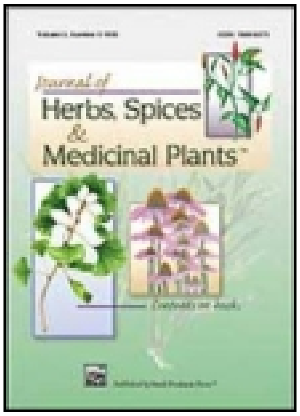

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An Overview of Agastache Research

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REVIEW

An Overview of *Agastache* Research

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ABSTRACT. A comprehensive review of research investigations on the genus *Agastache*, sections *Agastache* and *Brittonastrum*, is presented. Morphologic, cytogenetic, taxonomic, agonomic/horticultural, and biochemical studies, along with protocols for extraction and analyses of a total of 16 enzyme systems, are analyzed for the 22 morphologically distinct, diploid (haploid chromosome number of n = 9) *Agastache* species. In addition, the extraction procedures of flavonoids and terpenoids (common constituents of many medicinal plants with biological effects demonstrated in humans or animals) from inflorescences, leaves, stems, and roots of *Agastache* are surveyed. Details on the safety and

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uses of methylchavicol (estragole), the main constituent among the 77 compounds reported in the essential oil of *Agastache*, in the food industry are included and the herbal, flavoring, and medicinal uses of *Agastache* per se are summarized. *[Article copies available for a fee from The Haworth Document Delivery Service: 1-800-342-9678. E-mail address: getinfo@haworthpressinc.com]*

KEYWORDS. Carcinogenicity, electrophoresis, GRAS, methylchavicol, pharmaceutical

INTRODUCTION

The genus *Agastache* (Lamiaceae) includes 22 species of aromatic herbaceous perennials, almost exclusively native to North America. Research on this genus has been conducted in many parts of the world, but has been disproportionately focused on only a few species. *Agastache foeniculum* and *rugosa* have been the main foci of studies on the uses, composition, and cultivation; other species, such as *A. palmeri* and *parvifolia*, are generally only encountered in floristic or taxonomic studies. In this report, a critical review of much of the current and past work on *Agastache* is presented, with a desire to provide the reader with an overview that summarizes the description, taxonomy, biochemistry, uses, and agronomic and horticultural aspects of this increasingly popular genus. Extensive references to published studies on all aspects of the genus are provided for those readers needing more detail.

An increasing number of publications from many nations indicates that *Agastache* is a candidate for large-scale cultivation as a source of nectar for honey bees (3) and as an aromatic plant for essential oils constituents, such as methylchavicol and linalool, important in the flavoring and perfume industries (11,55,59,78,92). This report emphasizes studies focused on food, flavoring, and fragrance rather than studies related to use as a bee forage for two reasons: the interests of the readers of this journal and the existence of a recent comprehensive review of *Agastache* as a bee forage (3,4,5).

MORPHOLOGY, CYTOGENETICS, AND TAXONOMY

Members of the genus *Agastache* are robust perennial plants with upright growth habit and oppositely arranged oval to triangular leaves.

Of the two sections in the genus, section *Brittonastrum* includes species with leaf laminas varying in size from 2 to 6 cm long (70). The other section, *Agastache*, has species ranging in laminar size from 1 to 15 cm long (86). Stems in the genus *Agastache* are simple or branched. Under greenhouse conditions, the amount of branching seems quite variable both within and between populations (86). *Agastache* species possess squarish stems and creeping root systems resembling other mints, but without the invasiveness common to many related genera (83). The inflorescences of *Agastache* are located in the terminal tips, differing from many other mint species that flower from axillary buds (37,38).

Lint and Epling (53) described the flowers of *Agastache* species as being in sessile or pedunculated verticils with either whitish or colored calyces and rose, violet, or white corollas. The inflorescences of section *Agastache* are usually spike-like in appearance, being composed of very compact verticillasters. Less frequently, the inflorescences are moniliform. Often the lower verticillasters are remote, but this does not occur with much systematic regularity (86). Section *Brittonastrum* possesses inflorescences either continuous and spikelike to brushlike or discontinuous and moniliform to loosely ramified, having their lower cymose clusters often separated by greater distance than those higher in the inflorescences (69). *Agastache* inflorescences contain many small blossoms that open over a prolonged period of time. Widrlechner (90) reported flowering periods for *A. foeniculum* and *rugosa* extending more than 80 days from mid-June to mid-September. The flowering period of *A. nepetoides*, however, was reported to be shorter than 45 days (90). *Agastache pallida* was reported to flower from mid-June to late August (38).

Cytogenetic studies of members of both sections of the genus *Agastache* reported all members of the genus as being diploid organisms. Vogelmann (87) described the procedures for fixing and staining chromosomes from buds and root tips of *Agastache* section *Agastache*. For the eight species of section *Agastache*, Vogelmann (87) reported the haploid chromosome number to be n = 9. Sanders (69) reported the haploid number of chromosomes for 12 section *Brittonanstrum* species as also being n = 9. The length of the chromosomes at metaphase I in section *Agastache* is reported to range between 1 and 2 microns (87). Similar ranges in the length of the chromosomes have also been reported (69) for species of section *Brittonastrum*.

Cantino et al. (10) in a recent review of the genera of Lamiaceae, classified the genus *Agastache* as being in the subfamily Nepetoideae of the Mentheae tribe. Results of a molecular systematic study of subfamily Nepetoideae revealed that the most closely related genus to *Agastache* seems to be Glechoma (47). These results are based on a single molecular marker (the *rbcL* gene), and studies incorporating additional markers may lead to different conclusions.

The most recent taxonomic study of the entire genus, conducted by Lint and Epling (53) in 1945, divided the genus into two sections, *Brittonastrum* and *Chiastandra*. Following the International Code of Botanical Nomenclature, section *Chiastandra* is more properly named section *Agastache*. Section *Agastache* has flowers with the lower stamens ascending under the upper lip of the corolla and the upper stamens thrust down, exerted between them. Section *Brittonastrum* has flowers with parallel stamens, with both pairs thrust similarly out from the tube (53). According to Lint and Epling (53), eight species form section *Agastache* and 14 species form section *Brittonastrum*. Members of section *Agastache* were noted to present little intraspecific variation in comparison with the species of section *Brittonastrum* (53).

