

XXIII. ULUSAL BİYOKİMYA KONGRESİ

Biyomoleküllerin Yaşamdaki Önemi ve Klinik Kararda Laboratuvar



29 Kasım - 2 Aralık
Hilton Hotel - Adana



DOĞAL KAYNAKLARDAN BİYOAKTİF STEROİT TÜREVLERİ

İhsan ÇALIŞ

Yakın Doğu Üniversitesi, Eczacılık Fakültesi,
Farmakognozi Anabilim Dalı, Lefkoşa, KKTC

STEROİTLER

- Steroitler, hayvanlar, mantarlar, yosunlar ve yüksek bitkilerde tek bir bileşikten, **skualen-epoksit**, meydana gelirler.
- Ancak, **biyosentez yolaklarındaki** önemli farklılıklar nedeniyle, yapısal olarak çok zengin bir bileşik grubuna sahiptirler.

STEROİTLER

2 x C₁₅

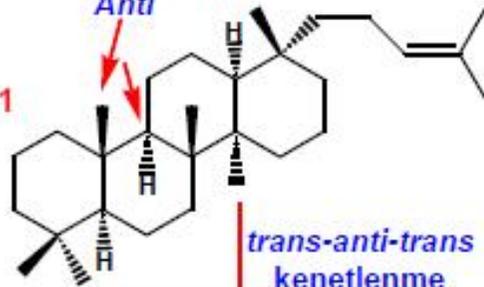
SKUALEN
Squalene C₃₀

Siklizasyon | Konformasyon degisimi

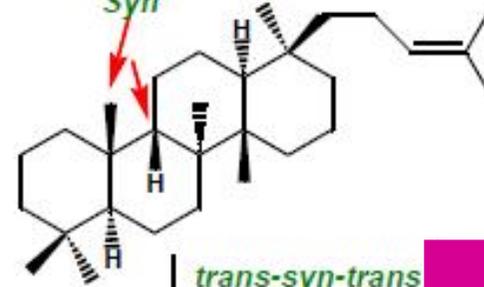
C₃₀

Kasyon 1

Anti



Syn

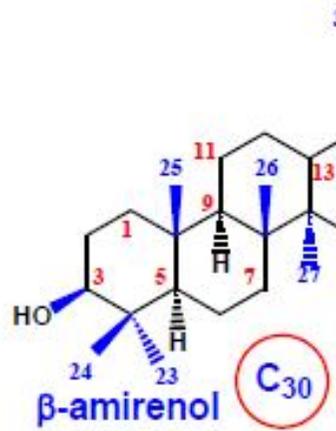


Kasyon 2

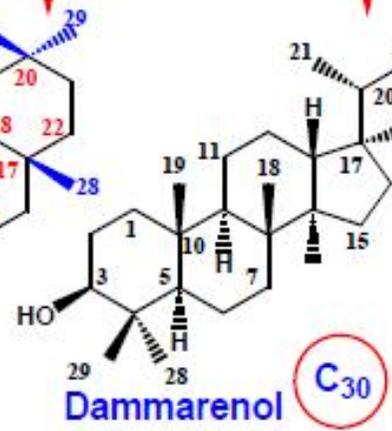
trans-anti-trans
kenetlenme

trans-syn-trans
kenetlenme

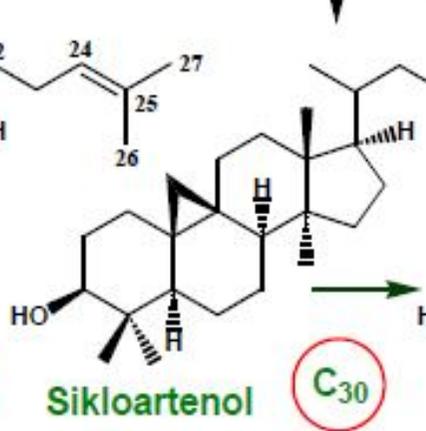
**Me-KAYMASI
HALKA DARALMASI**



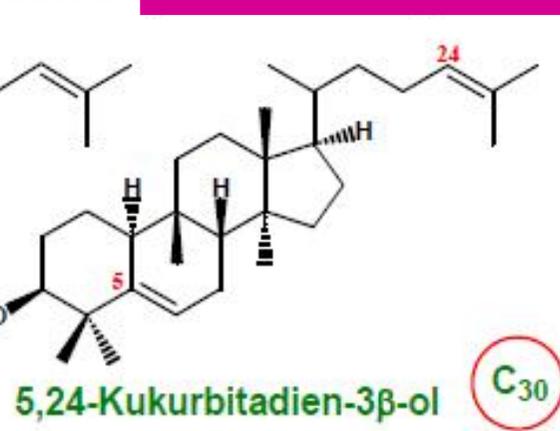
β-amirenol C₃₀



Dammarenol C₃₀



Sikloartenol C₃₀



5,24-Kukurbitadien-3β-ol C₃₀

C₂₈
C₂₉

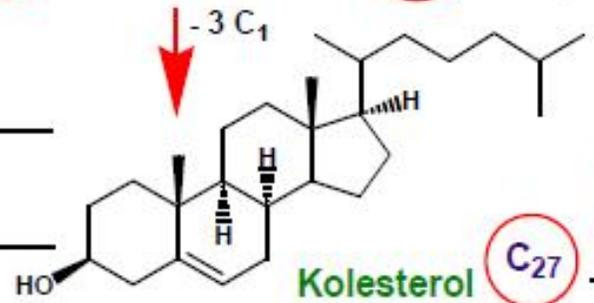
Fitosteroller

Yan zincirde UZAMA

C₂₃
C₂₄

**Kardenolit
Bufadienolit**

Yan zincirde KISALMA



Kolesterol C₂₇

Yan zincirde
OKSİDASYON
KETALİZASYON

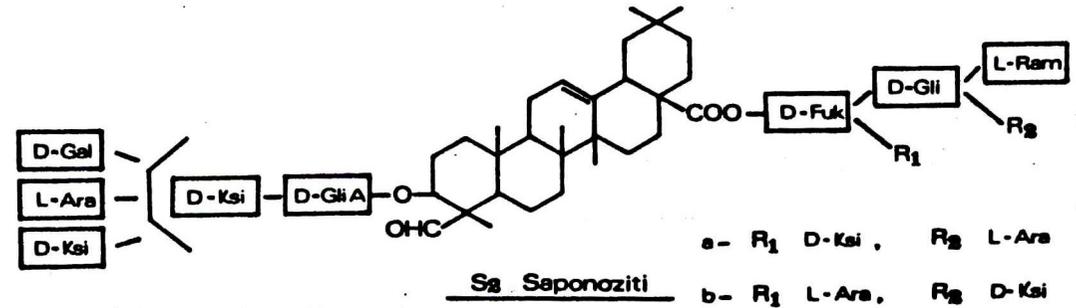
**Steridal
sapogenol** C₂₇

- 1972 – (1977) 1978:

Doktora Tezi:

Saponaria kotschyi
BOISS. ÜZERİNDE
FARMAKOĞNOZİK
ARAŞTIRMALAR

Konu: Triterpenik Saponozitler



EKSPEKTORAN, MUKOLİTİK, HEMOLİZAN, YÜZEY AKTİF, SOĞUK KANLI HAYVANLARA TOKSİK



Ekspektoran

TRİTERPENLER

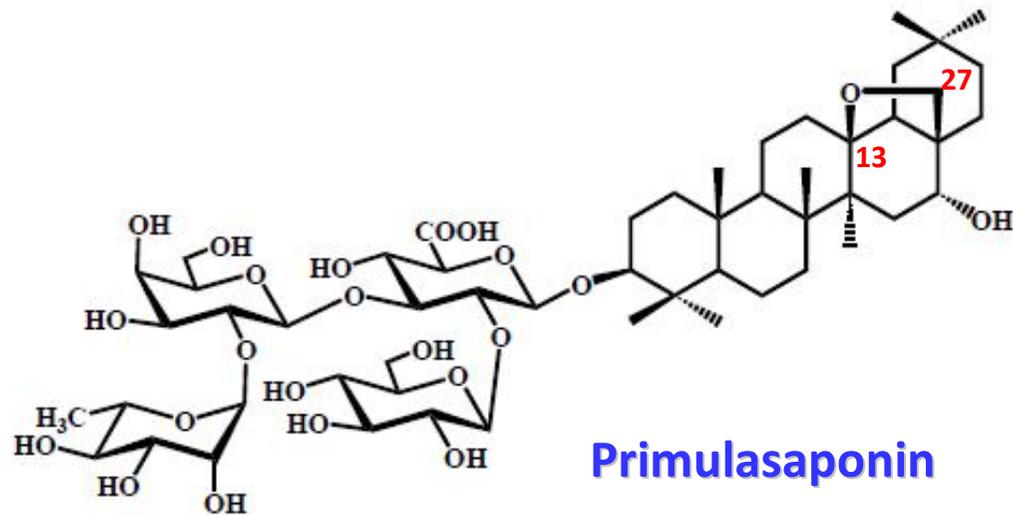
1978 – 2010: Doktora sonrası çalışmalar
Primula & Cyclamen Saponinleri



