibility of the formation of genotoxic metabolites in humans. Moreover, 1-sulfooxyestragole cannot be detected directly in biological fluids due to its high reactivity and instability.[92] Of note, estragole has been demonstrated to be genotoxic and carcinogenic, but the European Commission did not establish a safe exposure limit. The committee was unable to estimate the relative contributions to total exposure to estragole from food containing herbs and spices or from the use of added flavorings; however, reductions in the compound's consumption were advised.

Methyleugenol. Methyleugenol (1,2-dimethoxy-4-prop-2-en-1-ylbenzene) is another common component of *A. dracunculus* essential oil and considered to be potentially toxic. This is another topic addressed in the EU Commission opinion.[94] It is a multisite, multispecies carcinogen, which induces different types of liver tumors as well as neuro-endocrine tumors in the glandular stomach in both mice and rats. In rats, other types of tumors include neoplasms in the forestomach, kidney, mammary gland, and subcutaneous tissue as well as mesotheliomas. Tumors were observed at the lowest used dose of methyleugenol (37 mg/kg body weight/day). By analogy with estragole, this is probably due to insufficient metabolic activation. Methyleugenol has also demonstrated genotoxicity. A consumption threshold was not established for methyleugenol, although reductions in exposure and restrictions in use levels are indicated by the commission.

EXTRACTS

Whereas estragole and methyleugenol as individual compounds might be toxic, water and water−alcohol extracts of *A. dracunculus* showed no acute toxicity in rodents, with a maximum tolerated dose up to 200 mL of extract (1:10)/kg body weight.[12,13] Additionally, Ribnicky[60] reported no mutagenic activity of the ethanolic extract at 1000 mg/kg in rodents.[60] Gross necropsy and clinical chemistry did not reveal any effects on organ mass or blood chemistry, and microscopic examinations found no lesions associated with treatment.

Overall, using adequate production procedures, the amount of potentially harmful compounds (estragole and methyleugenol) in extracts can be limited without affecting the overall pharmacological

dx.doi.org/10.1021/jf202277w |J. Agric. Food Chem. XXXX, XXX, 000–000

activities of these preparations, that is, using water extracts with low estragole and methyleugenol content and avoiding ethanolic extracts (S. E. Weinöhrl, B. Feistel, I. Pischel, B. Kopp, and V. Butterweck. Comparative evaluation of two different *Artemisia dracunculus* L. cultivars for blood sugar lowering effects in rats. Submitted for publication to *Phytotherapy Research*; Doi: 10.1002/PTR.3605.

CURRENT INTELLECTUAL PROPERTY STATUS

A search of the patent database of the European Patent Office[96] yielded a total of 1582 hits for the query "Artemisia" and 159 for "tarragon", whereas the term "*Artemisia dracunculus*" gave 14 hits and "Russian tarragon" 4 hits.

The intellectual property documents ("*Artemisia dracunculus*" 14 and "Russian tarragon" 4 hits) mainly refer to blends of several plants or botanical products, such as essential oils of aromatic herbs. Of the 14 patent hits for "*Artemisia dracunculus*", 4 are related to food and flavoring purposes and another 4 to external use (cosmetic or personal care applications). The remaining 6 hits and the 2 additional hits for the database query "Russian tarragon" claim medicinal or biofunctional benefits regarding lowering of blood glucose levels, in particular for type II diabetes, and weight loss. Only 3 of them, which were filled recently, disclose the sole use of Russian tarragon or its extract.[97−99]

ECONOMIC IMPORTANCE

In many countries, cultivation and culinary uses of French tarragon are described. It is said to be a tasty, very aromatic, and valuable herb, whereas the Russian cultivar's culinary characteristics are given as bitter herb, leading to the opinion that "Russian" tarragon is of no commercial value.[100] It is used, fresh or dried, as a gourmet herb in French cooking and as a popular herb in other European countries. In general, all information refers to the essential oil-producing French tarragon, with its main constituent estragole. It is an ingredient in diverse commercial preparations including vinegar, mustard, liqueurs, and perfumes. The essential oil of *A. dracunculus* is included in similar commercial products.