All species of *Agastache* are native to North America, except for *A. rugosa*, which is native to eastern Asia. The other species of section *Agastache* are native to western, north central, and eastern North America, whereas the species of section *Brittonastrum* are native to the southwestern part of North America, including Mexico.

More recent taxonomic studies of *Agastache*, conducted by Vogelmann (86) and Sanders (70) for sections *Agastache* and *Brittonastrum*, respectively, generally agree with conclusions of Lint and Epling (53) (Table 1). Vogelmann (86) noted that the species *A. parvifolia*, *occidentalis*, and *urticifolia* of Lint and Epling (53) closely resemble each other and could possibly be combined into one highly polymorphic species with three subspecies. In that instance, section *Agastache* would include only six species: *A. cusickii*, *foeniculum*, *nepetoides*, *rugosa*, *scrophulariifolia*, and *urticifolia* (86).

In section *Brittonastrum*, a taxonomic study conducted by Sanders (70) produced six significant differences in the taxonomy of the section when compared with Lint and Epling's (53) treatment. Those points were (1) division of section *Brittonastrum* into five series; (2) recognition of a new species, *A. eplingiana*, as a result of new collections made since 1950; (3) reestablishment of *A. pallida* as the

TABLE 1. An enumeration of *Agastache* taxa.

Agastache section Agastache[1]	*Agastache section Brittonastrum*[2]
A. cusickii (Greenm.) Heller	*A. aurantiaca* (A. Gray) Lint & Epling
A. foeniculum (Pursh) Kuntze	*A. breviflora* (A. Gray) Epling
A. nepetoides (L.) Kuntze	*A. cana* (W.J. Hooker) Wooton & Stand.
A. occidentalis (Piper) Heller	*A. coccinea* (Greene) Lint & Epling
A. parvifolia Eastw.	*A. eplingiana* R. W. Sanders
A. rugosa (Fisher & Meyer) Kuntze	*A. mearnsii* Wooton & Stand.
A. scrophulariifolia (Willd.) Kuntze	*A. mexicana* (Humb., Bonpl., & Kunth) Lint & Epling
A. urticifolia (Bethman) Kuntze	*A. micrantha* (A.Gray) Wooton & Standl.
	A. palmeri (B.L. Robinson) Lint & Epling
	A. pallida (Lindl.) Cory
	A. pallidifora (Heller) Rydberg
	A. pringlei (Briq.) Lint & Epling
	A. rupestris (Greene) Standley
	A. wrightii (Greenm.) Wooton & Standley

[1] Data of Vogelmann (86) and Sanders (70).

correct name for the most common representative of the genus in western Mexico; (4) *A. mearnsii* as a species distinct from *A. pallidifora*; (5) partition of variation in *A. pallidifora* into a hierarchy of two subspecies with two and three varieties each, rather than into four equal subspecies; and (6) formal recognition of geographic races as varieties in *A. micrantha, pallida, palmeri,* and *pringlei.*

Vogelmann and Gastony (88) conducted a biosystematic study of section *Agastache*, employing starch gel electrophoresis of isozymes to assess genetic relationships among those species and to estimate the amount of genetic divergence between North American and Asian taxa. Parameters of genetic diversity, such as total heterogeneity, average number of alleles per locus, and percentage polymorphic loci, as well as descriptions of genetic structure and types of mating system were reported for all the species of section *Agastache* (88). *Agastache nepetoides* and *rugosa* had the lowest levels of heterozygosity with average values for heterozygosity/locus/individual of 0.008 and 0.000, respectively. In contrast, the highest levels of heterozygosity were observed in *A. cusickii, occidentalis*, and *parvifolia* with values of 0.166, 0.122, and 0.107, respectively. Vogelmann and Gastony (88) concluded that species of section *Agastache* from the western United States are much more polymorphic with respect to the number of alleles per locus than are those from eastern North America or eastern Asia. Under greenhouse conditions, the four western United States species, *A. cusickii, occidentalis, parvifolia*, and *urticifolia*, rarely self-pollinate. Of the species that more commonly self, *A. nepetoides* is evidently the most efficient self-pollinator (88). In studies on the breeding system and reproductive biology of Canadian Lamiaceae, Gill (32,33) reported that *A. foeniculum* is normally an outbreeding insect-pollinated species, but that bagged plants produced a small number of seeds; *A. nepetoides* is a self-compatible and self-pollinating species; and *A. urticifolia* is an outbreeder that produced no seed from bagged plants.

Electrophoretic data led to the partition of section *Agastache* into four distinctive groups: *A. nepetoides* forms one group, *A. scrophulariifolia* and *foeniculum* form a second group, the four western species form a third group, and *A. rugosa* alone forms the final group. *Agastache rugosa* from eastern Asia is substantially different from the other three groups and seems to be slightly more similar to the eastern rather than the western North American populations (88).

In Mexico, taxonomic research by Bye et al. (8) on ethnobotanical samples of the species *A. mexicana* in Mexican markets have revealed a new taxon of this species, *A. mexicana* subsp. *xolocotziana* Bye et al., that differs from typical *A. mexicana* morphologically, chemically, and pharmacologically. Fuentes-Granados and Widrlechner (20) estimated patterns of genetic diversity in *A. foeniculum*, described the type of mating system for this species, and determined the biosystematic relationships among populations of *A. foeniculum* maintained by the U.S. National Plant Germplasm System. Among and within the 11 populations of *A. foeniculum*, significant genetic diversity was observed with seven polymorphic loci of 19 evaluated (20). The mating system of *A. foeniculum* was reported as being generally typical of a cross-pollinated species (20).