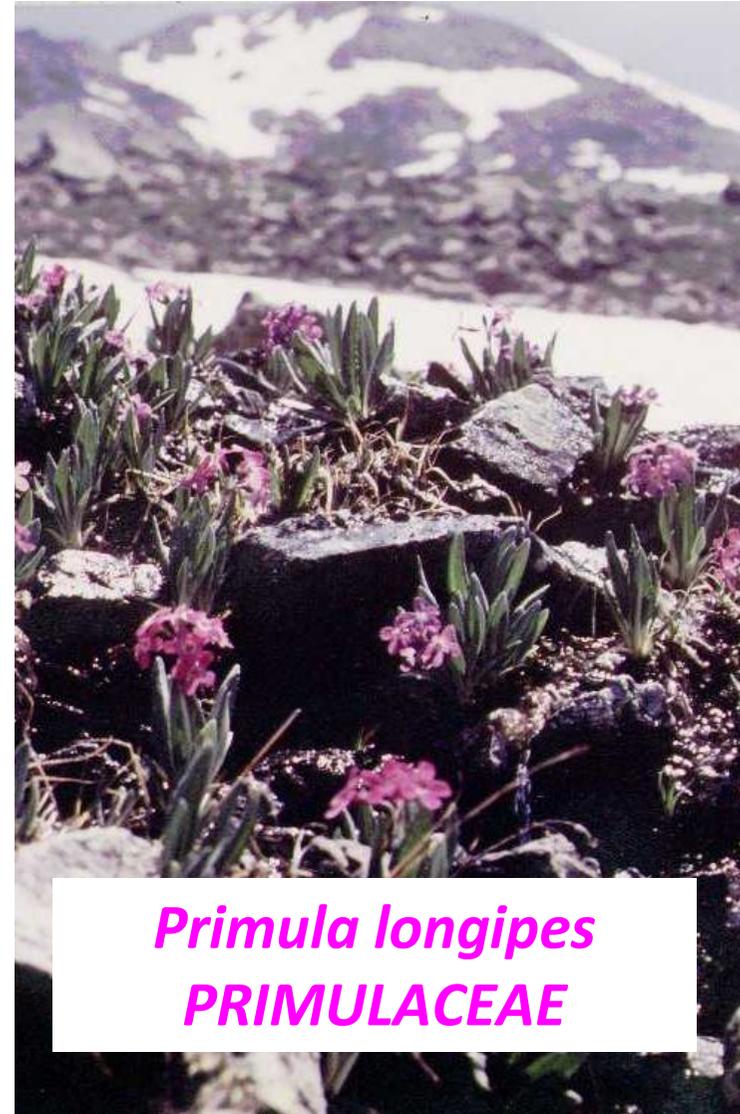
EKSPEKTORAN, MUKOLİTİK, HEMOLİZAN, YÜZEY AKTİF, SOĞUK KANLI HAYVANLARA TOKSİK



Primula Saponinleri: Oleanan-tip

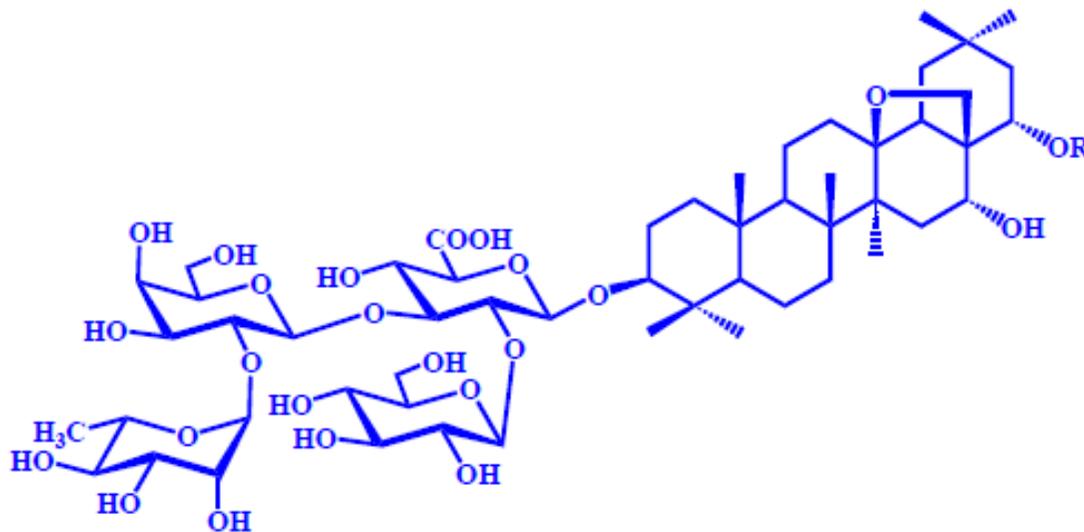


3,16-dihidroksi,
13 β ,27-epoksi-oleanan



Primula Saponinleri: Oleanan-tip

3,16,22-trihidroksi,
13 β ,27-epoksi-oleanan



R = H Priverosaponin B

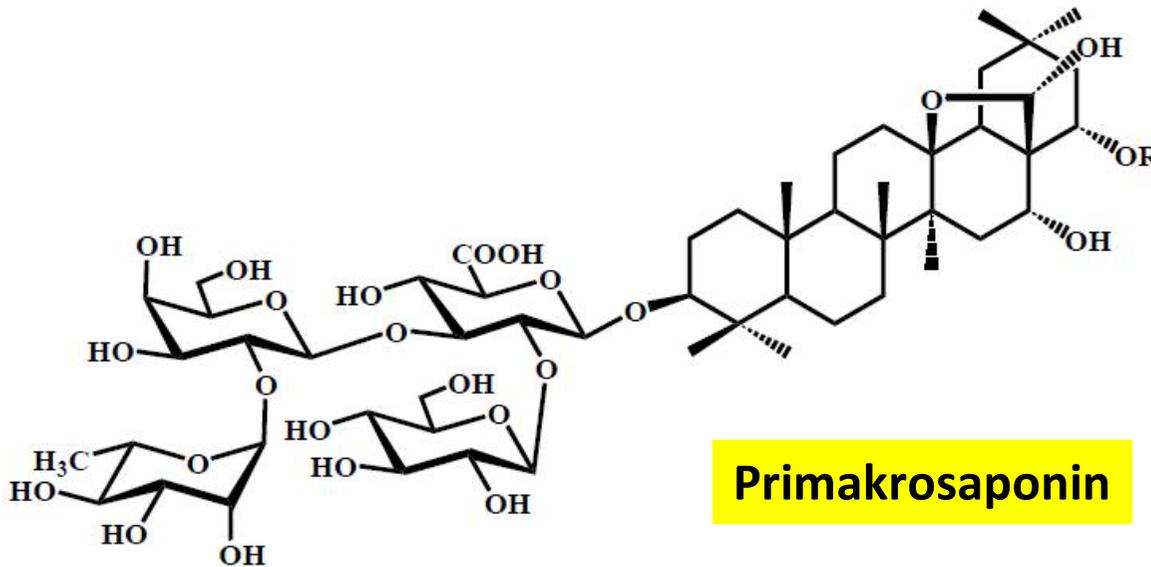
R = Ac Priverosaponin B Asetat

Primula elatior
PRIMULACEAE



Primula Saponinleri: Oleanan-tip

3,16,22,28-tetrahidroksi,
13 β ,27-epoksi-oleanan



Primula veris
PRIMULACEAE



Infertilite

TRİTERPENLER

Cyclamen species

❖ TÜBİTAK



❖ (Proje No. SBAG-1233)



Cyclamen coum

Çorum, Yozgat civarında çocuğu olmayan Kadınlar tarafından kullanılıyor.

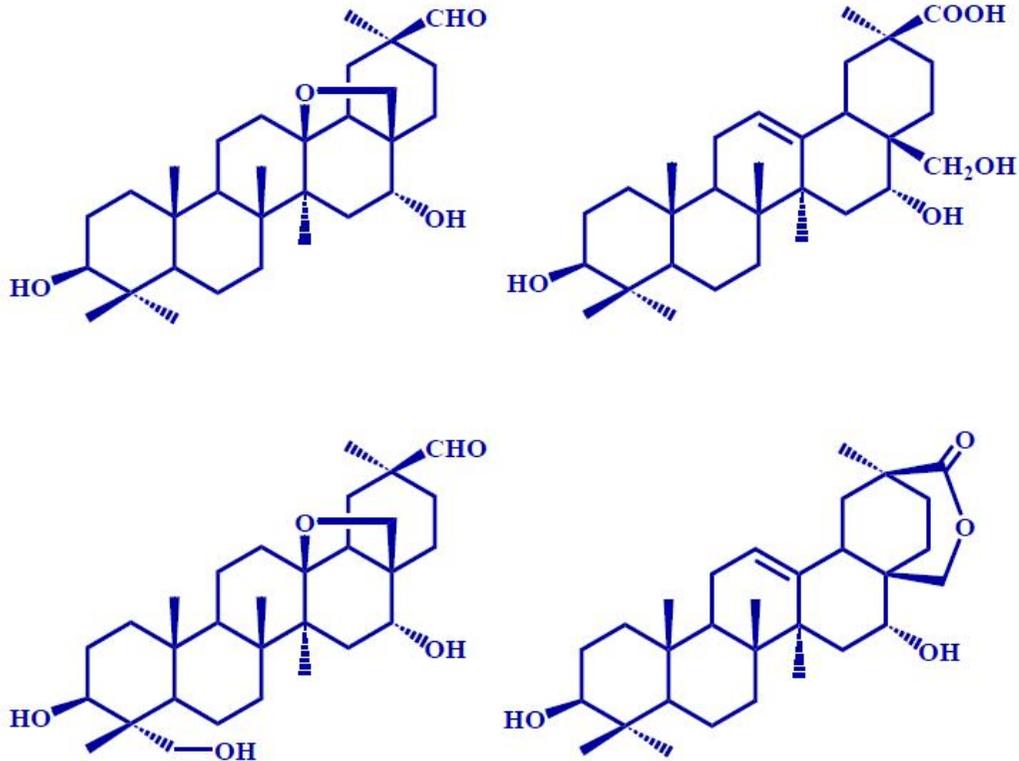


Cyclamen mirabile

Çalışmaya karşılaştırma amaçlı alındı

Endemik, Süs bitkisi

Cyclamen saponinleri : Oleanan-tip

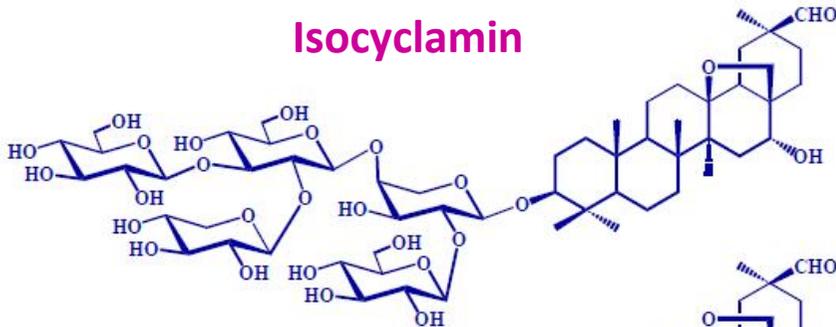


Calis et al., J. Nat. Prod. 60, 315-318 (1997)
 Calis et al., Planta Med. 63, 166-170 (1997)

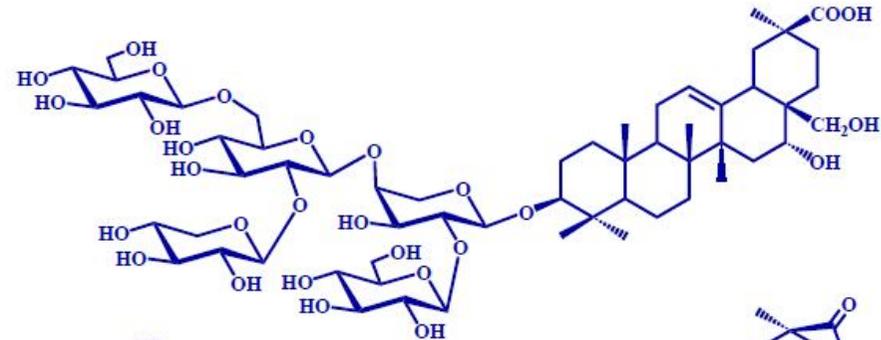
Cyclamen coum
 PRIMULACEAE

Cyclamen Saponinleri: Oleanan-tip

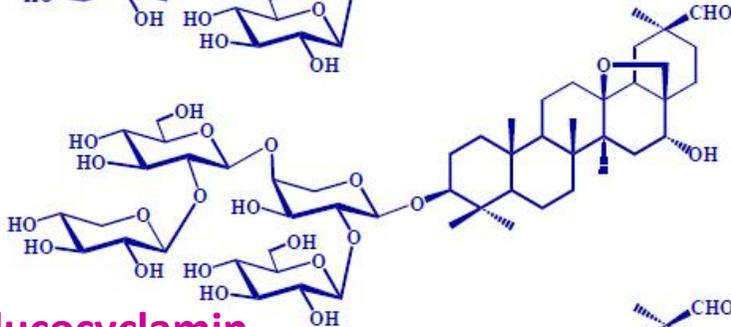
Isocyclamin



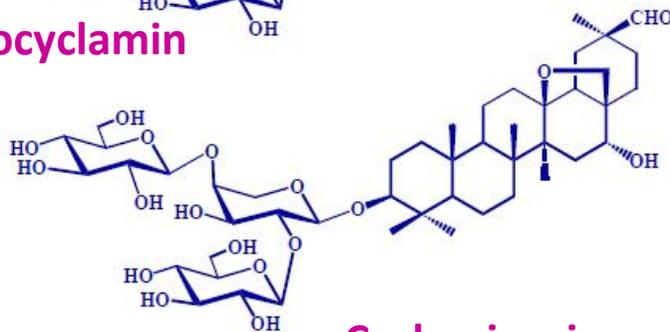
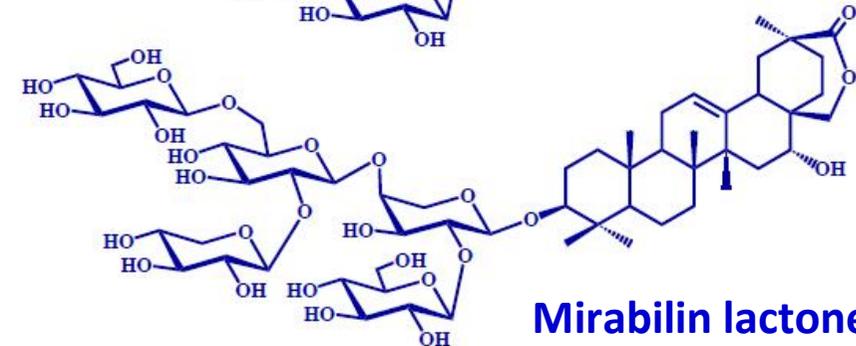
Mirabilin



Deglucocyclamin



Mirabilin lactone



Cyclaminorin

Cyclamen coum, C. mirabile
PRIMULACEAE

Calis et al., *J. Nat. Prod.* **60**, 315-318 (1997)

Calis et al., *Planta Med.* **63**, 166-170 (1997)

Cyclamen Saponinleri: Oleanan-tip

Antimikrobiyal Aktivite

- **Gram Pozitif Bakteriler**
 - *S. aureus*, *E. faecalis*
- **Gram Negatif Bakteriler**
 - *E. coli*, *P. aeruginosa*
- **Maya Mantarları**
 - *C. albicans*, *C. crusei*,
 - *C. parapsilosis*,
 - *C. pseudotropicalis*,
 - *C. Stellatoidea*
 - *C. tropicalis*, *Cr. neoformans*

SONUÇLAR*

- **Antibakteriyal aktivite**
 - Zayıf (400 µg/ml)
- **Antifungal aktivite**
 - Tüm saponinlerde gözlemlendi
 - Cyclamin, Cylaminorin, ve Deglukosiklamin'de en yüksek aktivite
 - (60, 80, 160 µg/ml)

*Calis et al., J. Nat. Prod. 60, 315-318 (1997)
Calis et al., Planta Med. 63, 166-170 (1997)