In Europe it is one of the 20 most commonly grown herbs. The publicly available market data on prices mainly of fresh French tarragon in the United States and Europe vary between ca. $15 and 25/kg in 2008−2010.[101] In 2004 in the European Union *A. dracunculus* was cultivated over an area of 236 ha (3 ha of this are organic).[102] In the early 1990s, France was the second main European producer, with 310 ha under *A. dracunculus* cultivation.[103]

DISCUSSION

A. dracunculus has a long history of traditional use, and a growing number of studies confirm this species' beneficial medicinal properties. Alongside available scientific papers, this review includes a number of studies that are not well-known internationally, most importantly from Soviet and Russian sources. Compared to other health foods and spices, considerable in vivo data are available for *A. dracunculus* (mostly in Russian). In particular, investigation of the hypoglycemic activity and potential use of *A. dracunculus* in type II diabetes deserves increased attention.

Existing problems with the classification of *A. dracunculus* are mainly associated with incorrect identification or improper taxonomic classification and with the levels of polyploidy. Thus, the source of the plant material and a full taxonomic description are essential in the investigation of its pharmacological activity, as various cytotypes accumulate divergent phytochemical profiles, thus having different biological activities.

Estragole and methyleugenol, two of the main components of *A. dracunculus* essential oil, were shown to be toxic in rodents. However, estragole's quantities in the essential oil of Russian tarragon are considerably lower than in the French tarragon (<10% vs up to 75%, respectively). At the same time a number of papers have recorded no toxicity for *A. dracunculus* extracts when studied in mice. Moreover, water extracts of *A. dracunculus* were shown to lack both estragole and methyleugenol and, hence, are considered to be "safer" than ethanolic extracts. Overall, because *A. dracunculus* is normally used as a spice or a tea, the maximum daily dose of dry plant material will be below 10 g/day, which corresponds to minor amounts of estragole and methyleugenol.

Several in vivo studies claim beneficial pharmacological activities of *A. dracunculus* preparations, including anti-inflammatory, hepatoprotective, antihyperglycemic, and hypolipidaemic actions; however, most of the reported effects have been evaluated in rodents, and only one study involved healthy men in a randomized double-blind trial.[69] Therefore, additional research involving a larger number of subjects is needed for confirmation of the active principles of *A. dracunculus* preparations.

AUTHOR INFORMATION

Corresponding Author

*Phone: +62-2-6620-3010. Fax: +62-2-66222080. E-mail: michael.heinrich@scu.edu.au.

ABBREVIATIONS USED

ALR, aldose reductase; CGRP, calcitonin gene related peptide; ED_{50}, effective dose 50; PTP-1B, tyrosine phosphatase; EU, European Union; GLP-1, glucagon-like peptide; HSMC, human skeletal muscle culture; LD_{50}, median lethal dose; MIC, minimal inhibitory concentration; NS, not stated; PEPCK, phosphoenolpyruvate carboxykinase; RSHI, Refik Saydam Hifzissihha Institute; SCF, Scientific Committee on Food.

REFERENCES

(1) Aglarova, A. M.; Zilfikarov, I. N.; Severtseva, O. V. Biological characteristics and useful properties of tarragon (*Artemisia dracunculus* L.) [translated from Russian]. *Pharm. Chem. J. [Khim.-Farm. Zh.]* **2008**, *42*, 81−86.

(2) Uhl, S. R.; Strauss, S. *Handbook of Spices, Seasonings and Flavorings*; Technomic Publishing: Lancaster, PA, 2000; pp 170−171.

(3) Gerard, J. *The Generall Historie of Plants*; London, U.K., 1633; pp 249.

(4) Culpepper, N. *Culpeper's Complete Herbal: Consisting of a Comprehensive Description of Nearly All Herbs with Their Medicinal Properties and Directions for Compounding the Medicines Extracted from Them*; London, U.K., 1880; pp 363.

(5) Dragendorff, G. *Heilpflanzen der verschiedenen Völker und Zeiten. Ihre Anwendung, wesentlichen Bestandtheile und Geschichte*; Stuttgart, Germany, 1898.

(6) Eisenman, S. W.; Struwe, L. The global distribution of wild tarragon (*Artemisia dracunculus* L.; Asteraceae) cytotypes with twenty-seven new records from North America. *Genet. Resour. Crop Evol.* **2011**, 1–14.

(7) Tomitaka, Y.; Kimura, M.; Asano, K.; Boo, H. O. Morphological characters and the essential oil in *Artemisia dracunculus* (French tarragon)

and *A. dracunculoides* (Russian tarragon). *J. Agric. Sci.* **1997**, *41*, 229−238

(8) Vienne, M.; Braemer, R.; Paris, M.; Couderc, H. Chemotaxonomic study of two cultivars of *Artemisia dracunculus* L.: ("French" and "Russian" tarragon). *Biochem. Syst. Ecol.* **1989**, *17*, 373–374.