Although *Agastache* has been the subject of considerable taxonomic study, a surprising degree of misidentification of these species still occurs, especially in European and North American horticulture. No *Agastache* species is native to Europe, and species of *Agastache* are frequently misidentified with Europeans cultivating *A. rugosa* under the names *foeniculum* or *scrophulariifolia* (19). Straightforward and reliable morphological keys for the identification of *Agastache* species have been presented by Lint and Epling (53), Vogelmann (86), and Sanders (70). Key characteristics can help distinguish among three of the most commonly cultivated *Agastache* species (Table 2).

BIOCHEMICAL STUDIES

An electrophoretic survey of enzyme variability of *Agastache* section *Agastache* was made by Vogelmann and Gastony (88) to determine whether four western taxa could be distinguished electrophoretically and to determine the amount of genetic divergence between American and Asian species. As part of this project, Vogelmann (85) described extraction procedures, electrophoretic separation, and staining protocols for 13 isozyme systems (Table 3). Senechal (73) employed nine isozyme systems to discriminate between sterile interspecific hybrids involving *A. rugosa* and *foeniculum* and the two parental species and to help determine the parentage of individual plants observed to have characters distinct from either parent. Fuentes-Granados and Widrlechner (20) used isozymes to determine the diversity among and within populations of *A. foeniculum* maintained in the U.S. National Germplasm System, reporting extraction procedures, electrophoretic mobility, and staining protocols for 11 enzyme systems encompassing a total of 19 loci. The inheritance of a malate dehydrogenase variant in *A. rugosa* has been reported by Fuentes-Granados and Widrlechner (22). Among all four studies, protocols for 16 enzyme systems have been described for *Agastache* section *Agastache*.

Flavonoids, an ubiquitous class of plant products often imparting a yellow hue, are common constituents of many medicinal plants, including *Agastache*, with diverse biological effects demonstrated in humans or animals. Effects of flavonoids include antiallergenic, antianginal, anti-inflammatory, antihepatotoxic, antimicrobial, antiulcer, antiviral, estrogenic, and spasmolytic (15,64). Flavonoids are of interest in the investigation of disease processes and as potential new drugs (15,64). The biological activity of these compounds may often be related to a tendency to inhibit multiple enzyme systems including hydrolases, ATPases, cAMP phosphodiesterases, kinases, lipases, and transferases (15,64).

TABLE 2. Key characteristics to help distinguish *A. foeniculum*, *mexicana*, and *rugosa*.

Taxon	Leaf blade base	Leaf blade margin	Leaf blade color and texture	Corolla color	Corolla tube length
A. foeniculum	cuneate to truncate	serrate with mucronate serrations	upper surface–bright green, glossy, glabrous lower surface–whitened with dense felt-like hairs	blue-violet to pale blue-violet	6.5-10 mm
A. mexicana	rounded to truncate	dentate to crenate-serrate along lower half of blade, entire above	upper surface–dark green, nearly glabrous lower surface–resembling upper, but lighter in color	deep orange-pink to deep magenta or bright red infrequently pink or white	19-27 mm
A. rugosa	rounded to (mostly) cordate	coarsely cre-nate to coarsely serrate	upper surface–dull green, rugose, nearly glabrous lower surface–light green, with curled hairs along veins	blue-violet to purple, infrequently pure white	7-10 mm

TABLE 3. Enzyme systems of *Agastache* section *Agastache*.

Enzyme system	Reference
Aconitase (EC 4.2.1.3)	73,85
Alcohol dehydrogenase (EC 1.1.1.1)	20
Aspartate aminotransferase (EC 2.6.1.1)	20,73,85
Catalase (EC 1.11.1.6)	20
Glutamate dehydrogenase (EC 1.4.1.2)	20,85
Glyceraldehyde-3-phosphate dehydrogenase (NAD) (EC 1.2.1.12)	85
Glyceraldehyde-3-phosphate dehydrogenase (NADP) (EC 1.2.1.13)	85
Isocitrate dehydrogenase (NADP) (EC 1.1.1.41)	20,73,85
Leucine aminopeptidase (EC 3.4.11)	85
Malate dehydrogenase (EC 1.1.1.37)	20,22,73,85
Menadione reductase (EC 1.6.99.2)	20,73
Phosphoglucoisomerase (EC 5.3.1.9)	20,85
Phosphoglucomutase (EC 2.7.5.1)	20,73,85
6-Phosphogluconate dehydrogenase (EC 1.1.1.44)	20,85
Shikimate dehydrogenase (EC 1.11.1.25)	20,73,85
Triose-phosphate-isomerase (EC 5.3.11)	20,73

As components of foods, flavonoids usually occur as O-glycosides, with D-glucose as the most frequent sugar residue, in leaves and outer parts of plants (40). Flavonoids have been reported to contribute to the astringency of tea powders, and the flavonoids of citrus plants are notable because of the potential use of these compounds as synthetic sweeteners (19,68). The polyphenolic character of flavonoids and the ability of these compounds to sequester metals have aroused interest in possible value as antioxidants for fats and oils (19). Flavonoids are relatively stable during heat processing in aqueous canned foods, but to date little research has been done on this aspect (19).

In biosystematic studies of *Agastache* section *Agastache*, Vogelmann (86) investigated variation in flavonoid composition and extracted the flavonoids, luteolin-7-O-glucoside, apigenin-7-O-glucoside, acacetin, acacetin-7-O-glucoside, diosmetin-7-O-glucoside, and an unidentified aglycone from leaves, stems, and inflorescences of the eight species of *Agastache* section *Agastache*. Zakharova et al. (93) isolated acacetin, tilianine, agastachoside, and acacetin 7-O-rutinoside from *A. rugosa*. The presence of acacetin, tilianine, and agastachoside in the roots of *A. rugosa* has been confirmed by Zou and Cong (95). Itokawa et al. (45) isolated two new glucosylflavones from *A. rugosa*, isoagastachoside and agastichin, and Ishitsuka et al. (44) isolated a unique flavonoid, 4′, 5-dihydroxy-3,3′,7-trimethoxyflavone, from the leaves of *A. rugosa*.

