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Molecular Diversity in the Alkaloids of Turkish *Fumaria* L. Species

Türkiye'de Yetişen *Fumaria* L. Türlerinde Bulunan Alkaloit Grupları

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Abstract

The aerial parts of 14 *Fumaria* species growing in Turkey afforded 49 alkaloids belonging to the skeletally eleven different groups of the isoquinoline alkaloids. These alkaloids alongwith their antiplatelet and acetylcholinesterase inhibitory activities were also given in this study.

Key words *Fumaria,* alkaloids, isoquinolines, biological activity

Introduction

Discoveries for the advancement of medicine and understanding of life sciences constitute one of the most powerful ways in which biological diversity can contribute to human society. Bioresources have tremendous potential in providing bioactive compounds for the development of new lead candidates for pharmaceuticals, nutraceuticals and agrochemicals. Turkey is one of the rich countries in the world for biological sources. The floristic diversity provides a wide choise of species represented 11.000 taxa of which 3.700 is endemic. Alkaloids are widespread secondary metabolites and many of them are medically active such as morphine, codeine, papaverine, ephedrine, galanthamin, reserpine, vinblastine, taxol etc. During our researches on bioactive compounds from Turkish plants, a project has been initiated which aims to search, identify and develope new biologically active compounds from *Fumaria* L. species. There are 19 *Fumaria* L. species growing in Turkey (Davis, 1965; Davis *et al.*,1988; Güner *et al.*,2000) and 14 of them have been investigated in terms of alkaloids and their biological activities. Molecular diversity in the alkaloids and their potential biological activities have been presented in this publication.

Results

The genus *Fumaria* L. (Fumarioideae) is represented by 19 species in Turkey. They are all small annual herbs and known in Turkish as "Şahtereotu" (Baytop, 1999). Some of them

are used in folk medicine in the treatment of eczema, rheumatism, stomach ache and dysentery. In Anatolia, one of them, *Fumaria vaillantii* Lois. is widespread where its extracts are used in folk medicine as a blood purifier in the treatment of skin diseases. Morphological characters used for the description of 13 *Fumaria* species were also determined (Şener, 1982). These species are given as follows:

Fumaria asepala Boiss. (Davis, 1965)

F. bastardii Bor. (Davis, 1965)

F. boissieri Hausskn. (Davis *et al.*, 1988)

F. bracteosa Pomel (Güner *et al.*,2000)

F. capreolata L. (Davis, 1965)

F. cilicica Hausskn. (Davis, 1965)

F. densiflora DC. (Syn: *F. micrantha* Lag.) (Davis, 1965)

F. flabellata Gasp. (Davis, 1965)

F. gaillardotii Boiss. (Davis, 1965)

F. judaica Boiss. (Davis, 1965)

F. kralikii Jordan (Syn: *F. anatolica* Boiss.) (Davis, 1965)

F. macrocarpa Parlatore (Davis, 1965)

F. microcarpa Boiss. ex Hausskn. (Davis, 1965)

F. officinalis L. (Davis, 1965)

F. parviflora Lam. (Davis, 1965)

F. petteri Reichb. subsp. *thuretii* (Boiss.) Pugsley (Syn: *F. thuretii* Boiss., *F. pikermiaana* Boiss. (Davis, 1965)

F. rostellata Knaf (Davis *et al.*, 1988)

F. schleicheri Soyer-Willement (Davis *et al.*, 1988)

F. vaillantii Lois. (Syn: *F. schrammii* Valenovsky) (Davis, 1965)

The *Fumaria* species are an invaluable source of isoquinoline alkaloids many of which possess a wide diversity of molecular structures and biological activities. According to the standard extraction, isolation and purification procedure described in previous paper (Şener, 1983); 49 isoquinoline alkaloids have been isolated from 14 *Fumaria* species. All alkaloids were identified on the basis of their extensive spectral data reported in the relevant literatures.

Table 1 summarize the alkaloid contents of *Fumaria* species with their molecular types.