(9) Werker, E.; Putievsky, E.; Ravid, U.; Dudai, N.; Katzir, I. Glandular hairs, secretory cavities, and the essential oil in the leaves of tarragon (*Artemisia dracunculus* L). *J. Herbs Spices Med. Plants* **1994**, *2*, 19–32.

(10) Eisenman, S. W. Qualitative variation of anti-diabetic compounds in different tarragon (*Artemisia dracunculus* L.) cytotypes. *Fitoterapia* **2011**, doi: 10.1016/j.fitote.2011.07.003.

(11) Kreitschitz, A.; Vallès, J. New or rare data on chromosome numbers in several taxa of the genus *Artemisia* (Asteraceae) in Poland. *Folia Geobot.* **2003**, *38*, 333–343.

(12) Aglarova, A. M. *Comparative Analysis of Secondary Metabolites of Artemisia dracunculus L., Russian and French cultivars*. Ph.D. thesis, Mahachkala, 2006.

(13) Supilnikova, A. V. *Developing of Methods of Quantitative and Qualitative Analysis for Tarragon (Artemisia dracunculus L.)*. Ph.D. thesis, Samara, 2004.

(14) Hosseini, A. A. M. *Quality, Energy Requirement and Costs of Drying Tarragon (Artemisia dracunculus L.)*. Thesis, Wageningen University, 2005; pp 39−53.

(15) Khodakov, G. V.; Kotikov, I. V.; Pankovetskii, V. N. Component composition of essential oil from *Artemisia abrotanum* and *A. dracunculus* [translated from Russian]. *Chem. Nat. Compds [Khim. Prir. Soedin.]* **2009**, *45*, 905–908.

(16) Komarov, V. L. *Flora of USSR* [in Russian]; Academy of Science of the USSR: Moscow, Russia, 1961; Vol 26, pp 525−535.

(17) Olszewska-Kaczynska, I.; Suchorska, K. Evaluation of three forms of cultivated tarragon (*Artemisia dracunculus* L.). *Folia Hortic.* **1996**, *8*, 29–37.

(18) Pappas, R. S.; Sturtz, G. Unusual alkynes found in the essential oil of *Artemisia dracunculus* L. var. *dracunculus* from the Pacific Northwest. *J. Essent. Oil Res.* **2001**, *13*, 187–188.

(19) Sayyah, M.; Nadjafnia, L.; Kamalinejad, M. Anticonvulsant activity and chemical composition of *Artemisia dracunculus* L. essential oil. *J. Ethnopharmacol.* **2004**, *94*, 283–287.

(20) Lopes-Lutz, D.; Alviano, D. S.; Alviano, C. S.; Kolodziejczyk, P. P. Screening of chemical composition, antimicrobial and antioxidant activities of *Artemisia* essential oils. *Phytochemistry* **2008**, *69*, 1732–1738.

(21) Kamarainen-Karppinen, T.; Makinen, A.; Kolehmainen, S.; Hamalainen, A.; Laine, K.; Hohtola, A.; Mattila, S.; Pirttila, A. M. Overwintering, chemical variation, and genetic diversity in three vegetatively propagated lines of French tarragon (*Artemisia dracunculus* var. *sativa*). *J. Hortic. Sci. Biotechnol.* **2008**, *83*, 765–769.

(22) Flora of North America, http://www.efloras.org/florataxon.aspx?flora_id=1&taxon_id=200023201, accessed Nov 21, 2010.

(23) U.S. Department of Agriculture Agricultural Research Service, http://www.ars-grin.gov/cgi-bin/npgs/html/taxon.pl?4282, accessed Sept 11, 2010.

(24) Bordeaux Undiscovered, http://bordeaux-undiscovered.blogspot.com/2010/06/love-food-love-bordeaux-bordeaux-white.html, accessed Nov 21, 2010.

(25) Goldstein, D. *The Georgian Feast: The Vibrant Culture and Savory Food of the Republic of Georgia*; University of California Press: Los Angeles, CA, 1999; pp 229.

(26) Mamedov, N.; Grdner, Z.; Craker, L. E. Medicinal plants used in Central Asia for the treatment of selected skin conditions. *J. Herbs Spices Med. Plants* **2004**, *11*, 191–222.