According to Sticher (77), various mono-, sesqui-, di-, and triterpenes possess more than 26 different pharmacological activities, including analgesic, antibiotic, anticancer, anti-inflammatory [as reviewed by Duwiejua and Zeitlin (15)], hypotensive, and sedative. Terpenes are the active ingredients of many medicinal plants and help explain the traditional use of such plants to treat a variety of complaints including coughs, fever, hypertension, skin diseases, and wounds (64).

Extraction procedures and analyses of diterpenes and triterpenes from *Agastache* have been described (30,50). Lee et al. (50) isolated the diterpenoid quinone, agastaquinone, and the oxime derivative of agastaquinone, compounds that have demonstrated, general nonspecific cytotoxic activity against five human cancer cell lines. Ganeva et al. (30) isolated the triterpenoid and sterol constituents in a petrol extract of the aerial parts of *A. foeniculum*, including the triterpenes, α-amyrin, β-amyrin, and phytol, and the sterols, campesterol, campestanol, stigmastanol, stigmasterol, and sitosterol. β-sitosterol was isolated from the roots of *A. rugosa* by Zou and Cong (95), along with two other sterols, daucosterol and a newly described compound, dehydroagastol. The high concentration of triterpenoids (35.8% of the extract) and the various therapeutical properties of these compounds led Ganeva et al. (30) to propose the use of the petrol extract for preparation of cosmetics.

Tannins display a remarkable array of biological activities (61). Important effects include antidiarrheal activity, detoxification of venoms and bacterial toxins, modification of enzyme dynamics, inhibition of mutagenicity, antitumor effects, viral inhibition, free-radical scavenging, and modification of lipid metabolism. Isolation and purification protocols to measure tannins from the leaves of *A. rugosa* have been described by Okuda et al. (60). The primary tannin isolated from

A. rugosa, rosmarinic acid, is known to inhibit the peroxidation of linoleic acid (26) through free-radical scavenging.

APPLICATIONS

Essential oil. The essential oils of *Agastache* are of great economic value and research interest. The fragrance of crushed *Agastache* leaves and inflorescences often has an attractive, anise-like aroma (88,92). Several studies (11,23,24,49,55,59,78,79,92) have reported the composition and content of the essential oils of *A. foeniculum* and *rugosa* from analyses using equilibrium headspace, solvent extraction, and hydrodistillation. In general, analyses using equilibrium head space yield the lowest number of compounds.

A total of 77 compounds has been reported as components of the essential oils of *Agastache* (Table 4). Methylchavicol, [benzene, 1-methoxy-4-(2-propenyl)] (estragole), and limonene have been consistently reported as the main components of *Agastache* essential oils, but considerable variability exists in the composition and content of the volatiles. Wilson et al. (92) described populations of *A. foeniculum* in which methylchavicol was the major component of the essential oils, but present at a much lower concentration than typical for the species. In populations with low methylchavicol, the amount of myrcene in the essential oils was higher than in other populations. Tucker (82) remarked that the aroma of *A. foeniculum* resembles tarragon more than anise, a plant high in trans-anethole, but not methylchavicol. A resemblance to tarragon could result from variability in aromatic composition caused by genetic and/or environmental factors.

Fujita and Fujita (23) analyzed four populations of *A. rugosa*, identified under the synonym *A. formosanum* Hay, that displayed an essential oil chemotype dominated by menthone and pulegone and derivatives of these compounds. Later, an atypical population of *A. rugosa* that contained very high amounts of methyleugenol in the essential oil (85-92%) was also reported (25). Compared with typical populations of *A. rugosa* which contain levels of methylchavicol reaching 95 percent, this high-methyleugenol population was totally different, and thus was classified as a new variety of *A. rugosa*, provisionally named *A. rugosa* var. *methyleugenolifera*.

Variability in the content and composition of the oils is observed among different populations and species of *Agastache* and among

TABLE 4. Components of the essential oils of *Agastache*.

Compound	Kovats indice[1]	Species	Reference
trans-anethole	1270	*A. foeniculum*	55,59, 79
anisaldehyde	1234	*A. foeniculum, A. rugosa*	55,89
benzaldehyde	974	*A. foeniculum*	55
borneol	1164	*A. scrophulariifolia*	49
bornyl acetate	----	*A. foeniculum, A. rugosa*	11,92
β-bourbonene	1406	*A. foeniculum, A. nepetoides, A. rugosa*	11, 14, 49
butanol	655	*A. foeniculum*	59
γ-cadinene	1518	*A. foeniculum, A. rugosa*	24,49
δ-cadinene	1524	*A. foeniculum A. nepetoides A. rugosa*	25,49, 59,79
α-cadinol	----	*A. foeniculum, A. rugosa*	11,14, 55,79, 92
δ-cadinol	----	*A. foeniculum, A. nepetoides, A. rugosa*	14,79
calamenene	1518	*A. rugosa*	24
camphene	954	*A. foeniculum, A. mexicana, A. nepetoides*	11,49, 54,55, 92
camphor	1136	*A. rugosa*	14
carvacrol	1297	*A. foeniculum*	59
carvone	1228	*A. rugosa*	14
β-caryophyllene	1428	*A. foeniculum, A. mexicana, A. nepetoides A. rugosa, A. scrophulariifolia, A. urticifolia*	11,24, 25,49, 55,59, 79,92
caryophyllene oxide	----	*A. foeniculum, A. nepetoides*	49,79
chavicol	1238	*A. rugosa*	89