Cyclamen Saponinleri: Oleanan-tip

Uterokontraktif aktivite

- İzole sıçan uterusu
- 120 – 200 g dişi sıçan
 - Organ Banyosu:
 - 25 ml De Jalon's Çöz.
- Kontrol:
- Asetilkolin
 - 10^{-8} – 10^{-4} M
 - konsantrasyonlarda

SONUÇLAR*

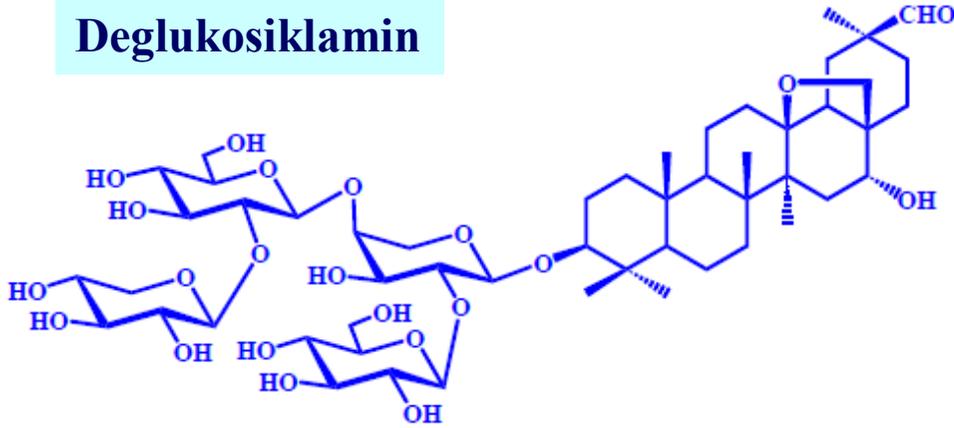
- Siklaminorin ($8.6 - 10^{-6}$ M)
Asetilkolin ($10^{-4.9}$ M)
- Deglukosiklamin ($7.5 - 10^{-6}$ M)
Asetilkolin ($10^{-5.2}$ M)
- Siklocoumin ($7.4 - 10^{-6}$ M)
Asetilkolin ($10^{-5.2}$ M)
- Siklamin ($6.5 - 10^{-6}$ M)
Asetilkolin ($10^{-4.9}$ M)

*Calis et al., J. Nat. Prod. 60, 315-318 (1997)
Calis et al., Planta Med. 63, 166-170 (1997)

Benzer kullanım, aynı yapı, farklı bitki ve ülke

Saponinler: Oleanan türevleri

Deglukosiklamin



Ardisiakrenatozit A ve B

Uterokontraktif aktivite

Kullanıldığı Ülkeler: Tayland ve Çin

TCM

Solunum Enfeksiyonları,

Antifertilite Etki,

“Wash out dirty blood” in women

Who suffer from menstrual disorders”

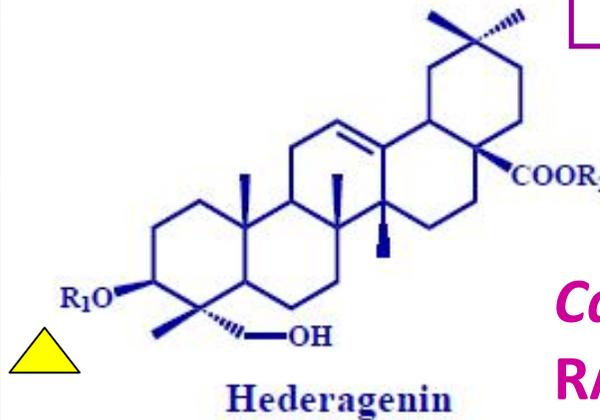


Ardisia crenata (Myrsinaceae)

*****ABD'de KISIRLIKTA KULLANILAN
MUKOLİTİK ÖKSÜRÜK ŞURUBU*****

Jansakul et al., *Planta Med.* 53, 405 (1987)

Caltha polypetale: Saponinler: Oleanan-tip



Kull.: SEDATİF

Caltha polypetale
RANUNCULACEAE

R₁

R₂

1	β -D-Gal-(1→3)- α -L-Rham-(1→2)- α -L-Ara
2	β -D-Gal-(1→3)- α -L-Rham-(1→2)- α -L-Ara
3	α -L-Ara
4	α -L-Rham-(1→2)- α -L-Ara
5	α -L-Ara
6	α -L-Rham-(1→2)- α -L-Ara

α -L-Rham-(1→4)- β -D-Glu-(1→6)- β -D-Glu
H
H
H
α -L-Rham-(1→4)- β -D-Glu-(1→6)- β -D-Glu
α -L-Rham-(1→4)- β -D-Glu-(1→6)- β -D-Glu

Schaffhausen (İsviçre) Şelalesi

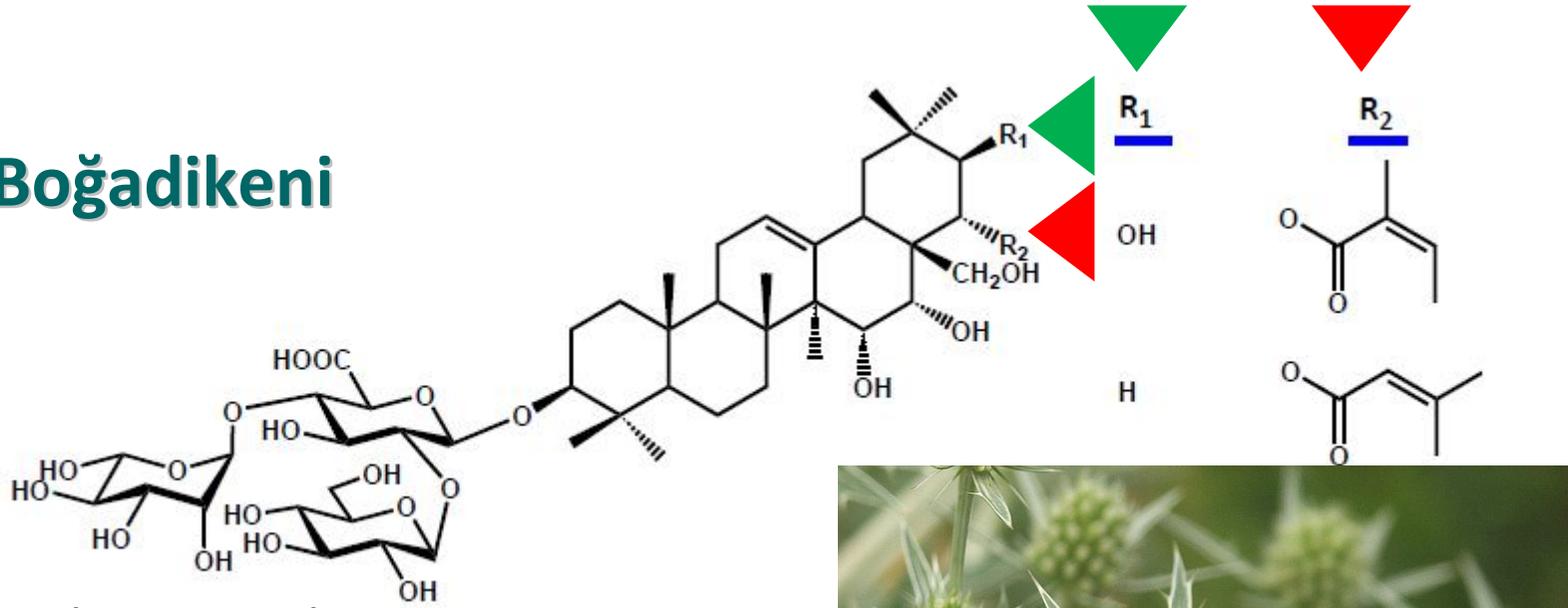


Ranunculus fluitans



Eryngium campestre (Apiaceae)

Boğadikeni



- Kök ve topraküstü
- infüzyon
- **Halk arasında:**
 - Öksürük kesici
 - Diüretik
 - İştah açıcı
 - Uyarıcı
 - Afrodisyak

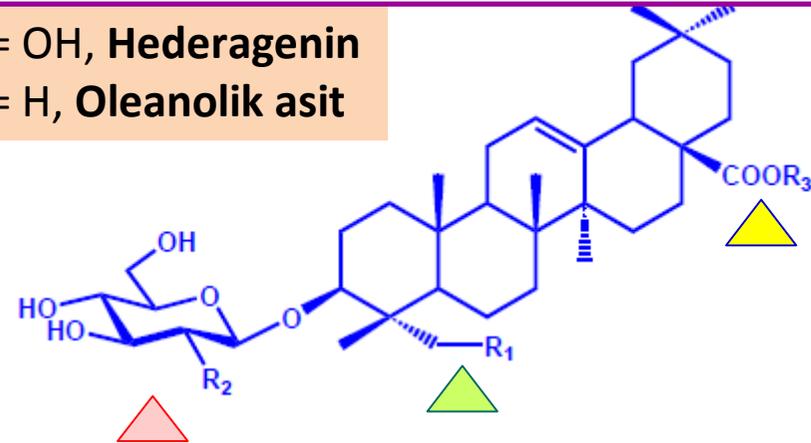


Hedera helix: Saponinler: Oleanan-tip*Hedera helix* (ARALIACEAE)

Kull.: Yapraklar, ekspektoran,
dermatitler, selulit (haricen)

$R_1 = \text{OH}$, Hederagenin

$R_2 = \text{H}$, Oleanolik asit

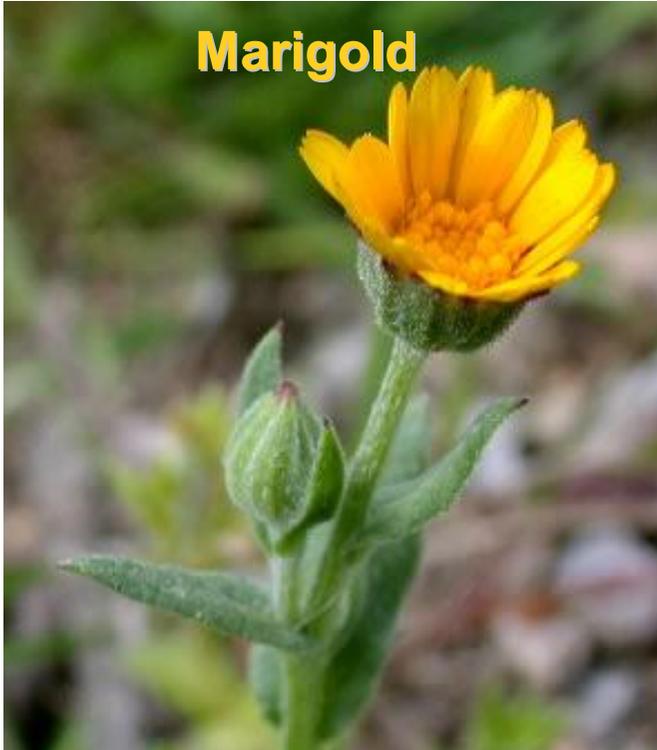


	R1	R2	R3
1	OH	H	H
2	H	Glu	H
3	OH	Glu	H
4	OH	H	Glu-(1→6)Glu
5	OH	Glu	Glu-(1→6)Glu
6	H	Glu	Glu-(1→6)Glu

Calendula arvensis: Saponinler: Oleanan-tip

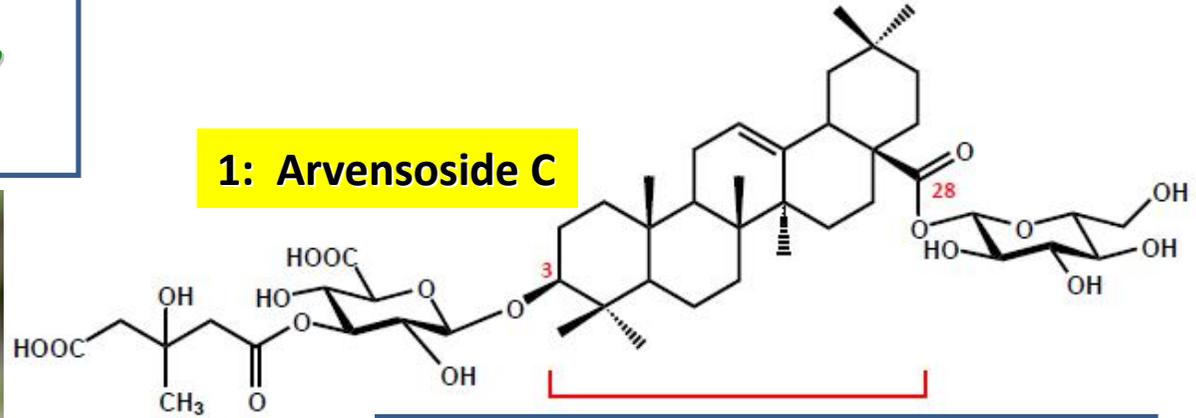
KULL.: Deri rahatsızlıları,
uçuk, yara, yanıklarda