(27) Alakbarov, F. U. Medicinal plants used in medieval Azerbaijan phytotherapy. *J. Herbal Pharmacother.* **2001**, *3*, 35–49.

(28) Miraldi, E.; Ferri, S.; Mostaghimi, V. Botanical drugs and preparations in the traditional medicine of West Azerbaijan (Iran). *J. Ethnopharmacol.* **2001**, *75*, 77–87.

(29) Singh, V.; Kapahi, B. K.; Srivastava, T. N. Medicinal herbs of Ladakh especially used in home remedies. *Fitotarapia* **1995**, *67*, 38–48.

(30) Densmore, F. *How Indians Use Wild Plants for Food, Medicine, And Crafts*; Dover Publications,: New York, 1974; pp 397.

(31) Moerman, D. E. *Native American Ethnobotany*. Timber Press: Portland, OR, 1998; pp 927.

(32) Palmer, P. A. Shuswap Indian ethnobotany. *Syesis* **1998**, *8*, 29–51.

(33) Barnaulov, O. D. *Fitotherapy of Catarrhal Diseases* [in Russian]; Lan: St. Petersburg, Russia, 1998; pp 146.

(34) Gubanov, I. A.; Krilova, I. L.; Tikhonova, V. L. *Wild-Growing Useful Plants of USSR* [in Russian]; Misl: Moscow, Russia, 1976; pp 360.

(35) Isaev, A. I. *Plant Resources of USSR* [in Russian]; Nauka: St. Petersburg, Russia, 1993; pp 30−73.

(36) Kazhevnikov, A. E.; Probatova, N. S. *Plant Resources of Russia and Neighboring States* [in Russian]; Mir i Semya: St. Petersburg, Russia, 1996; pp 313−315.

(37) Mashanov, V. I.; Pokrovski, A. A. *Spicy and Aromatic Plants* [in Russian]; Agropromizdat: Moscow, Russia, 1991; pp 25−29.

(38) Cronquist, A.; Holmgren, A. H.; Holmgren, N. H. *Intermountain Flora: Vascular Plants of the Intermountain West, U.S.A. Vol. 5. Asterales*; New York Botanical Garden:New York, 1994; pp 496.

(39) Hammond, C. R. A gallery of herbs: a botanical guide to some common and uncommon herbs. *Horticulture* **1976**, *54*, 52–63.

(40) Stubbendieck, J.; Coffin, M. J.; Landholt, L. M. *Weeds of the Great Plains*, 3rd ed.; Nebraska Department of Agriculture, Bureau of Plant Industry, in cooperation with the University of Nebraska: Lincoln, NE, 2003; pp 605.

(41) Deans, S. G.; Svoboda, K. P. Antibacterial activity of French tarragon (*Artemisia dracunculus* Linn.) essential oil and its constituents during ontogeny. *J. Hortic. Sci.* **1988**, *63*, 503–508.

(42) Kordali, S.; Kotan, R.; Mavi, A.; Cakir, A.; Ala, A.; Yildirim, A. Determination of the chemical composition and antioxidant activity of the essential oil of *Artemisia dracunculus* and of the antifungal and antibacterial activities of Turkish *Artemisia absinthium*, *A. dracunculus*, *Artemisia santonicum,* and *Artemisia spicigera*. *J. Agric. Food Chem.* **2005**, *24*, 9452–9458.

(43) Greger, H. Aromatic acetylenes and dehydrofalcarinone derivatives within the *Artemisia dracunculus* group. *Phytochemistry* **1979**, *18*, 1319–1322.

(44) Kavvadias, D.; Abou-Mandour, A. A.; Czygan, F. C.; Beckmann, H.; Sand, P.; Riederer, P.; Schreier, P. Identification of benzodiazepines in *Artemisia dracunculus* and *Solanum tuberosum* rationalizing their endogenous formation in plant tissue. *Biochem. Biophys. Res. Commun.* **2000**, *269*, 290–295.

(45) Logendra, S.; Ribnicky, D. M.; Yang, H.; Poulev, A.; Ma, J.; Kennelly, E. J.; Raskin, I. Bioassay-guided isolation of aldose reductase inhibitors from *Artemisia dracunculus*. *Phytochemistry* **2006**, *67*, 1539–1546.