Compound	Kovats indice[1]	Species	Reference
methoxycinnamaldehyde	1504	*A. rugosa*	14,89
methoxycinnamic alcohol	1300	*A. rugosa*	89
citral	1222	*A. foeniculum, A. rugosa*	92
citronellal	1137	*A. mexicana*	54
1, 8-cineole	1027	*A. mexicana, A. rugosa, A. scrophulariifolia*	14,49, 54
α-copaene	1398	*A. nepetoides*	49
p-cymene	1020	*A. foeniculum, A. mexicana, A. rugosa*	23,25, 49,54
damascenone	----	*A. foeniculum, A. nepetoides, A. rugosa*	11
dehydroterpineol	----	*A. foeniculum, A. rugosa*	11
α-p-dimethylstyrene	1080	*A. scrophulariifolia*	49
β-elemene	----	*A. foeniculum, A. mexicana, A. rugosa*	24,49
γ-elemene	----	*A. foeniculum*	79
elemol	805	*A. scrophulariifolia*	49
eugenol	1351	*A. foeniculum*	59, 79
(E)-β-farnesene	----	*A. foeniculum, A. rugosa*	24,49
furfural	815	*A. mexicana*	54
geraniol	1243	*A. foeniculum*	59,79
germacrene A and B	----	*A. foeniculum*	59
germacrene D	----	*A. foeniculum, A. mexicana, A. nepetoides, A. rugosa, A. scrophulariifolia, A. urticifolia*	49,79
ethyldimethyl heptane	----	*A. foeniculum*	55
dimethyl hexanal	----	*A. foeniculum*	55
hexanol	858	*A. scrophulariifolia*	49
cis-β,γ-hexenol	----	*A. rugosa*	25
α-humulene	1465	*A. foeniculum, A. rugosa*	14,25, 59,79

TABLE 4 (continued)

Compound	Kovats indice[1]	Species	Reference
β-humulene	----	*A. rugosa*	24
β-ionone	1474	*A. foeniculum*	79
isomenthone	----	*A. foeniculum, A. mexicana, A. rugosa, A. scrophulariifolia A. urticifolia*	11,14, 23,49, 78
cis-isopulegone	----	*A. mexicana, A. rugosa, A. scrophulariifolia*	23,49
trans-isopulegone	----	*A. mexicana, A. rugosa, A. scrophulariifolia*	49
jasmone	1378	*A. rugosa*	89
limonene	1030	*A. foeniculum, A. mexicana, A. nepetoides, A. rugosa, A. scrophulariifolia, A. urticifolia*	11,14, 23,25, 49,54, 55,59, 78,79, 89,92
linalool	1092	*A. foeniculum, A. mexicana, A. nepetoides, A. rugosa, A. scrophulariifolia*	11,14, 25,49, 55,59, 79,92
menthofuran	----	*A. scrophulariifolia*	49
menthol	1171	*A. rugosa*	14
menthone	1143	*A. foeniculum, A. mexicana, A. rugosa, A. scrophulariifolia, A. urticifolia*	23,49, 54,55, 78,79
methylchavicol	1182	*A. foeniculum, A. rugosa, A. scrophulariifolia*	11,14, 23,25, 49,55, 59,78, 79,89, 92
methyleugenol	----	*A. foeniculum, A. rugosa*	11,25, 49,59, 79
myrcene	986	*A. foeniculum, A. mexicana, A. nepetoides, A. rugosa, A. scrophulariifolia, A. urticifolia*	11,49, 55,59, 79,92

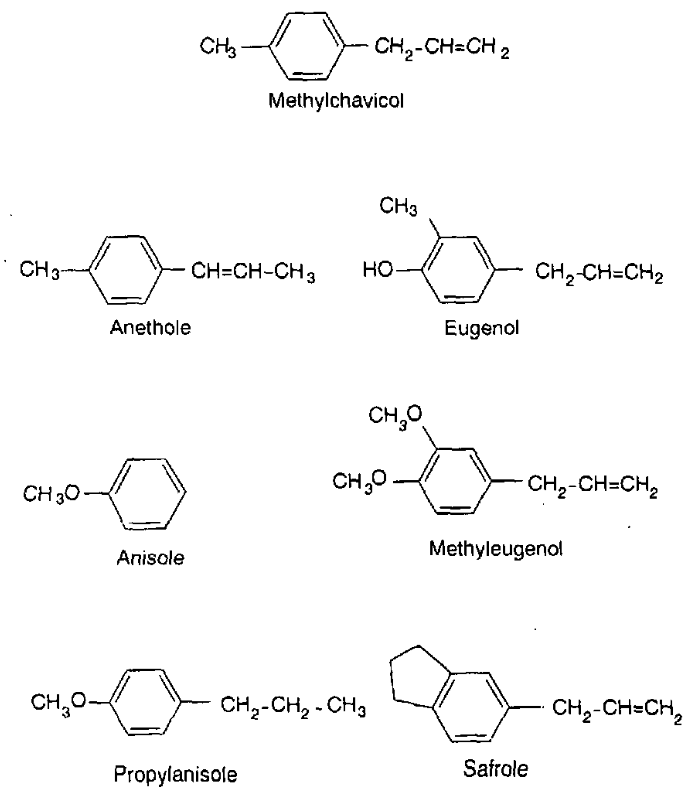
Compound	Kovats indice[1]	Species	Reference
ocimene	1025	*A. foeniculum, A. nepetoides, A. rugosa, A. urticifolia*	11,49, 55
3-octanol	1041	*A. foeniculum, A. nepetoides, A. rugosa, A. urticifolia*	14,23, 25,49
3-octanone	991	*A. foeniculum, A. rugosa*	14,23, 25,49, 59,79
1-octen-3-ol	968	*A. foeniculum, A. mexicana, A. rugosa, A. scrophulariifolia*	14,23, 49,79
1-acetate octen-3-yl	----	*A. foeniculum, A. rugosa, A. scrophulariifolia*	1,49,58, 79
octen-7-4-ol	----	*A. foeniculum, A. rugosa*	25
octyl-3-acetate	----	*A. scrophulariifolia*	49
α-pinene	942	*A. foeniculum, A. mexicana, A. nepetoides, A. rugosa, A. scrophulariifolia, A. urticifolia*	11,14, 23,25, 49,55, 59,78, 89,92
β-pinene	981	*A. foeniculum, A. mexicana, A. nepetoides, A. rugosa, A. scrophulariifolia, A. urticifolia*	23,49, 54
pinocamphone	----	*A. foeniculum*	59
piperitone	1247	*A. mexicana, A. rugosa, A. scrophulariifolia, A. urticifolia*	14,23, 49
pulegone	1230	*A. foeniculum, A. mexicana, A. rugosa, A. scrophulariifolia, A. urticifolia*	11,23, 49,54, 78
sabinene	976	*A. foeniculum*	49,59
safrole	1278	*A. rugosa*	25
spathulenol	----	*A. foeniculum, A. nepetoides*	11,55, 79
α-terpinene	----	*A. foeniculum*	49
terpinen-4-ol	1175	*A. foeniculum*	49
α-terpineol	1185	*A. scrophulariifolia*	49
thymol	1287	*A. foeniculum*	59
α-ylangene	----	*A. rugosa*	24