Marigold



Calandula arvensis
(ASTERACEAE)

1: Arvensoside C



	R1 (C ₃ -OH)	R2 (C ₂₈ -COOH)
2	Gal-(1→4)Glu	H
3	Gal-(1→4)Glu	Glu
4	Gal-(1→4)Glur	Glu
5	Glu-(1→2), Gal-(1→4)Glu	Glu

Gal: Galaktoz, Glu: Glukoz; Glur: Glukuronik asit

**Antibakteriyal, antiviral, antiviral,
immunostimulan**

Phlomis spec. (LAMIACEAE)

Halk arasında kullanılıřları:

TÜRKİYE'DE

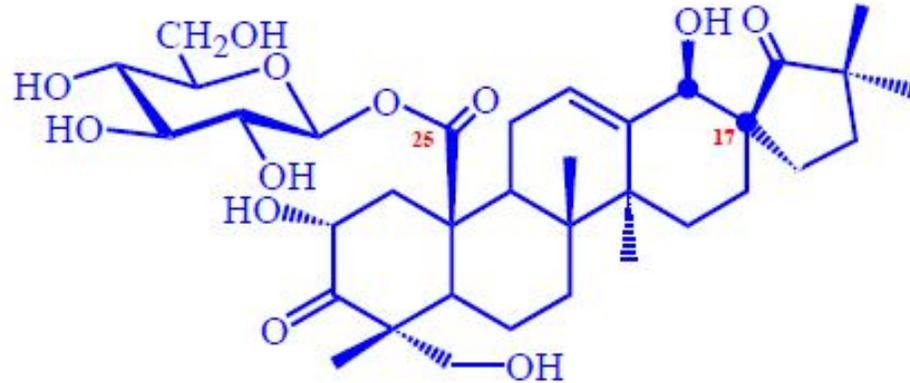
- TONİK ve STİMLAN
- ÜLSER TEDAVİSİNDE
- DİÜRETİK

DİÜER ÜLKELERDE

- ATEŞ DÜŞÜRÜCÜ
- ÜŞÜTMEDE
- ANALJEZİK
- ANTIİNFLAMMATUAR
- YARA İYİLEŐTİRİCİ



Phlomis kotschyana

Saponin: **Noroleanan-tip** - Norviskozit

❖ **TÜBİTAK**

❖ (Project No. SBAG-2304)

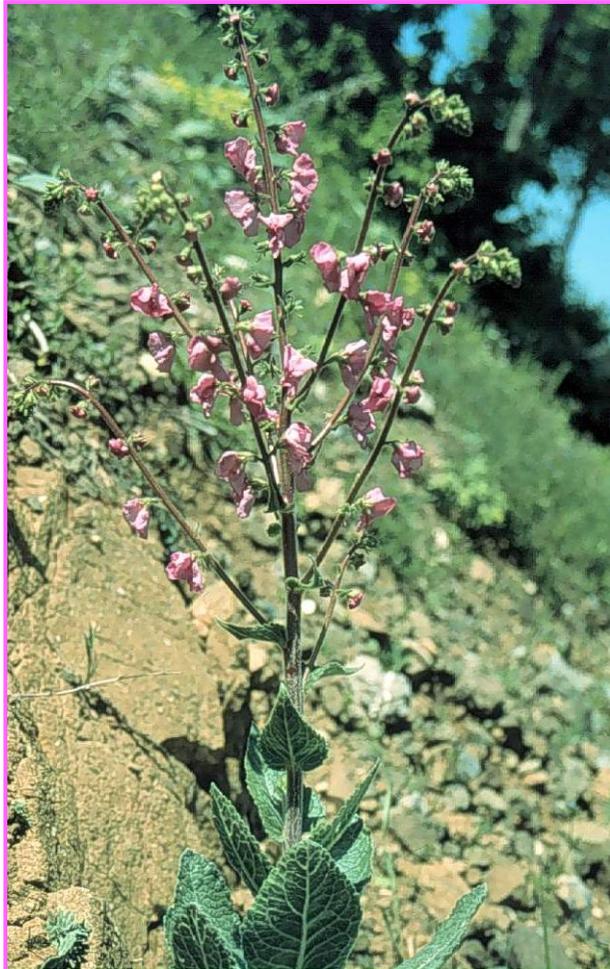
✓ **34 *Phlomis* species**

- IRİDOİTLER*
- FENİLETANOİT GLİKOZİTLER*
- LİGNAN&NEOLİGNANLAR, OXYLİGNAN*
- FLAVONOİTLER
- MONO- ve DİTERPENLER,
- **NORTRİTERPENLER**
- ALİFATİK (OKTENOL) GLİKOZİT*

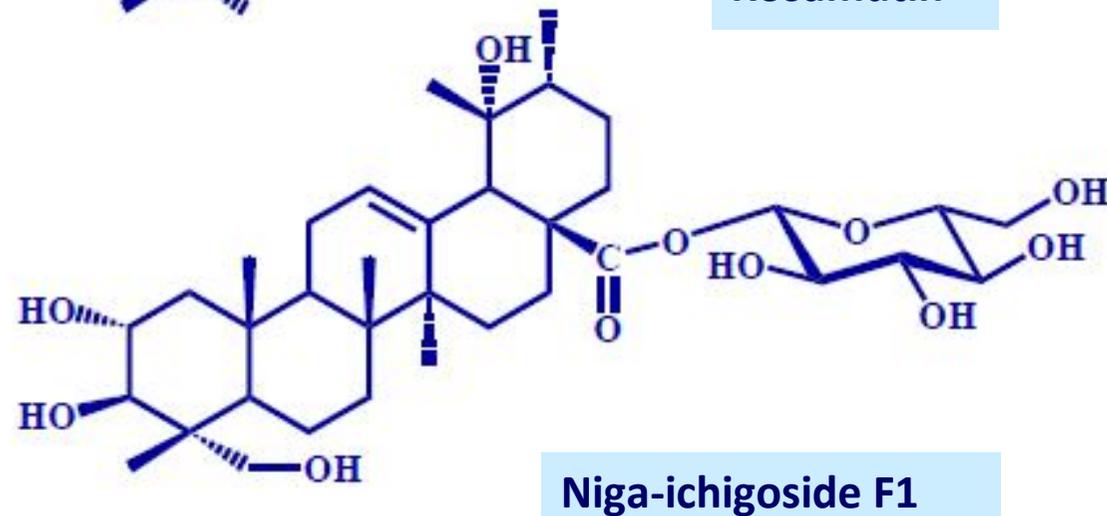
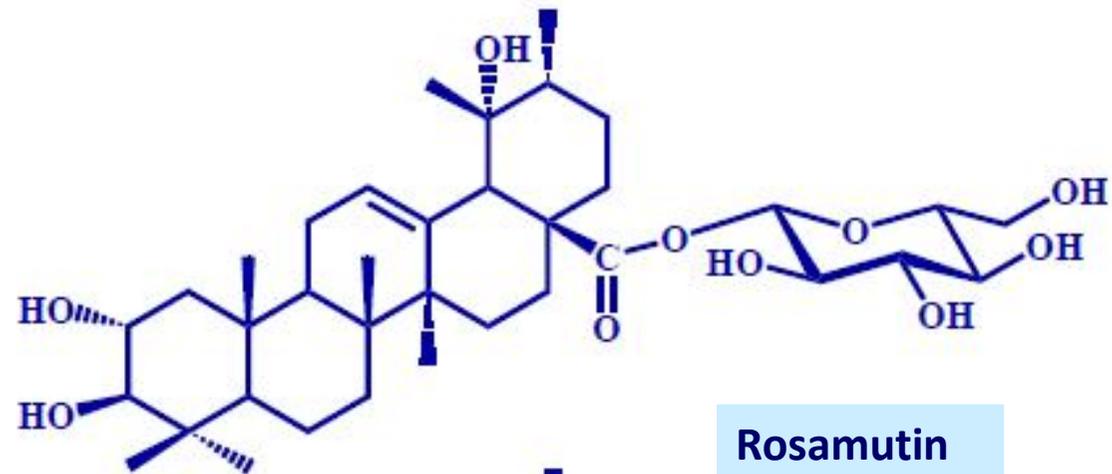