(46) Kurkin, V. A.; Zapesochnaya, G. G.; Avdeeva, E. V. Structure and properties of estragonoside — a new flavonoid from the epigeal part of *Artemisia dracunculus* [in Russian]. *Chem. Nat. Compd. [Khim. Prir. Soedin.]* **1997**, *33*, 61–65.

(47) Balza, F.; Towers, G. H. N. Dihydroflavonols of *Artemisia dracunculus*. *Phytochemistry* **1984**, *23*, 2333–2337.

(48) Hofer, O.; Szabó, G.; Greger, H. 2-Hydroxy-4-methoxy-*trans*-cinnamic acid as a precursor of herniarin in *Artemisia dracunculus*. *Chem. Monthly [Monatshefte Chem.]* **1986**, *117*, 1219–1222.

(49) Mallabaev, A.; Saitbaeva, I. M.; Sidyakin, G. P. The isocoumarin artemidinal from *Artemisia dracunculus* [in Russian]. *Chem. Nat. Compd. [Khim. Prir. Soedin.]* **1971**, *7*, 257–259.

(50) Faini, F.; Labbe, C.; Salgado, I.; Coll, J. Coumarins of *Artemisia dracunculoides* and 3′,6-dimethoxy-4′,5,7-trihydroxyflavone in *A. arctica*. *Phytochemistry* **1970**, *9*, 891–894.

(51) Engelmeier, D.; Hadacek, F.; Hofer, O.; Lutz-Kutschera, G.; Nagl, M.; Wurz, G.; Greger, H. Antifungal 3-butylisocoumarins from Asteraceae-Anthemideae. *J. Nat. Prod.* **2004**, *67*, 19–25.

(52) Saadali, B.; Boriky, D.; Blaghen, M.; Vanhaelen, M.; Talbi, M. Alkamides from *Artemisia dracunculus*. *Phytochemistry* **2001**, *58*, 1083–1086.

(53) Chumbalov, T. K.; Mukhamedyarova, M. M.; Fadeeva, O. V. The flavonoids of *Artemisia dracunculus* [in Russian]. *Chem. Nat. Compd. [Khim. Prir. Soedin.]* **1969**, *5*, 323.

(54) Onuchak, L. A.; Kurkin, V. A.; Minakhmetov, R. A.; Kurkina, A. V. HPLC analysis of *Artemisia dracunculus* extracts [in Russian]. *Chem. Nat. Compd. [Khim. Prir. Soedin.]* **2000**, *36*, 115–117.

(55) Meepagala, K. M.; Sturtz, G.; Wedge, D. E. Antifungal constituents of the essential oil fraction of *Artemisia dracunculus* L. var. *dracunculus*. *J. Agric. Food. Chem.* **2002**, *24*, 6989–6992.

(56) Rutskih, I. B. Essential oil composition of tarragon (*Artemisia dracunculus* L.) collected in Siberia [in Russian]. *Chem. Herbal Mater. [Khim. Prir. Mater.]* **2000**, *3*, 65–76.

(57) Pino, J. A.; Rosado, A.; Correa, M. T. Chemical composition of the essential oils of *Artemisia dracunculus* L. from Cuba. *J. Essent. Oil Res.* **1996**, *8*, 563–564.

(58) Curini, M.; Epifano, F.; Genovese, S.; Tammaro, F.; Menghini, L. Composition and antimicrobial activity of the essential oil of *Artemisia dracunculus* "Piemontese" from Italy [translated from Russian]. *Chem. Nat. Compd. [Khim. Prir. Soedin.]* **2006**, *42*, 738–739.

(59) Zhang, Y.; Zhang, J.; Yao, J.; Yang, Y. L.; Wang, L.; Dong, L. N. Studies on the chemical constituents of the essential oil of *Artemisia dracunculus* [in Chinese]. *Chin. J. Chin. Mater. Med.* **2005**, *30*, 594–596.

(60) Ribnicky, D. M.; Poulev, A.; O'Neal, J.; Wnorowski, G.; Malek, D. E.; Jäger, R.; Raskin, I. Toxicological evaluation of the ethanolic extract of *Artemisia dracunculus* L. for use as a dietary supplement and in functional foods. *Food Chem. Toxicol.* **2004**, *42*, 585−598.

(61) Ribnicky, D. M.; Poulev, A.; Watford, M.; Cefalu, W. T.; Raskin, I. Antihyperglycemic activity of Tarralin™, an ethanolic extract of *Artemisia dracunculus* L. *Phytomedicine* **2006**, *13*, 550–557.