Table 1. Distribution of Isoquinoline alkaloids in Turkish *Fumaria* Species

Alkaloids	Species
ISOQUINOLONES	
N-Methylcorydaldine	*F. vaillantii*
Corydaldine	*F. bastardii*
Oxylhydrastinine	*F. bastardii*
BENZYLISOQUINOLINES	
(+)-Juziphine	*F. bastardii, F. vaillantii*
(-)-Norjuziphine	*F. vaillantii*
(+)-Reticuline	All species
PROTOPINES	
Protopine	all species
Cryptopine	*F. asepala, F. capreolata, F. cilicica, F. kralikii, F. officinalis, F. macrocarpa*
β-Allocryptopine	*F. capreolata, F. judaica*
PROTOBERBERINES	
(-)-Cheilanthifoline	*F. vaillantii*
Coptisine	*F. capreolata, F. judaica, F. macrocarpa, F. petteri* ssp. *thuretii*
(-)-Corydaline	*F. cilicica, F. officinalis*
(-)-Scoulerine	*F. asepala, F. capreolata, F. cilicica,F. densiflora, F.judaica,F. kralikii, F. officinalis, F. petteri* ssp.*thuretii, F. macrocarpa, F. vaillantii*
(-)-Sinactine	*F. cilicica, F. densiflora ,F. macrocarpa, F. officinalis, F. petteri* ssp. *thuretii*
(-)-Stylopine	*F.asepala, F. bastardii, F. capreolata, F. judaica, F.gaillardotii, F. microcarpa, F. vaillantii*
(+)-Tetrahydropalmatine	*F. bastardii*
PHTHALIDEISOQUINOLINES	
(+)-Adlumidine	*F. judaica*
(-)-Adlumine	*F. kralikii, F. macrocarpa, F. vaillantii*
(+)-Bicuculline	*F. asepala, F. bastardii, F. kralikii, F.microcarpa, F. parviflora, F. vaillantii*
(±)-Bicuculline	*F. cilicica, F. gaillardotii, F. officinalis*
(-)-Capnoidine	*F. capreolata, F. petteri* ssp. *thuretii,F. vaillantii*
(-)-Corledine	*F. vaillantii*
(-)-Corlumine	*F. bastardii*
Fumaramidine	*F. vaillantii*
(+)- Hydrastine	*F. microcarpa, F.parviflora, F. vaillantii*
(-)-β-Hydrastine	*F. bastardii*

Table 1 continued

SECOPHTHALIDEISOQUINOLINES	
Adlumidiceine	*F. vaillantii*
Z-Fumaramine	*F. vaillantii*
Microcarpine	*F. microcarpa, F. parviflora, F. Vaillantii*
N-Methylhydrasteine	*F.gaillardotii, F.microcarpa, F. parviflora, F.petteri* ssp.*thuretii, F.vaillantii*
N-Methylhydrastine	*F.microcarpa, F.parviflora, F. vaillantii*
APORPHINES	
(+)-Isoboldine	*F. vaillantii*
(+)-Isocorydine	*F. vaillantii*
BENZOPHENANTHRIDINES	
(±)-8-Acetonyldihydrosanguinarine	*F. vaillantii*
Dihydrosanguinarine	*F. vaillantii*
(±)-8-Methoxydihydrosanguinarine	*F. vaillantii*
Norsanguinarine	*F. vaillantii*
Oxysanguinarine	*F. densiflora, F. kralikii, F. microcarpa, F. vaillantii*
Sanguinarine	*F. asepala, F. capreolata, F. cilicica, F. kralikii, F. officinalis, F. parviflora*
SPIROBENZYLISOQUINOLINES	
(-)-Fumaricine	*F. densiflora, F. gaillardotii, F.petteri* ssp. *thuretii*
(-)-Fumariline	*F. densiflora, F.macrocarpa, F. officinalis, F.petteri* ssp. *thuretii*
(+)-Fumariline	*F. bastardii*
(-)- Fumaritine	*F. bastardii, F. capreolata, F.gaillardotii, F. judaica, F. petteri* ssp. *thuretii*
(-)-O-Methylfumarophycine	*F. bastardii*
(-)-Norfumaritine	*F. kralikii*
(-)-Parfumine	*F. kralikii, F. parviflora, F. vaillantii*
(+)-Parfumidine	*F. vaillantii*
SECOSPIROBENZYLISOQUINOLINES	
Secodensiflorine	*F. densiflora*
INDENOBENZAZEPINES	
Fumarofine	*F. cilicica, F. densiflora, F. officinalis, F. microcarpa*

As indicated in Table 1, protopine is found as a major alkaloid in all *Fumaria* species. (+)-Reticuline was also reported in all species depends on the precursor of isoquinoline alkaloids. From the eleven different groups; isoquinolone- , aporphine- and benzyliso-quinoline- (except reticuline) type alkaloids were only determined in *F. bastardii* and *F. vaillantii*. The remaininig groups were rather widespread in *Fumaria* species. Besides, secospirobenzylisoquinoline-type alkaloid was simply obtained from *F. densiflora*.
The isoquinoline alkaloid groups found in Turkish *Fumaria* species are given in Table 2.