Phlomis viscosa

Saponinler: Urgan-tip

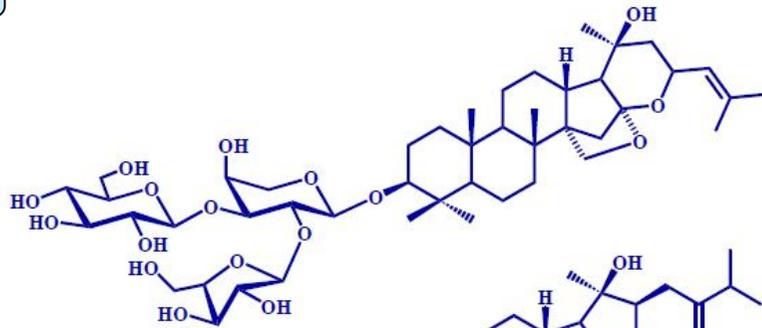


Verbascum wiedemannianum
SCROPHULARIACEAE

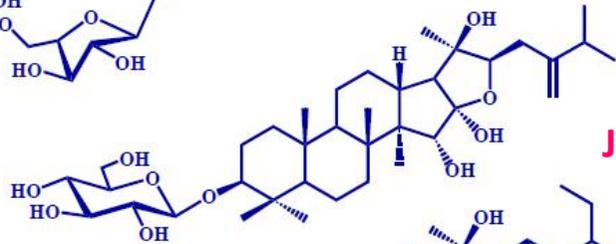


Abou Gazar, H., Ph.D. Thesis (H.U.) 2001

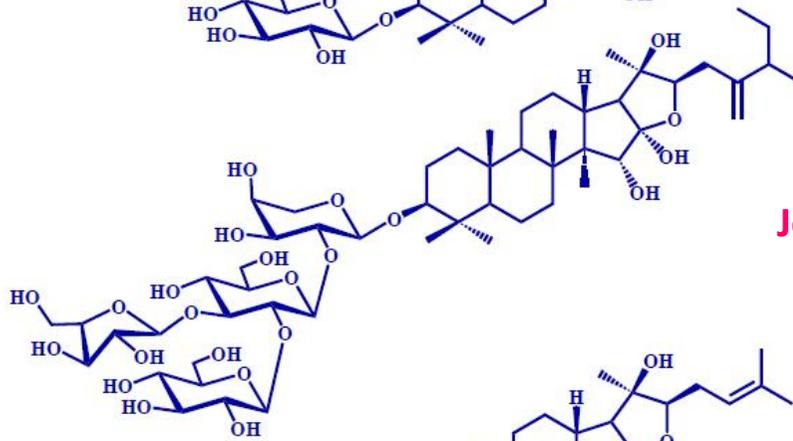
Saponin: Dammaran-tip



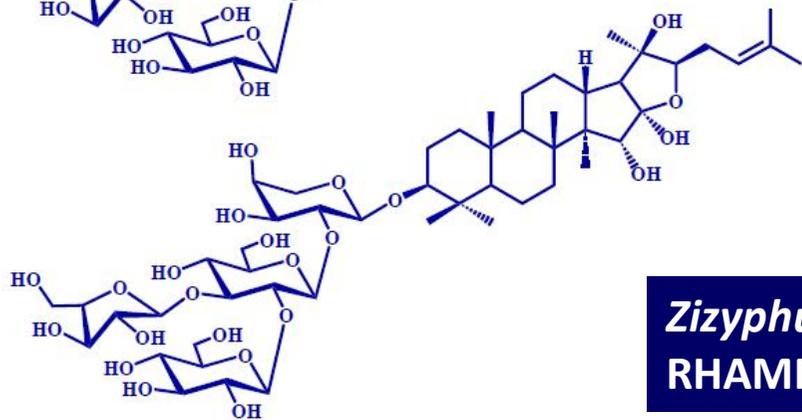
Jujuboside



Joazerioside A



Joazerioside B

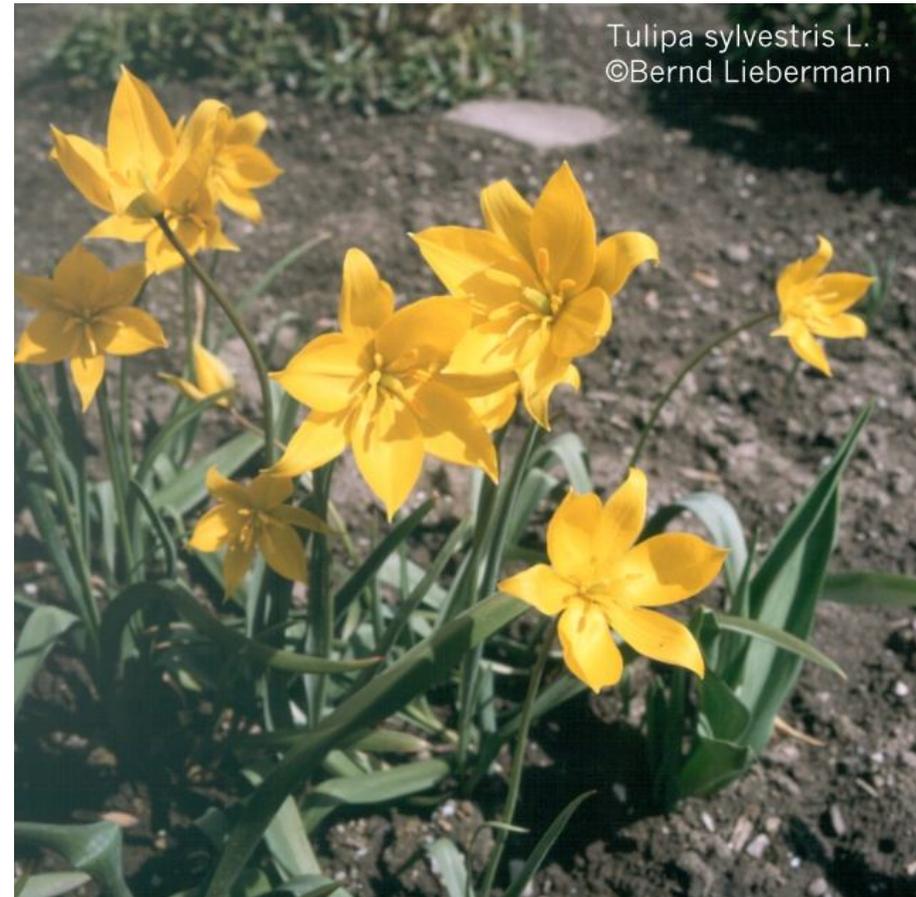
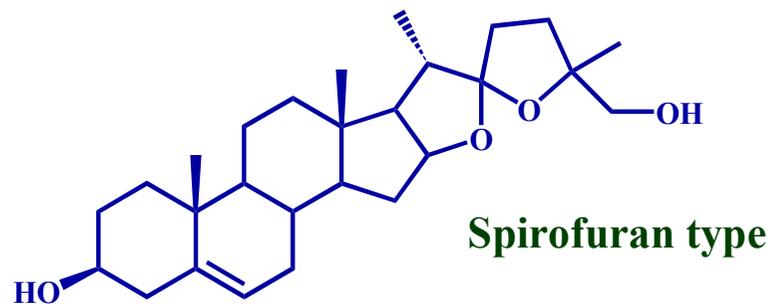
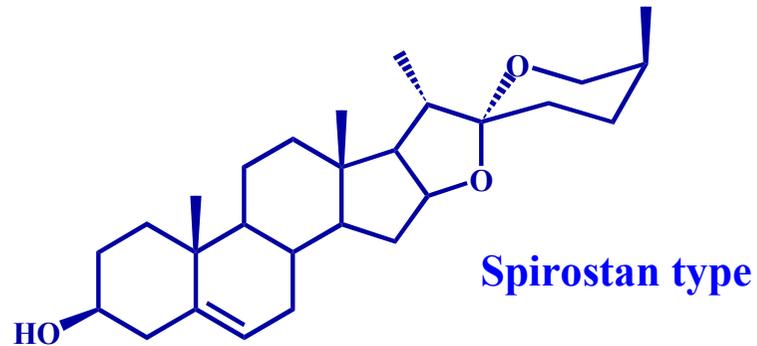
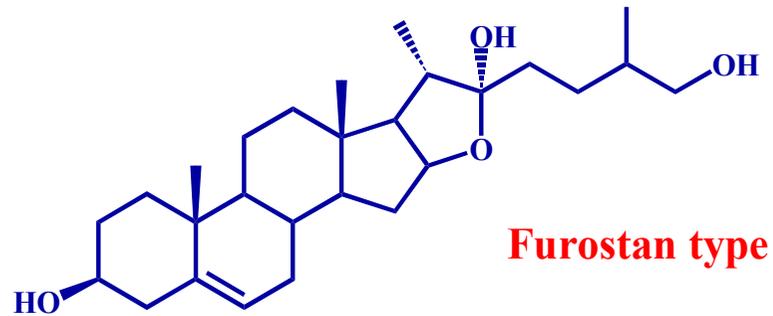


Lotoside A

Zizyphus joazeiro
RHAMNACEAE

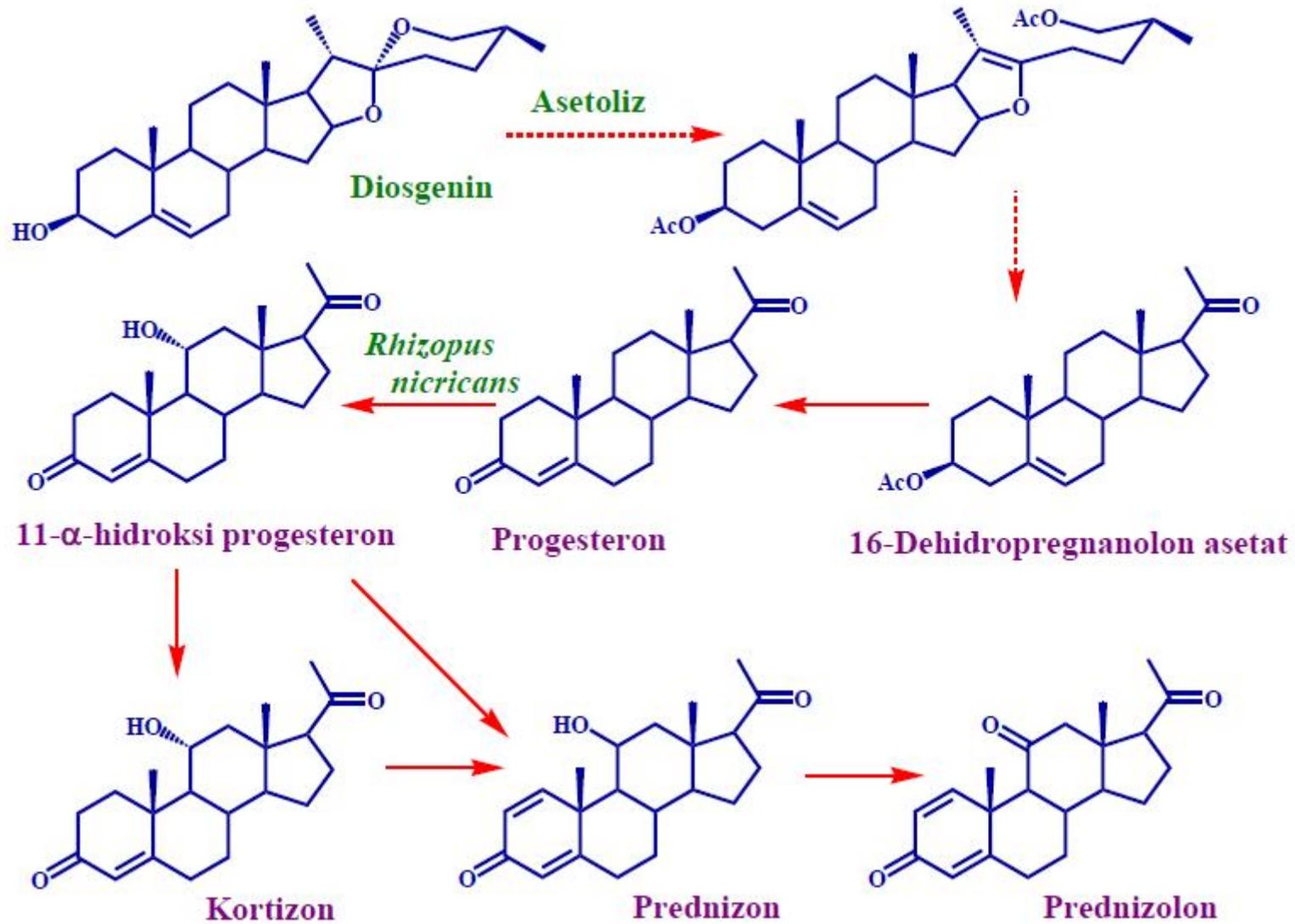


Steroidal Sapogenoller (Aglikonlar)



MONOCOTYLEDONS
Liliaceae, Dioscoreacea

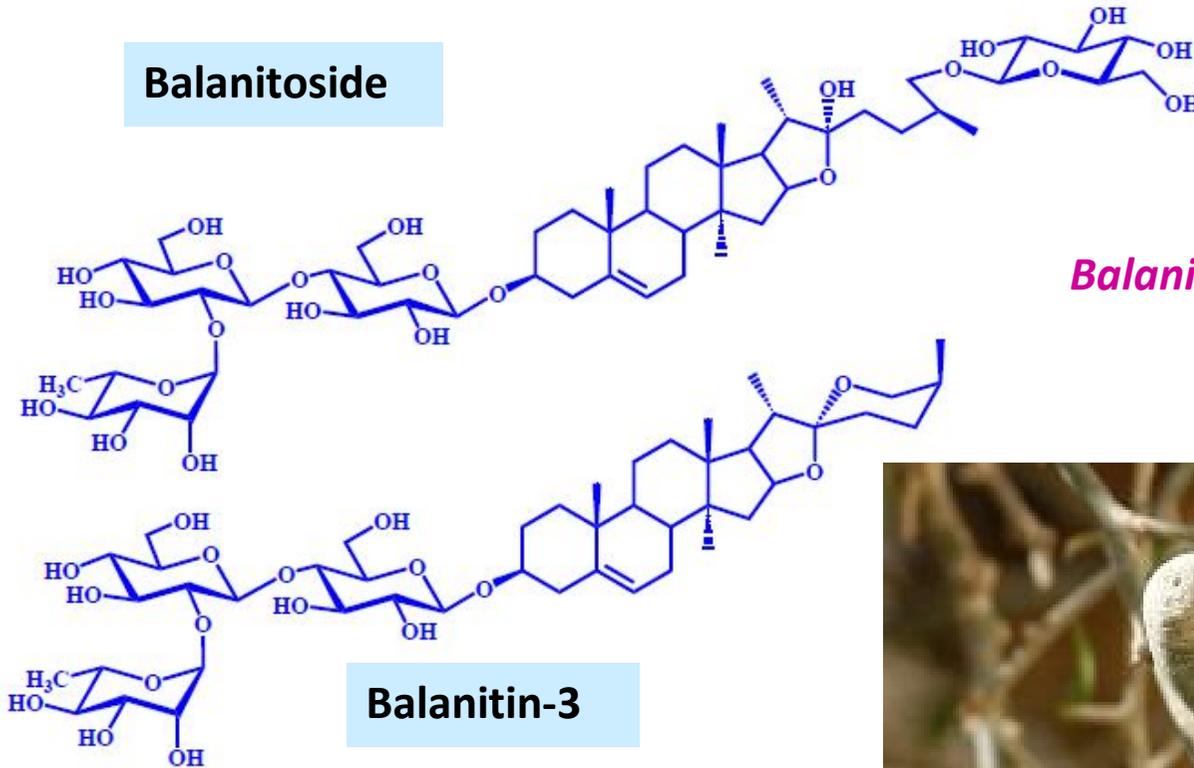
Diosgenin'den kortikosteroidlerin sentezi



STEROİDAL SAPOGENİNLER

Steroida! Sapogenoller – Furostan & Spirostan tip

Balanitocide



Balanitin-3

Hosny et al.,
Phytochemistry 31, 3565 (1992)