(62) Ribnicky, D. M.; Kuhn, P.; Poulev, A.; Logendra, S.; Zuberi, A.; Cefalu, W. T.; Raskin, I. Improved absorption and bioactivity of active compounds from an anti-diabetic extract of *Artemisia dracunculus* L. *Int. J. Pharm.* **2009**, *370*, 87–92.

(63) Wang, Z. Q.; Ribnicky, D.; Zhang, X. H.; Raskin, I.; Yu, Y.; Cefalu, W. T. Bioactives of *Artemisia dracunculus* L enhance cellular insulin signaling in primary human skeletal muscle culture. *Metab., Clin. Exp.* **2008**, *57*, S58–64.

(64) Benli, M.; Kaya, I.; Yigit, N. Screening antimicrobial activity of various extracts of *Artemisia dracunculus* L. *Cell Biochem. Funct.* **2007**, *25*, 681–686.

(65) O'Mahony, R.; Al-Khtheeri, H.; Weerasekera, D.; Fernando, N.; Vaira, D.; Holton, J.; Basset, C. Bactericidal and anti-adhesive properties of culinary and medicinal plants against *Helicobacter pylori*. *World J. Gastroenterol.* **2005**, *47*, 7499–7507.

(66) Shahriyary, L.; Yazdanparast, R. Inhibition of blood platelet adhesion, aggregation and secretion by *Artemisia dracunculus* leaves extracts. *J. Ethnopharmacol.* **2007**, *114*, 194–198.

(67) Govorko, D.; Logendra, S.; Wang, Y.; Esposito, D.; Komarnytsky, S.; Ribnicky, D.; Poulev, A.; Wang, Z.; Cefalu, W. T.; Raskin, I. Polyphenolic compounds from *Artemisia dracunculus* L. inhibit PEPCK gene expression and gluconeogenesis in an H4IIE hepatoma cell line. *Am. J. Physiol.: Endocrinol. Metab.* **2007**, *293*, E1503–E1510.

(68) Shamsudinov, Sh. N. *Physiological Efficacy of Tarragon in Various Experimental Conditions*. Ph.D. thesis, Dushanbe, 1994.

(69) Bloomer, R. J.; Canale, R. E.; Pischel, I. Effect of an aqueous Russian tarragon extract on glucose tolerance in response to an oral dextrose load in non-diabetic men. *Nutr. Diet. Suppl.* **2011**, *3*, 43–49.

(70) Yazdanparast, R.; Saee, A. Effects of aqueous tarragon, *Artemisia dracunculus*, extract on lipid and coagulatory parameters in rats. *Biomed. Lett.* **1999**, *59*, 137–141.

(71) Watcho, P.; Stavniichuk, R.; Ribnicky, D. M.; Raskin, I.; Obrosova, I. G. High-fat diet-induced neuropathy of prediabetes and obesity: effect of PMI-5011, an ethanolic extract of *Artemisia dracunculus* L. *Mediators Inflamm.*. **2010**, *2010:268547*, Epub 8-04-2010.

(72) Swanston-Flatt, S. K.; Day, C.; Bailey, C. J.; Flatt, P. R. Evaluation of traditional plant treatments for diabetes: studies in streptozotocin diabetic mice. *Acta Diabetol.* **1989**, *26*, 51–55.

(73) Kheterpal, I.; Coleman, L.; Ku, G.; Wang, Z. Q.; Ribnicky, D.; Cefalu, W. T. Regulation of insulin action by an extract of *Artemisia dracunculus* L. in primary human skeletal muscle culture: a proteomics approach. *Phytother. Res.* **2010**, *24*, 1278–84.

(74) Tsai, P. J.; Tsai, T. H.; Yu, C. H.; Ho, S. C. Evaluation of NO-suppressing activity of several Mediterranean culinary spices. *Food Chem. Toxicol.* **2007**, *45*, 440–447.

(75) Punt, A.; Jeurissen, S. M.; Boersma, M. G.; Delatour, T.; Scholz, G.; Schilter, B.; van Bladeren, P. J.; Rietjens, I. M. Evaluation of human interindividual variation in bioactivation of estragole using physiologically based biokinetic modeling. *Toxicol. Sci.* **2010**, *113*, 337–348.

(76) De Vincenzi, M.; Silano, M.; Maialetti, F.; Scazzocchio, B. Constituents of aromatic plants: II. Estragole. *Fitoterapia* **2000**, *71*, 725–729.