Table 2. Isoquinoline alkaloid groups in Turkish *Fumaria* species

Species	Isoquinoline groups
F. asepala (Şener, 1985a, 1986)	protopines, protoberberines, phthalideisoquinolines, benzophenanthridines, benzylisoquinolines
F. bastardii (Küçükboyacı *et al.*, 1998)	protopines, protoberberines, phthalideisoquinolines, benzylisoquinolines, spirobenzylisoquinolines, isoquinolones,
F. capreolata (Şener, 1985a, 1985b)	protopines, protoberberines, phthalideisoquinolines, benzophenanthridines, benzylisoquinolines, spirobenzylisoquinolines
F. cilicica (Şener, 1985c)	protopines, protoberberines, phthalideisoquinolines, benzophenanthridines, benzylisoquinolines, indenobenzazepines
F. densiflora (Şener, 1984a)	protopines, protoberberines, benzophenanthridines, spirobenzylisoquinolines, indenobenzazepines, secospirobenzylisoquinolines,
F. gaillardotii (Şener, 1983)	protopines, protoberberines, phthalideisoquinolines, secophthalideisoquinoline, benzylisoquinolines, spirobenzylisoquinolines
F. judaica (Şener, 1984c)	protopines, protoberberines, phthalideisoquinolines, benzylisoquinolines, spirobenzylisoquinolines
F. kralikii (Colton *et* al., 1985, Şener, 1988)	protopines, protoberberines, phthalideisoquinolines, secophthalideisoquinoline, benzophenanthridines, spirobenzylisoquinolines
F. macrocarpa (Şener, 1984d)	protopines, protoberberines, phthalideisoquinolines, benzylisoquinolines, spirobenzylisoquinolines
F. microcarpa (Blasko *et* al., 1981, Şener, 1984b)	protopines, protoberberines, phthalideisoquinolines, secophthalideisoquinolines, benzophenanthridines, indenobenzazepines
F. officinalis (Şener, 1985c)	protopines, protoberberines, phthalideisoquinolines, benzophenanthridines, benzylisoquinolines, spirobenzylisoquinolines, indenobenzazepines
F. parviflora (Şener, 1988)	protopines, phthalideisoquinolines, secophthalideisoquinolines, benzophenanthridines, benzylisoquinolines, spirobenzylisoquinolines
F. petteri ssp. *thuretii* (Şener,1988)	protopines, protoberberines, phthalideisoquinolines, benzylisoquinolines, spirobenzylisoquinolines
F. vaillantii (Blasko *et al.*, 1982, Şener *et al.*, 1983)	protopines, protoberberines, phthalideisoquinolines, secophthalideisoquinoline, benzophenanthridines, benzylisoquinolines, spirobenzylisoquinolines, aporphines, isoquinolones

Antiplatelet activity

The role of antiplatelet drugs in the control of cardiovascular diseases continues to be of prime importance. It is well recognized that platelet-vessel wall interactions are important in the development of thrombosis and atherosclerosis. Thus, inhibition of platelet function may be a promising approach for the prevention of thrombosis. The effect of some Turkish medicinal plants against human platelet aggregation induced by arachidonic acid, collagen and platelet activated factor(PAF) have been examined (Şener, Temizer, 1991). Among them, *Fumaria* species showed complete inhibition of platelet aggregation caused by arachidonic acid and collagen inhibitors of thromboxane formation. Bioassay-directed fractionation of the alkaloidal extract of *Fumaria vaillantii* resulted in the isolation of protopine as the active constituent (Şener, 1994).
Protopine also inhibits human platelet aggregation induced by platelet activated factor (PAF) (Şener *et al.*, 1991). Since PAF is an important mediator of inflammation, thrombosis and asthma, it can be deduced that protopine may be a useful compound possessing anti-PAF properties.

Acetylcholinesterase inhibitory activity

The clinical findings provide rationale for cholinergic enhancement as an approach to improving cognitive function in Alzheimer's disease which is the fourth leading cause of death after hearth disease, cancer and stroke in industrialized nations of the USA and Europe. The acetylcholinesterase catalyzes the hydrolysis of the neurotransmitter acetylcholine and it has long been an attractive target for rational drug design and development of mechanism-based inhibitors for the treatment of Alzheimer diseases. Therefore, acetylcholinesterase inhibitors are the only class of drugs which produce improvements in cognitive function. In the course of our studies on acetylcholinesterase inhibitors (Orhan, 2002); the alkaloidal extracts of *Fumaria* species displayed high inhibitory activity, ranging between 84.95±1.07 % and 96.89±0.17 % by *in vitro* and spectrophotometric Ellmann method. Bioassay-guided isolation of *Fumaria vaillantii* extract afforded a number of isoquinoline alkaloids with significant acetylcholinesterase inhibitory activity. Among them, β-allocryptopine, berberine and protopine were found the most potent inhibitory activity.

Özet

Türkiye'de yetişen *Fumaria* türlerinden 14 türün topraküstü kısımlarından onbir farklı izokinolin grubuna ait toplam 49 alkaloit elde edilmiştir. Alkaloitler ile alkaloitlerin antiplatelet ve asetilkolinesteraz inhibitörü aktiviteleri bu çalışmada verilmiştir.

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