Kull.: Meyvalar yenilebilir, Laktasyonu arttırmak için kullanılır

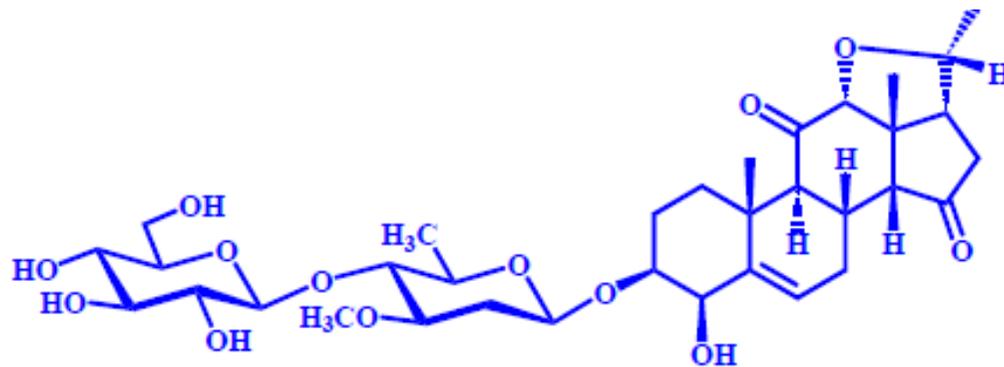
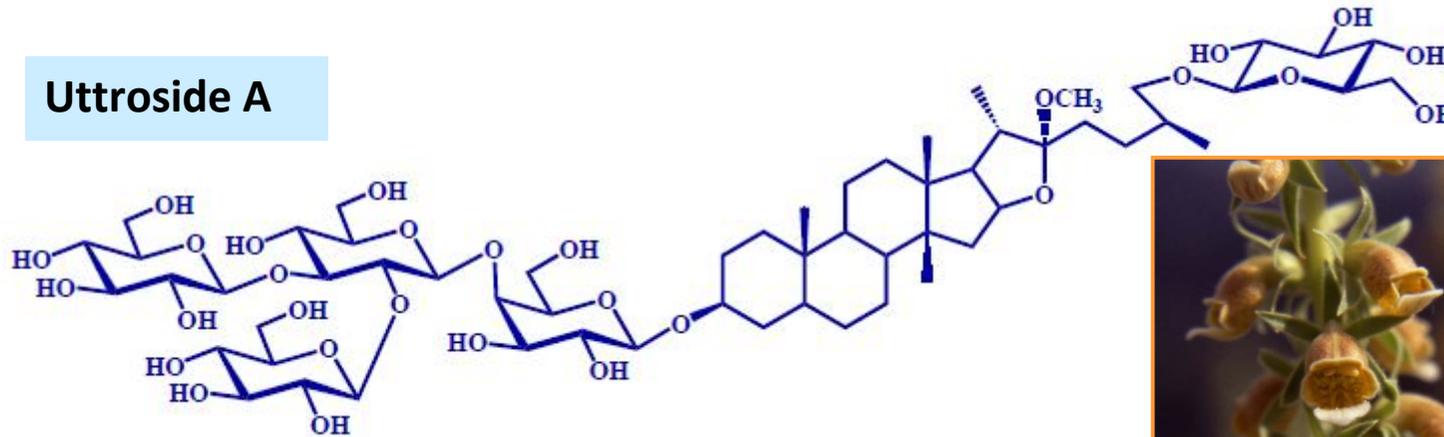
Balanites aegyptiaca



Zygophyllaceae

Steroidal Sapogenoller – Furostanol & Pregnan

Uttroside A



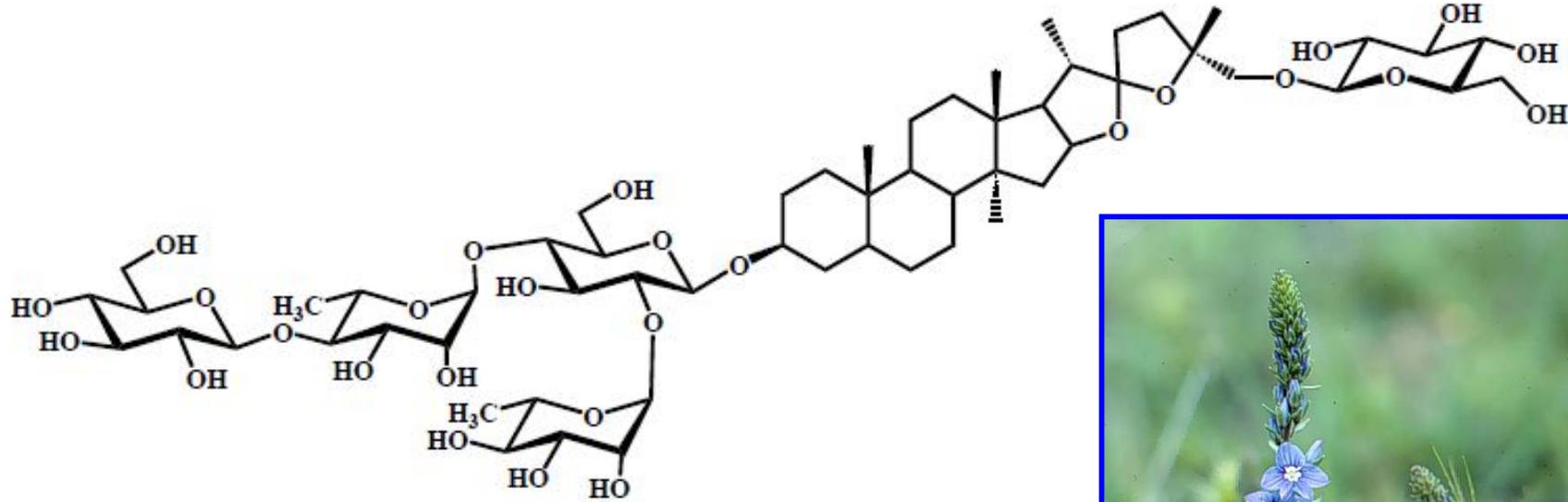
Digifoligenin

3-O- β -glucopyranosyl-(1 \rightarrow 4)- β -oleandropyranoside



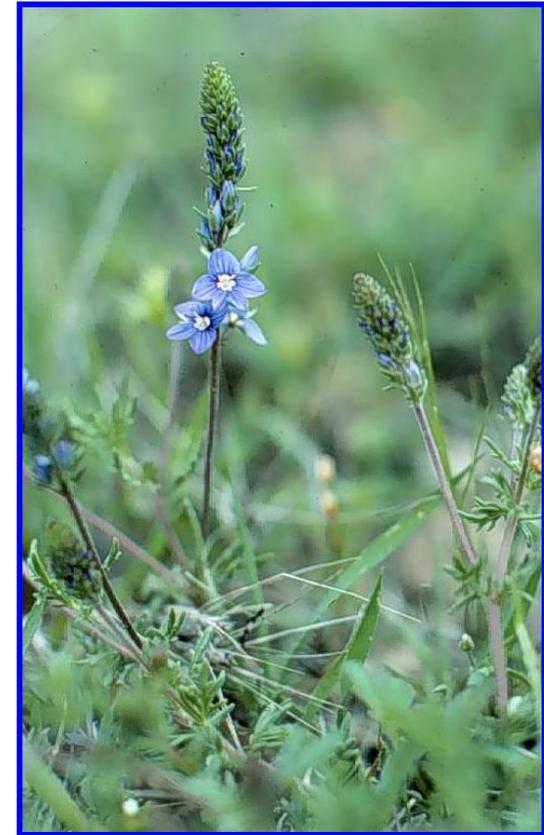
Digitalis cariensis
Scrophulariaceae

Steroida! Sapogenoller – Spirofuran tip

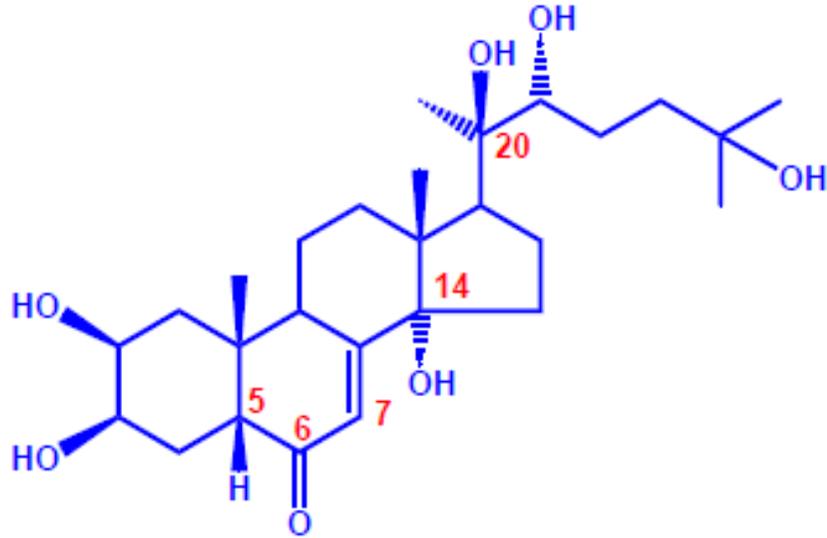


*Multifidoside
Aculeatoside A

Veronica fuhsii ve *V. multifida*
PLANTAGINACEAE



Ekdisteroitler (ES), Fitoektisteroitler (FES)



Dağılımları (Yayılılıları):

**EĞRELTİLER,
AÇIK ve KAPALI TOHURLU BİTKİLER**

Kullanım Alanları:

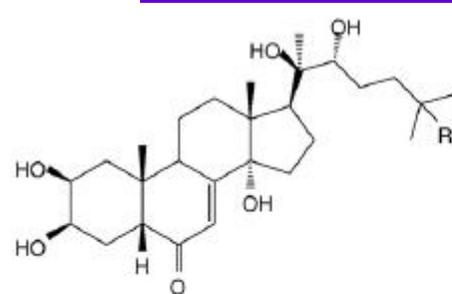
**Ziraai: İpek verimini art., insektisit,
ürünlerde "ES" seviyesini arttırmak
Biyomedikal: Anabolik, tonik, spermatisit,
Hepatoprotektif, Kanserden koruyucu**

- Fitoektisteroitler, **invertebrat** (omurgasız hayvan)'larda bulunan, bir hormon olan ekdisteroit, **20-hidroksiekdizon** yapısına benzer yapılı bitkisel steroidlerdir.
- Karbon sayısı deęişken (C_{27} , C_{28} veya C_{29}) **14 α -hydroxy-7-en-6-on** kromofor grubu taşıyan, **A/B** halkalarının kenetlenmesi **cis (5 β -H)** olan steroidal bileşiklerdir.

Fitosteroller - Fitoekdisteroitler

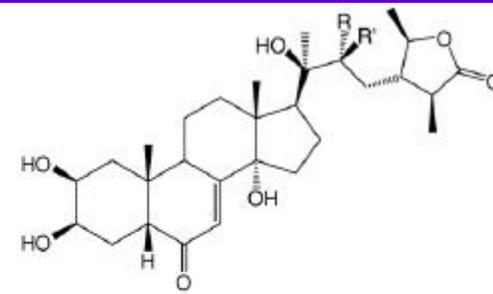
Ajuga nipponensis

- *Ajuga* türleri
- **Kull.: Performans arttırma (doping) amaçlı**



1, R=OH (20-hydroxyecdysone, 20E)

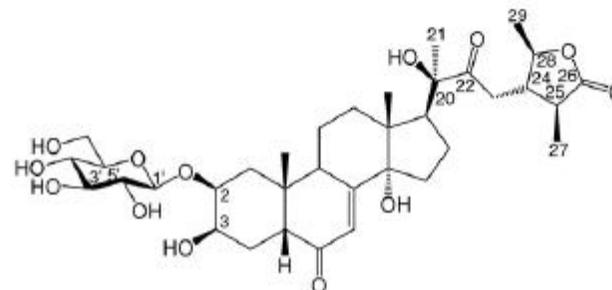
3, R=H (ajugasterone C, AJC)



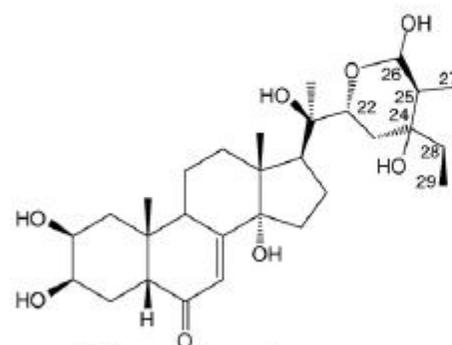
2, R=OH, R'=H (cyasterone)

4, R=OAc, R'=H (cyasterone 22-acetate)

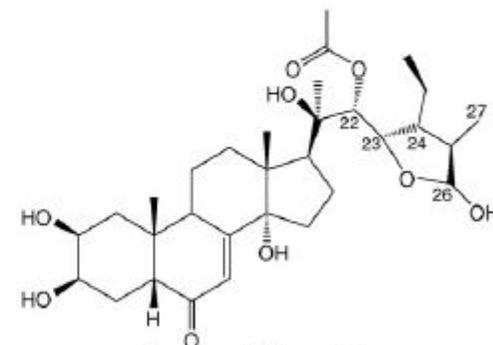
5, RR'=O (22-dehydrocyasterone)



6, 22-Dehydrocyasterone 2-glucoside



7, Ajugacetalsterone A



8, Ajugacetalsterone B

Fig. 4 – Structures of compounds 1–8.