[1] Kovats Indices calculated on a methyl-silicone column, OV 101.

different plant parts. Microanalysis of essential oils in the secretory trichomes of *A. foeniculum* (79) determined that these glandular hairs contain both γ-elemene (8.1%) and (E)-anethole (19.6%), compounds found only in trace amounts in a standard hydrodistillate from whole leaves. Wilson et al. (92) reported marked differences in the composition and content of the essential oils from inflorescences and from leaves of accessions of *A. foeniculum*. Differences in the composition and content of oils from different parts of a plant is not unique to *Agastache*; several authors have reported differences in the amount and composition of the oils from flowers and leaves (67,74). Seasonal and other environmental factors have also been reported to influence the content and composition of the oils of aromatic plants (2,67), including *Agastache* (57,78). Although a wide variety of compounds is reported in the oils of *Agastache*, most reports agree that methylchavicol plays a major role in defining the typical anise-like aroma. Other compounds, however, are important in giving balance and stability to the oils. Weyerstahl et al. (89) reported that methylchavicol was the predominant contributor to the aroma of oil from *A. rugosa*, but that trace constituents, such as anisaldehyde, chavicol, p-methoxy cinnamaldehyde, and jasmone, were important to the aroma.

Flavorings, fragrances, and pharmaceutical. Much of the culinary and fragrance value of *Agastache* is due to the presence of methylchavicol (11,55,92), an oil constituent that has become a component of perfumes and a flavoring for foods and liqueurs (55). Methylchavicol and other alkylbenzone derivatives are commnly observed in natrual and synthetic food products (Figure 1). Menghini et al. (56) noted that methylchavicol was also of interest to the pharmaceutical industry because the compound can easily be converted to its isomer, trans-anethole, a chemical with both flavoring and medicinal uses. Hall and Oser (35) listed methylchavicol as a substance generally recognized as safe (GRAS) in a report of the status of flavoring substances under the 1958 Food Additives Amendment to the Food, Drug and Cosmetic Act and noted that methylchavicol was listed as a food ingredient in ten technical reports in concentrations ranging from 10 to 150 ppm. FEMA (17) reported that methylchavicol was used in baked goods at 413 ppm, frozen dairy products at 120 ppm, soft candy at 300 ppm, gelatin and puddings at 166 ppm, and nonalcoholic beverages at 129 ppm, with an annual volume usage in the U.S. of 3150 kg and an estimated daily per capita intake of 0.07 mg. Opdyke (62) has summa-

FIGURE 1. Methylchavicol and other related compounds.



rized usual and maximum concentrations of methylchavicol in soaps, detergents, creams, lotions, and perfumes, and also presented some biological data for the compound. Acute oral and dermal LD_{50} values for rats and rabbits has been observed to be 1.23 g/kg and over 5 g/kg, respectively. No irritation nor sensitization reactions were induced in human volunteers by methylchavicol at a concentration of 3 percent in petrolatum (62). In Russia, Pisarnitskii et al. (65) described the use of methylchavicol as the flavorant, used to stabilize aroma and improve microbial stability, in a patent for the manufacture of a nonalcoholic carbonated beverage.

Some controversy regarding the hepatocarcinogenicity in mice of methylchavicol and related naturally occurring and synthetic alkenylbenzene derivatives, such as safrole, eugenol, anethole, and methyleugenol has occurred (58). Methylchavicol and the hydroxy and epoxy derivatives may be carcinogenic when fed to mice at relatively high concentrations (94). Experiments conducted by To et al. (80) to determine mutagenicity of trans-anethole, methylchavicol, eugenol, and safrole, detected significant differences in direct bacterial and microsomal mutagenicity counts, but event frequencies were low and of uncertain biological significance. To et al. (80) stated that, based on a criterion established by Gabridge and Legator (27), none of the compounds studied could be classified as mutagens.

Sangster et al. (72) investigated the metabolic disposition of trans-anethole, methylchavicol, and propylanisole in human volunteers at doses resembling typical human intake levels in comparison with similar studies conducted with mice and rats, species more commonly used for safety assessment, concluding that all three compounds were readily absorbed from the gastrointestinal tract, indicated by rapid and extensive elimination as various metabolites in urine and as exhaled carbon dioxide (72). The compounds were completely metabolized by oxidative demethylation and oxidation of their side chains before elimination. In humans, elimination rates of these compounds were far faster than in other test animals. A high proportion of the dose equivalent to normal human dietary intake was excreted in urine and exhaled as carbon dioxide within 12 hours, six times more rapidly than in mice and rats. Detailed examination of methylchavicol metabolism concentrated upon the formation of 1′-hydroxy-methylchavicol, a metabolite responsible for the hepatocarcinogenicity of methylchavicol in mice. In the two human volunteers examined by Sangster et al. (72), 1′-hydroxy-methylchavicol accounted for only 0.3 percent of the dose. In rodents, increasing methylchavicol dosages led to disproportionate increases in the formation of 1′-hydroxy-methylchavicol. At normal dietary intake levels in humans, however, the metabolite accounted for much less of a dose than for rodents receiving the smallest dose examined, clearly illustrating the problem of extrapolating rodent carcinogenicity data generated from extremely high doses to human consumption (72).

Agastache is useful *per se* for culinary purposes. Historical records (31,34) indicate that the leaves of *A. foeniculum* were used by the Northern Cheyenne and other native peoples of the upper Missouri River to make tea and to sweeten foods. More recently, Leighton (51) noted that a Woods Cree informant in Saskatchewan used the leaves to improve the flavor of commercial black tea.