(77) Opinion of the Scientific Committee on Food on Estragole (1-Allyl-4-methoxybenzene), SCF/CS/FLAV/FLAVOUR/6 ADD2 FINAL, Brussels, Belgium, 2001.

(78) Drinkwater, N. R.; Miller, E. C.; Miller, J. A.; Pitot, H. C. Hepatocarcinogenicity of estragole (1-allyl-4-methoxybenzene) and 1′-hydroxyestragole in the mouse and mutagenicity of 1′-acetoxyestragole in bacteria. *J. Natl. Cancer Inst.* **1976**, *57*, 1323–1331.

(79) Swanson, A. B.; Chambliss, D. D.; Blomquist, J. C.; Miller, E. C.; Miller, J. A. The mutagenicities of safrole, estragole, eugenol, *trans*-anethole, and some of their known or possible metabolites for *Salmonella typhimurium* mutants. *Mutat. Res.* **1979**, *60*, 143–153.

(80) Swanson, A. B.; Miller, E. C.; Miller, J. A. The side-chain epoxidation and hydroxylation of the hepatocarcinogens safrole and estragole and some related compounds by rat and mouse liver microsomes. *Biochim. Biophys. Acta* **1981**, *673*, 504–516.

(81) Miller, E. C.; Swanson, A. B.; Phillips, D. H.; Fletcher, T. L.; Liem, A.; Miller, J. A. Structure-activity studies of the carcinogenicities in the mouse and rat of some naturally occurring and synthetic alkenylbenzene derivatives related to safrole and estragole. *Cancer Res.* **1983**, *43*, 1124–1134.

(82) Miller, J. A.; Miller, E. C. The metabolic activation and nucleic acid adducts of naturally-occurring carcinogens: recent results with ethyl carbamate and the spice flavors safrole and estragole. *Br. J. Cancer* **1983**, *48*, 1–15.

(83) Phillips, D. H. DNA adducts derived from safrole, estragole and related compounds, and from benzene and its metabolites. *IARC Sci. Publ.* **1994**, *125*, 131–140.

(84) Phillips, D. H.; Reddy, M. V.; Randerath, K. ^{32}P-post-labelling analysis of DNA adducts formed in the livers of animals treated with safrole, estragole and other naturally-occurring alkenylbenzenes. II. Newborn male B6C3F1 mice. *Carcinogenesis* **1984**, *5*, 1623–1628.

(85) Randerath, K.; Haglund, R. E.; Phillips, D. H.; Reddy, M. V. ^{32}P-post-labelling analysis of DNA adducts formed in the livers of animals treated with safrole, estragole and other naturally-occurring alkenylbenzenes. I. Adult female CD-1 mice. *Carcinogenesis* **1984**, *5*, 1613–1622.

(86) Fennell, T. R.; Wiseman, R. W.; Miller, J. A.; Miller, E. C. Major role of hepatic sulfotransferase activity in the metabolic activation, DNA adduct formation, and carcinogenicity of 1′-hydroxy-2′,3′-dehydroestragole in infant male C57BL/6J × C3H/HeJ F1 mice. *Cancer Res.* **1985**, *45*, 5310–5320.

(87) Wiseman, R. W.; Fennell, T. R.; Miller, J. A.; Miller, E. C. Further characterization of the DNA adducts formed by electrophilic esters of the hepatocarcinogens 1′-hydroxysafrole and 1′-hydroxyestragole in vitro and in mouse liver in vivo, including new adducts at C-8 and N-7 of guanine residues. *Cancer Res.* **1985**, *45*, 3096–3105.

(88) Wiseman, R. W.; Miller, E. C.; Miller, J. A.; Liem, A. Structure-activity studies of the hepatocarcinogenicities of alkenylbenzene derivatives related to estragole and safrole on administration to preweanling male C57BL/6J × C3H/HeJ F1 mice. *Cancer Res.* **1987**, *47*, 2275–2283.

(89) Kaledin, V. I.; Pakharukova, M. Yu.; Pivovarova, E. N.; Kropachev, K. Yu.; Baginskaya, N. V.; Vasilieva, E. D.; Ilnitskaya, S. I.; Nikitenko, E. V.; Kobzev, V. F.; Merkulova, T. I. Correlation between hepatocarcinogenic effect of estragole and its influence on glucocorticoid induction of liver-specific enzymes and activities of FOXA and

HNF4 transcription factors in mouse and rat liver [translated from Russian]. *Biochemistry (Moscow)* **2009**, *74*, 377–384.