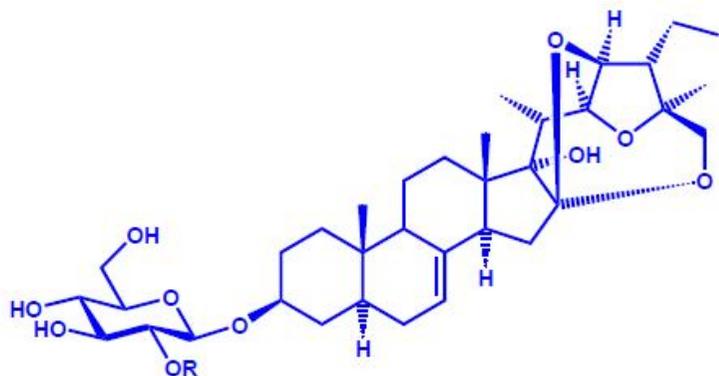
Coll J et al. (2007). **STERIODS** 72, 270 - 277

***Ajuga salicifolia* 'dan Antilösemik Sterol Glikozitleri**

- ***Ajuga*** (Lamiaceae)
- Türkiye Florası'nda 11 tür
- **Kull.:** Halk arasında, **yara iyileştirici, diüretik, diyare tedavisinde ve yüksek ateşte** kullanıldığı bilinmektedir.
- **Kimyasal kompozisyonu:** *Ajuga* türleri üzerindeki çalışmalar **fitoekdisteroitler and diterpenler**

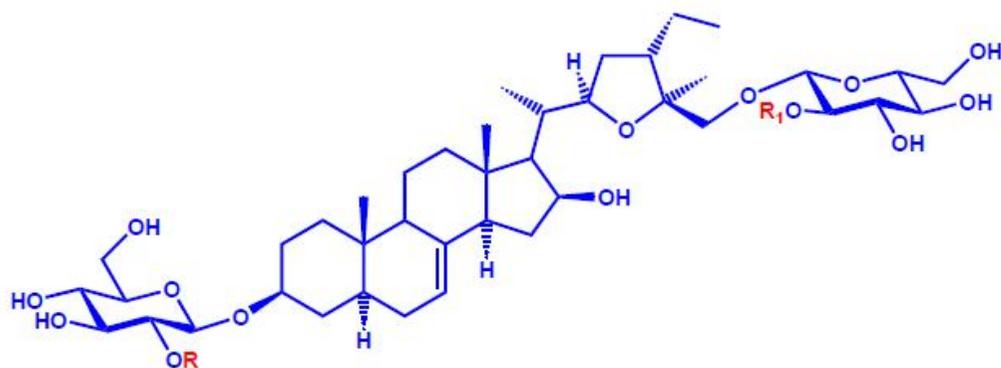


Ajuga salicifolia 'dan Antilösemik Sterol Glikozitleri



Ajugasalicifolioside A: R = H

Ajugasalicifolioside B: R = β -Glukoz

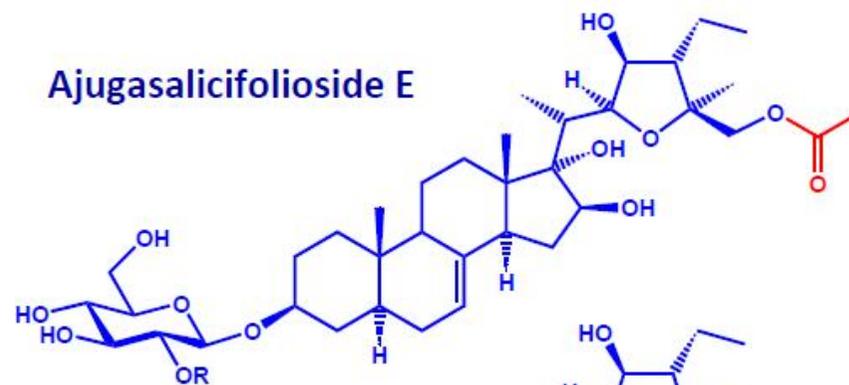


Ajugasalicifolioside C: R = H

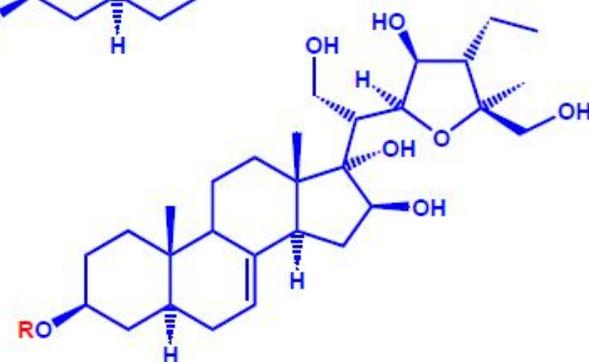
Ajugasalicifolioside D: R = β -Glukoz

Ajugasalicifolioside H: R = R₁ = β -Glukoz

Ajugasalicifolioside E



Ajugasalicifolioside G



Ajugasalicifolioside F; R = β -D-Glucose

Ajugasalicigenin; R = H

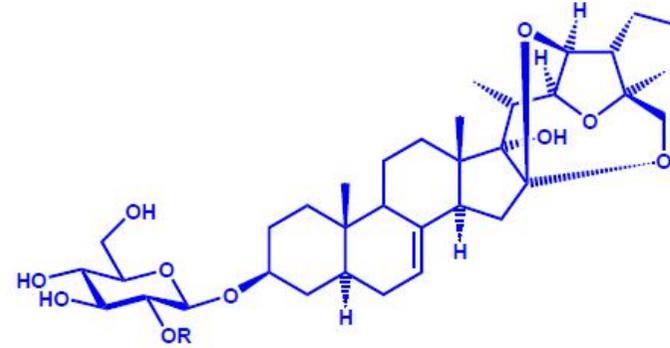
Akbay *et al.*, *Helv.Chim. Acta* **85**, 1930 – 1942 (2002)

Akbay *et al.*, *J. Nat. Prod.* **85**, 461 – 465 (2003)

Ajuga salicifolia – Sterol Glikozitleri

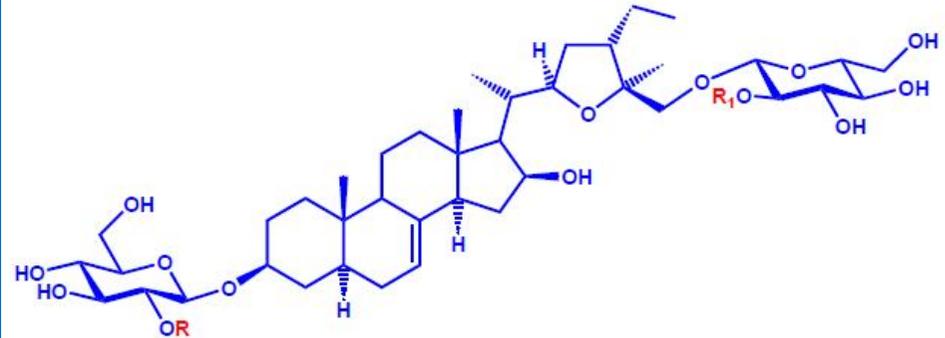
Sitotoksisite Çalışmaları:

- **KB (HeLa)** hücrelerinde aktivite gözlenmedi.
 - **Jurkat T** Lösemi hücrelerinde ise anlamlı ($IC_{50} < 10 \mu\text{m}$) etki.
 - **Ajugasalisiozit A, B, C** ve **D'** nin spesifik olarak Jurkat T- lösemi hücrelerinin yaşama özelliklerini (viability) ve gelişmesini $10 \mu\text{m}$ konsantrasyonun altında inhibe ettiği saptandı.
- En aktif bileşikler:
- **Ajugasalicioside A** ($IC_{50} = 6 \mu\text{m}$) ve **C** ($IC_{50} = 3 \mu\text{m}$)



Ajugasalicifolioside A: R = H

Ajugasalicifolioside B: R = β -Glukoz



Ajugasalicifolioside C: R = H

Ajugasalicifolioside D: R = β -Glukoz

Ajugasalicifolioside H: R = R₁ = β -Glukoz

Kukurbitasinler (CUCURBITACEAE)

- **Kudret Narı,**
 - *Momordica charantina*
- **Eşek Hıyarı,**
 - *Ecballium elaterium*
- **Şeytan şalgamı,**
 - *Bryonia dioica*
- **Ebucehil Karpuzu,**
 - *Citrullus colocynthis*
- **Balkabağı,**
 - *Cucurbita moschata*

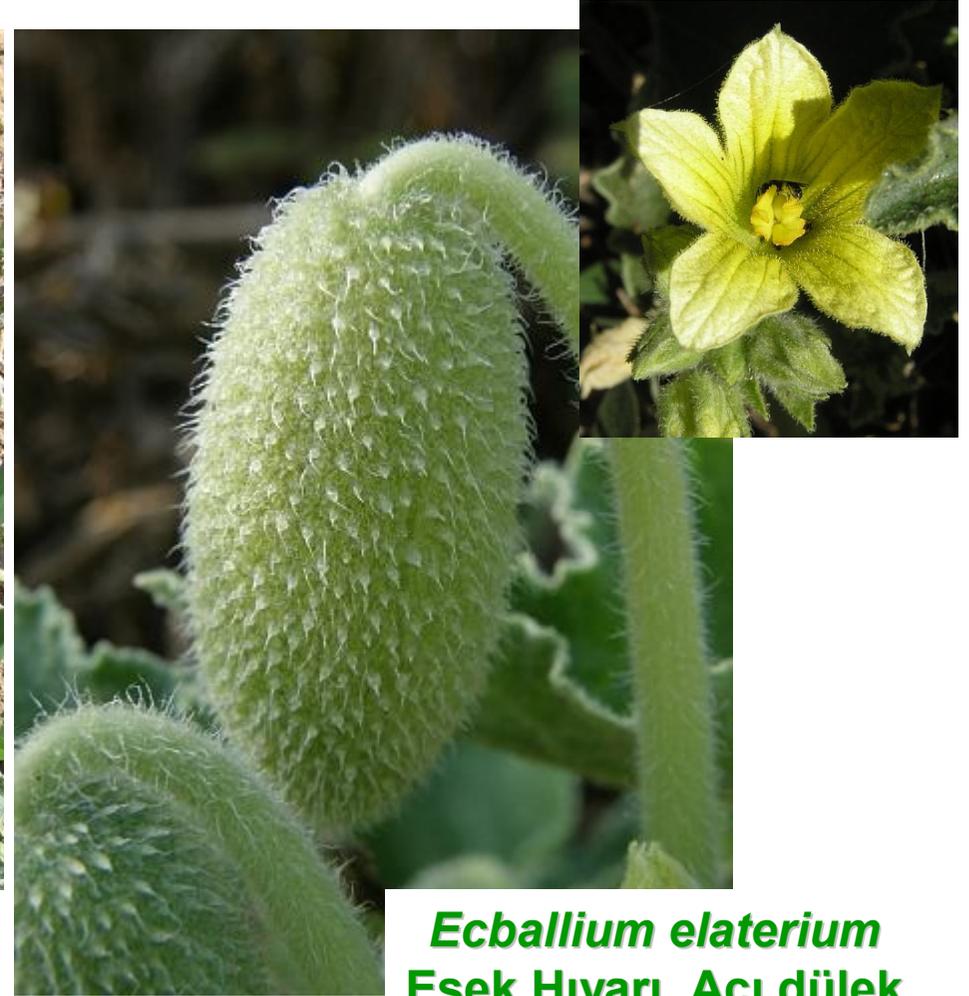


Kukurbitasinler (CUCURBITACEAE)