Poncavage (66) described *A. foeniculum* as one of 12 easy-to-grow plants as sources of tasty and elegant teas, including the following recipe: "two parts of anise hyssop to one part of lemon balm, with maybe a touch of basil." Galambosi and Galambosi-Szebeni (28) reported that in Finland, *A. foeniculum* has been gaining practical importance as a herb since 1981, when a commercial firm began to use and trade it in various tea mixtures. Tucker (82) indicated that *A. foeniculum* could conceivably be used as a substitute for French tarragon. In New Zealand, *Agastache* has been evaluated as a potential new ornamental crop for aromatic foliage and for the strong attraction for honey bees (75). The leaves and flowers of *A. foeniculum* have been reported to be used in cakes, ices, and sweets and can be added fresh to salads and desserts for a visual and tasty accent (28,37,41,52,83).

Agastache rugosa is used for culinary and flavoring purposes in Asia. Dung et al. (14) reported the use of *Agastache rugosa* year round as a flavoring agent in Vietnam and Lee et al. (50) noted that the leaves of this plant have been used as spice for fish-based foods in Korea. Wilson (91) has stated that all *Agastache* can be used for brewing teas and tisanes, for making piquant sauces for meats, and after drying, to make potpourris.

Many reports on *Agastache* as a medicinal plant originate in Asia, where *A. rugosa* has been used to treat cancers, cholera, vomiting, fever, headache, colds, indigestion, and abdominal pain, and as a mouthwash (13,14,50,63). The Institute of Chinese Materia Medica (43) reported specific application of *Agastache* as an emetic and for the treatment of (1) fever due to heat stroke; (2) distention of the chest; (3) poor appetite; (4) nausea; (5) diarrhea; and (6) tinea on hands and feet (external use). Chinese traditional medicine, which generally relies on complex formulas that combine various medicinal plants, utilizes *A. rugosa* as a key ingredient in Huo-Hsiang-Cheng-Chi-San (42) used for treating gastrointestinal problems and related ailments and in Huo-Po-Xia-Ling-Tang (6) used for alleviating fever and chills.

A constituent of *A. rugosa* also shows promise in western medicine. Potent anti-viral activity for 4′,5-dihydroxy-3,3′,7-trimethoxyflavone (also known as Ro-090179), isolated from the leaves of *A. rugosa*, has been demonstrated on rhinoviruses and coxsackieviruses in tissue culture by Ishitsuka et al. (44). Recent research by Sandoval and Carrasco

(71) indicated that the chemical is also effective in disrupting poliovirus infection in monkey cells through action on the Golgi complex.

Species of *Agastache* native to North America have been widely employed in traditional medicine. Most North American ethnographic reports describe medicinal uses for *A. foeniculum*. Leaves of the plant were used by the Northern Cheyenne to make an infusion to treat heart conditions and chest pain from coughing (34,36) and to make poultices and sweat baths to reduce fever and induce sweating (36). The Woods Cree in Saskatchewan made infusions of *Agastache* to treat people suffering from coughing blood (51), and included flowers of the plant in Cree medicine bundles (46). In Minnesota, Wisconsin, and Ontario, the Ojibwa steeped *Agastache* roots to make a medicine for treating coughs and chest pains and used the vegetative parts to make a poultice to treat burns (12). A Cayuga informant in New York (39) noted similar use of *A. nepetoides* leaves in poultices to relieve poison ivy and other itching and a Paiute informant in Nevada (81) noted *A. urticifolia* was used to reduce swelling. *Agastache urticifolia* was harvested in Nevada to make infusions to treat indigestion and stomach pain and a boiled tea was drunk for colds (81). Ramah Navajo informants have described use of *A. pallidiflora* for the treatment of coughs, sores, and cankers, and for the reduction of fevers (84). A decoction of the roots of *A. scrophulariifolia* was made by the Meskwaki for use as a diuretic (76). A report from Mexico (9) indicates the use of *A. mexicana* to treat stomach pain, poor digestion, flatulence, anxiety, insomnia, and cardiovascular problems.

Ornamental. The genus *Agastache* includes many ornamental plants that probably deserve greater recognition and use in American landscapes because of the range of flower colors and extended bloom season into late summer (83). Flower colors of *Agastache* species include the deep mauves, blue violet, magenta, white, orange, pink, and greenish yellow of natural populations and the vivid red apricots and hot pinks of interspecific hybrids (83), providing versatility for complementing and enhancing herb and perennial gardens (83). Demand for low-maintenance plants coupled with the availability of previously unknown *Agastache* cultivars will probably increase the popularity of these plants (37,38). The long bloom periods make the plants valuable additions to borders, and the narrow, erect growth habit is easily accommodated between existing plants (38). *Agastache* selections in cultivation are generally members of section *Agastache*, but the introductions most likely to expand this popularity of the genus are members of section *Brittonastrum*, such as *A. mexicana*, *coccinea*, and *pallida* (38).

Agastache foeniculum and *rugosa*, generally with violet-blue corollas, are the most commonly cultivated species of section *Agastache* today. *Agastache foeniculum*, a perennial that becomes a rather bushy plant, reaches one meter in height and is attractive to bees and butterflies during bloom with 8 to 10 cm terminal spikes with 0.5 to 1 cm dusky blue violet flowers (83). Fresh flowers have a relatively long vase life in arrangements and dried spikes can add interest to the winter landscape with several species of birds feeding on the seeds (83). *Agastache rugosa* resembles a denser, smaller version of *A. foeniculum* and generally has purple-blue flowers, sometimes with a touch of rose color in the center (83), although white-flowered variants of *A. rugosa* have also been reported (18,22,78). Fuentes-Granados and Widrlechner (22) documented the genetic control of anthocyanin production, responsible for flower color, in one population of *A. rugosa*, concluding that inheritance of anthocyanin production was controlled by a single gene whose dominant allele expressed production of anthocyanin. Because the inheritance of anthocyanin is controlled by a single gene in this population, development of a pure line of *A. rugosa* with white flowers would be straightforward and this attractive variant could be used for cut flowers or annual display plantings (22). Senechal (73) reported that interspecific hybrids of *A. rugosa* and *A. foeniculum* are extremely colorful and flower longer periods of time than either parent.