(90) Paini, A.; Punt, A.; Viton, F.; Scholz, G.; Delatour, T.; Marin-Kuan, M.; Schilter, B.; van Bladeren, P. J.; Rietjens, I. M. A physiologically based biodynamic (PBBD) model for estragole DNA binding in rat liver based on in vitro kinetic data and estragole DNA adduct formation in primary hepatocytes. *Toxicol. Appl. Pharmacol.* **2010**, *245*, 57–66.

(91) Punt, A.; Freidig, A. P.; Delatour, T.; Scholz, G.; Boersma, M. G.; Schilter, B.; van Bladeren, P. J.; Rietjens, I. M. A physiologically based biokinetic (PBBK) model for estragole bioactivation and detoxification in rat. *Toxicol. Appl. Pharmacol.* **2008**, *231*, 248–259.

(92) Zeller, A.; Horst, K.; Rychlik, M. Study of the metabolism of estragole in humans consuming fennel tea. *Chem. Res. Toxicol.* **2009**, *22*, 1929–1937.

(93) Rietjens, M. C. M.; Punt, A.; Schilter, B.; Scholz, G.; Delatur, T.; van Bladeren, P. J. In silico methods for physiologically based biokinetic models describing bioactivation and detoxification of coumarin and estragole: Implications for risk assessment. *Mol. Nutr. Food Res.* **2010**, *54*, 195–207.

(94) Opinion of the Scientific Committee on Food on Methyleugenol (4-Allyl-1,2-dimethoxybenzene), SCF/CS/FLAV/FLAVOUR/4 ADD1 FINAL, Brussels, Belgium, 2001.

(95) Mansfeld's World Database of Agriculture and Horticultural Crops, http://mansfeld.ipk-gatersleben.de/pls/htmldb_pgrc/f?p=185:46:3969706415337287::NO::module,mf_use,source,taxid,akzname:mf,,volksnam,32343,Artemisia, accessed June 4, 2011.

(96) European Patent Office, www. espacenet.com, accessed March 8, 2011.

(97) Jaeger, R.; Purpura, M. et al. *Synergistic enhancement of cellular ergogenic nutrient uptake, like creatine or carnitine, with tarragon*. Patent Applicant: PhytoLab GmbH & Co. KG, WO2009147229 (A1), 2009-12-10.

(98) Pischel, I.; Walbroel, B. et al. *Water-soluble extracts of Artemisia dracunculus (tarragon) for improvement of glucose metabolism*, Patent Applicant: Finzelberg GmbH & Co. KG, WO2009147228 (A1), 2009-12-10.

(99) Ribnicky, D.; Logendra, S. et al. . *Compounds from an extract of Artemisia and methods fortreating disorders*, Patent, Applicant: Rutgers the States University WO2007109217 (A2) 2007-09-27; WO2007109217 (A3) 2008-01-17.

(100) The NCAT Sustainable Agriculture Project, http://attra.ncat.org/attra-pub/gh-herbhold.html, accessed April 23, 2011.

(101) *Bulletin MNS, Spices Market News Service*, bimonthly ed.; International Trade Centre: Geneva, Switzerland, 2009; pp 16.

(102) *CBI Market Survey, The Spices and Herbs Market in the EU*, The Netherlands, 2009; pp 14.

(103) Verlet, N. Commercial aspects of essential oils. In *Volatile Oil Crops*; Hay, Waterman, Eds.; Longman Scientific and Technical: London, U.K., 1993.

(104) Felder, D. *Screening of Different Artemisia dracunculus L. Extracts for Antidiabetic Effects in Rats*. Master's thesis, University of Basel, Switzerland, 2009.

(105) Weinöhrl, S. E. *Screening of Various Extracts of Artemisia dracunculus L. for Antidiabetic Activity in Rats*. Diploma thesis, University of Vienna, Austria, 2010.

(106) Venskutonis, R.; Gramshaw, J. W.; Dapkevicius, A.; Baranauskiene, M. Composition of volatile constituents in tarragon (*Artemisia dracunculus* L.) at different vegetative periods. In *Flavour Science. Recent Developments*; Proceedings of the Eighth Weurman Flavour Research Symposium, Reading, U.K., July 23−26, 1996' Taylor, A. J., Mottram, D. S., Eds.; Royal Society of Chemistry: Cambridge, U.K., 1996; pp 46−51.