Agastache mexicana is probably the best known member of section *Brittonastrum*. Van Hevelingen (83) indicated that many variants of the species exist, a fact reflected by the detailed taxonomic description of Sanders (70), especially for corolla color, which usually varies from deep orange-pink to deep magenta or bright red, but also includes pink and white corolla types. A selection of *A. mexicana*, Toronjil morado, is a showy ornamental useful at the back of borders (83), providing bloom from late summer to fall and a steady nectar source for butterflies and hummingbirds. *Agastache cana* and *barberi* are noted for good ornamental characteristics (83). *Agastache rupestris*, recently included in a list of plants that thrive in the variable winters and hot summers of Colorado, has been described as presenting bold brushes of sunset orange flowers from August to frost with the whole plant exuding a rich, root beer aroma and making an exotic contribution to water-conserving gardens or perennial borders (48). Other attractive cultivars originating from interspecific crosses among species of section *Brittonanstrum* and possessing good ornamental characteristics are 'Tutti-Fruti,' 'Apricot Sunrise,' 'Pink Panther,' and 'Firebird' (83).

Commercial nurseries and seed companies stocking selections of *Agastache* have been listed by Ayers and Widrlechner (5), Henning (37,38), Poncavage (66), and Van Hevelingen (83). In addition, the North Central Regional Plant Introduction Station of the United States National Plant Germplasm System, located in Ames, Iowa is responsible for the maintenance, evaluation, increase, and distribution of *Agastache* germplasm and provides seed samples for research at no cost to the requestor.

CULTIVATION

Aspects related to large-scale cultivation of *Agastache* are reported by Ayers and Widrlechner (5) and Galambosi and Galambosi-Szebeni (28,29). Aflatuni (1), Bye et al. (8), Henning (37,38), Poncavage (66), and Van Hevelingen (83) have also detailed cultural information on the genus. Well-aerated, humus-laden soils of low fertility were described by Henning (37) as most suitable to maintain persistence of *Agastache*. Species of *Agastache* from the Southwestern U.S. may also benefit from the addition of lime to the soil (37).

Field establishment of *Agastache* species can be achieved by seeding or the use of cuttings and divisions. Cuttings and divisions are the only suitable method to propagate and establish the sterile, interspecific hybrids or species of *Agastache* that do not produce seeds when grown in specific environment (83). The relatively small size of *Agastache* seed limits the success of direct seeding in the field so Ayers and Widrlechner (5) suggest that *Agastache* be established by starting seedlings in flats with subsequent transplanting to a permanent location. Experience indicates that a moist chilling treatment of *Agastache* seed will improve both total germination and germination synchrony (5). For direct seeding to be successful, the seeds must be planted very shallowly, no deeper than 0.16 cm. The seeds require a steady moisture supply during germination and thus, gentle irrigation may be required (heavy irrigation may bury seeds too deeply in soil to germinate) (5).

Weed competition can hinder field establishment of *Agastache*. Galambosi and Galambosi-Szebeni (28,29) used black plastic mulch and ridged beds to reduce the need for manual weeding of *A. foeniculum* fields by 80 percent. Mulching and ridging also increases fresh yields of *Agastache* (28), probably through increases in soil temperature, decreases in evapotranspiration, and reduction of soil compaction (29). As alternative weed control methods in *Agastache* planting, Ayers and Widrlechner (5), suggest planting into a weed-free field, use of cover crops such as buckwheat with alleleopathic effects on weeds, mechanical cultivation, and relatively dense plant populations.

Plant adaptation, diseases, and pest susceptibility are factors that should be considered before establishment of *Agastache* plantings. Winter hardiness can limit the cultivation of *Agastache* species, although, in general, species from section *Agastache* are better adapted to the northern part of North America than are members of section *Brittonastrum*. Even within section *Agastache*, variability in hardiness exits. In much of the United States, *A. rugosa* does not overwinter nearly as well as *A. foeniculum*. In contrast, in Scotland, *A. rugosa* appeared better adapted to local conditions than *A. foeniculum* (78). Henning (37,38) and Van Hevelingen (83) have reported specific hardiness zones for various *Agastache* species as well as for named cultivars.

Block et al. (7) first noted populations of *A. rugosa* susceptible to *Verticillium dahliae* (verticillium wilt). Fuentes-Granados and Widrlechner (21) have noted interspecific variability among species of *Agastache* for susceptibility to *Verticillium* and, based on studies and reports of susceptibility of *A. rugosa* to *V. dahliae*, recommend not planting *A. rugosa* in infested soils. Field and greenhouse observations suggest that *A. foeniculum* and *A. nepetoides* are less susceptible to verticillium and that these species are better choices for establishing plantings of *Agastache* for honey bee nectar, aromatic-oil production, and other herbal and medicinal uses (21). Van Hevelingen (83) has noted powdery mildew on *Agastache* grown in climates with dry, hot summers. In a review of fungi on plants and plant products in the United States, Farr et al. (16) enumerate reports of fungi detected in association with *Agastache*. Insect pests reported on *Agastache* include two-spotted beetles which feed on foliage and which occasionally congregate on flower spikes and a green aphid that can cause damage under greenhouse conditions (83).

SUMMARY AND OUTLOOK

Several sources of information on *Agastache* exist with more than 60 scientific publications available on various aspects of the genus. Studies on *Agastache* range from descriptions of morphological criteria to distinguish among the 22 species to explanations of biochemical protocols for the identification and isolation of specific chemical constituents. The need for more research to understand the range of usefulness of the genus, however, was apparent as many reports on cultivation of *Agastache* are restricted to home gardening or small-commercial operations. As demand for natural products increases and research on the value and uses of *Agastache* becomes more available, the potential of cultivation of *Agastache* species on a larger scale may be commercially viable. Limitations to large-scale cultivation of *Agastache* species exist (5), but opportunities for improved cultivation methods and plant improvement are obvioius. The genetic variability among and within species and populations of *Agastache* suggests possible genetic improvement in vegetative and oil yields, winter hardiness, and disease resistance and the development of defined populations of *Agastache* with specific chemotypes.

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