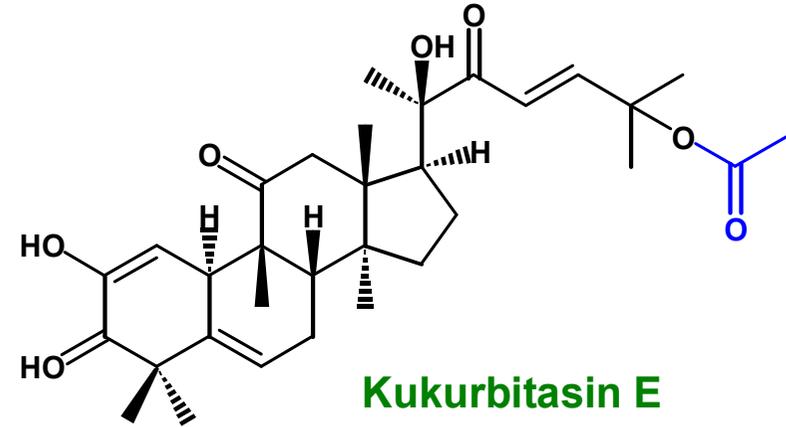
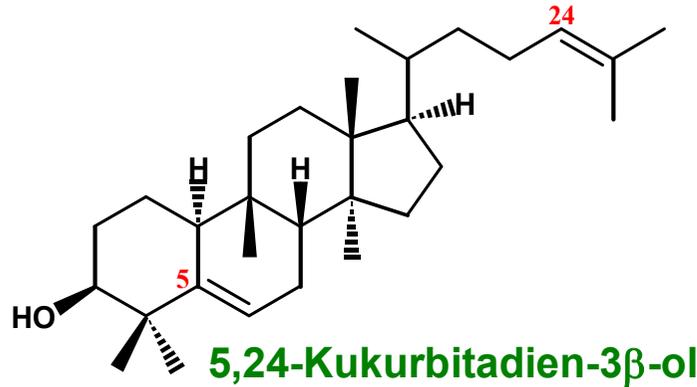
Citrullus colocynthis
Ebucehil karpuzu

KKTC



Ecballium elaterium
Eşek Hıyarı, Acı dülek

Kukurbitasinler (CUCURBITACEAE)



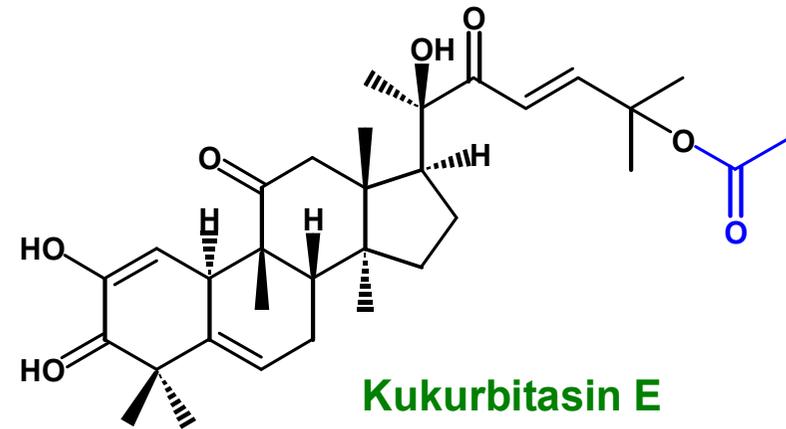
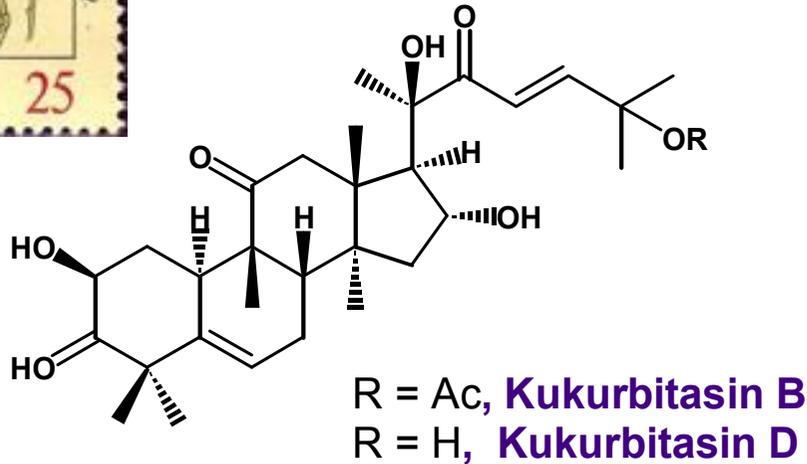
- **Antioksidan ve serbest radikal süpürücü**
 - T. Tannin-Spitz et al. (2007). **Biochem. Biophys. Res. Comm.** **364**, 181–186
- **Sitotoksik Aktivite** (human leukemia U937 cells)
 - S. Nakashima et al. (2010). **Bioorg. Med. Chem. Lett.** **20**, 2994–2997
- **Antienflammatuar Aktivite (*Ecballium elaterium*) Sinuzit**
 - E. Yeşilada et al. (1988). **J. Nat. Prod.** **51**, 504 - 508



KUKURBITASINLER

Bryonia cretica (CUCURBITACEAE)

Şeytan Şalgamı



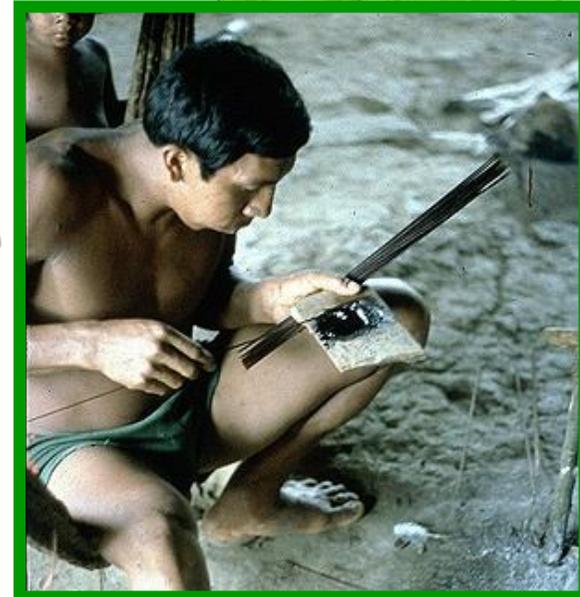
- **Sitotoksik Aktivite** (human leukemia U937 cells)
 - H. MATSUDA et al. (2010).
Chem.Pharm.Bull. 58, 747-751
- **Kukurbitasin B** ve **E** ile gözlenen sitotoksik aktivite ($IC_{50} = 9.2$ ve 16 nM after 72 h) **camptothecin** ile aynı.

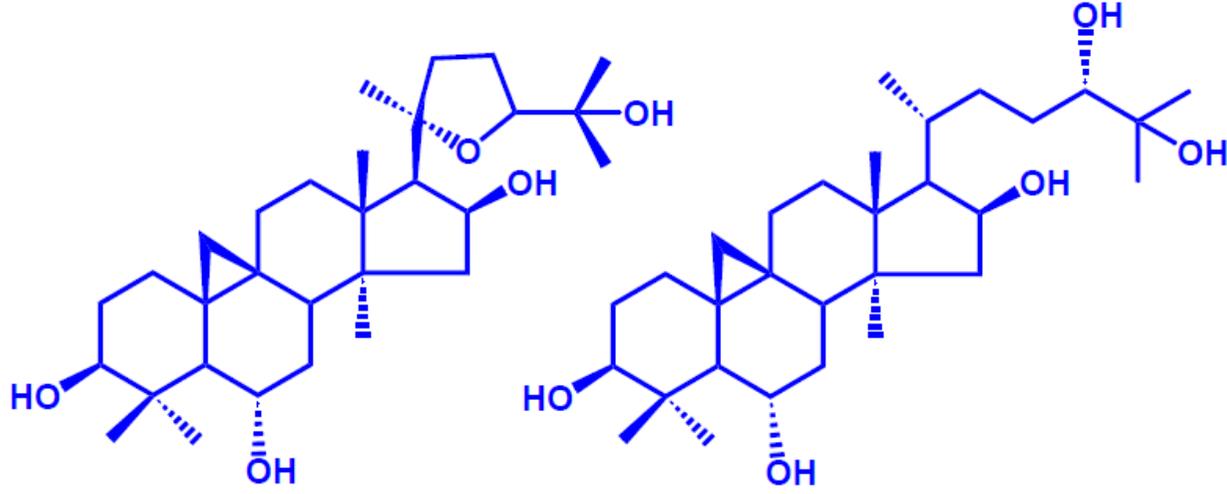


Kardenolitler - Bufadienolitler

KARDİYOAKTİF GLİKOZİTLER = KARDİYOTONİKLER

- **OK ZEHİRLERİ** →
- KARDİYOTONİK GLİKOZİTLER
- KARDENOLİT VE BUFADİENOLİTLERİN HAYVANSAL DOKUDA DA (adrenal bezler & beyin) SENTEZLERİ
- **Hipertansiyon, depresyon ve kanserde** POTANSİYEL İLAÇ ADAYLARI





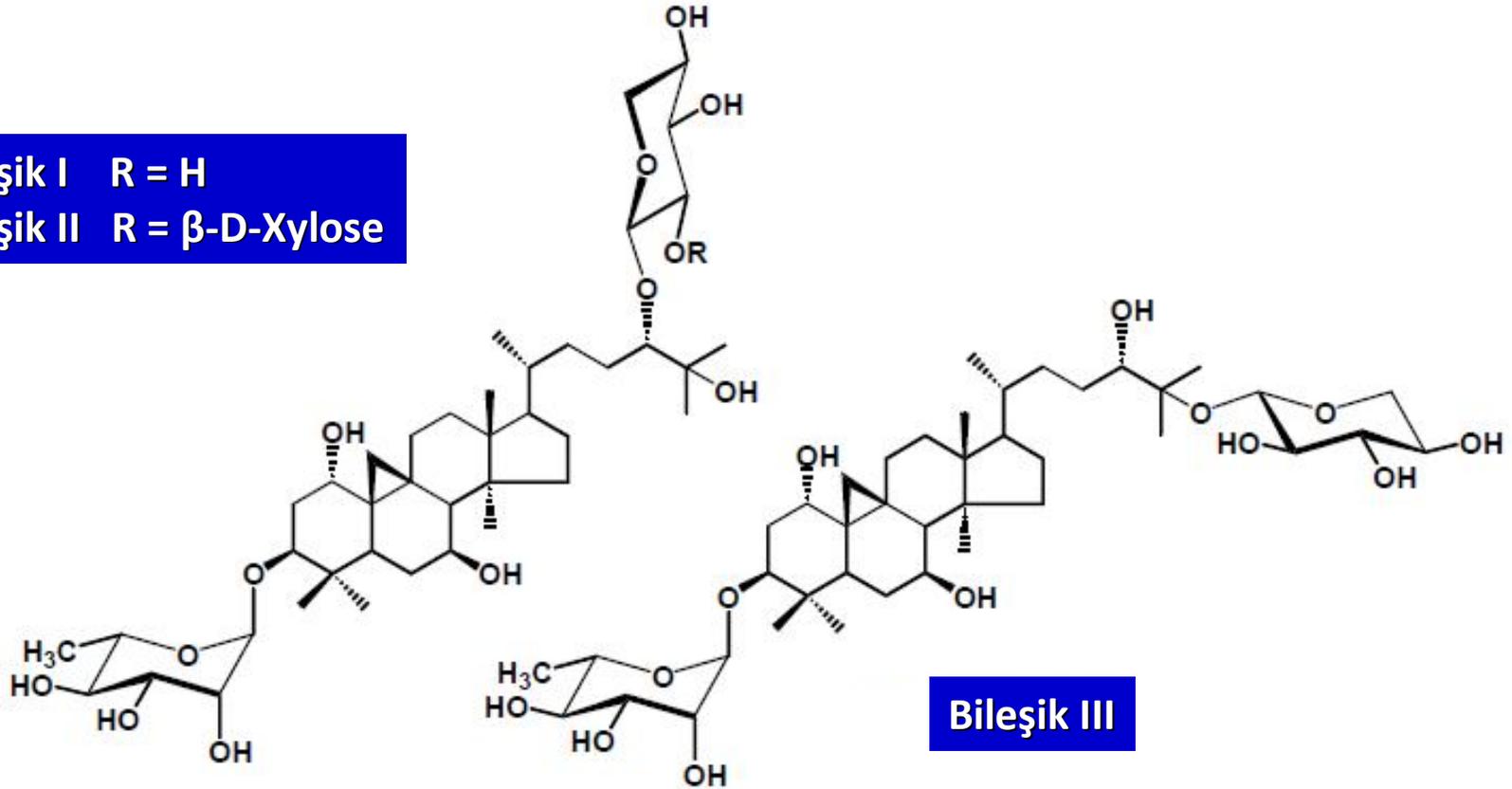
SİKLOARTAN GLİKOZİTLERİ

İlk çalışma

GATA: Lösemili Hasta Orijini belli olmayan kökler

Bileşik I R = H

Bileşik II R = β -D-Xylose



Bileşik III

1,3,7,24,25-pentahidroksi-sikloartan türevleri

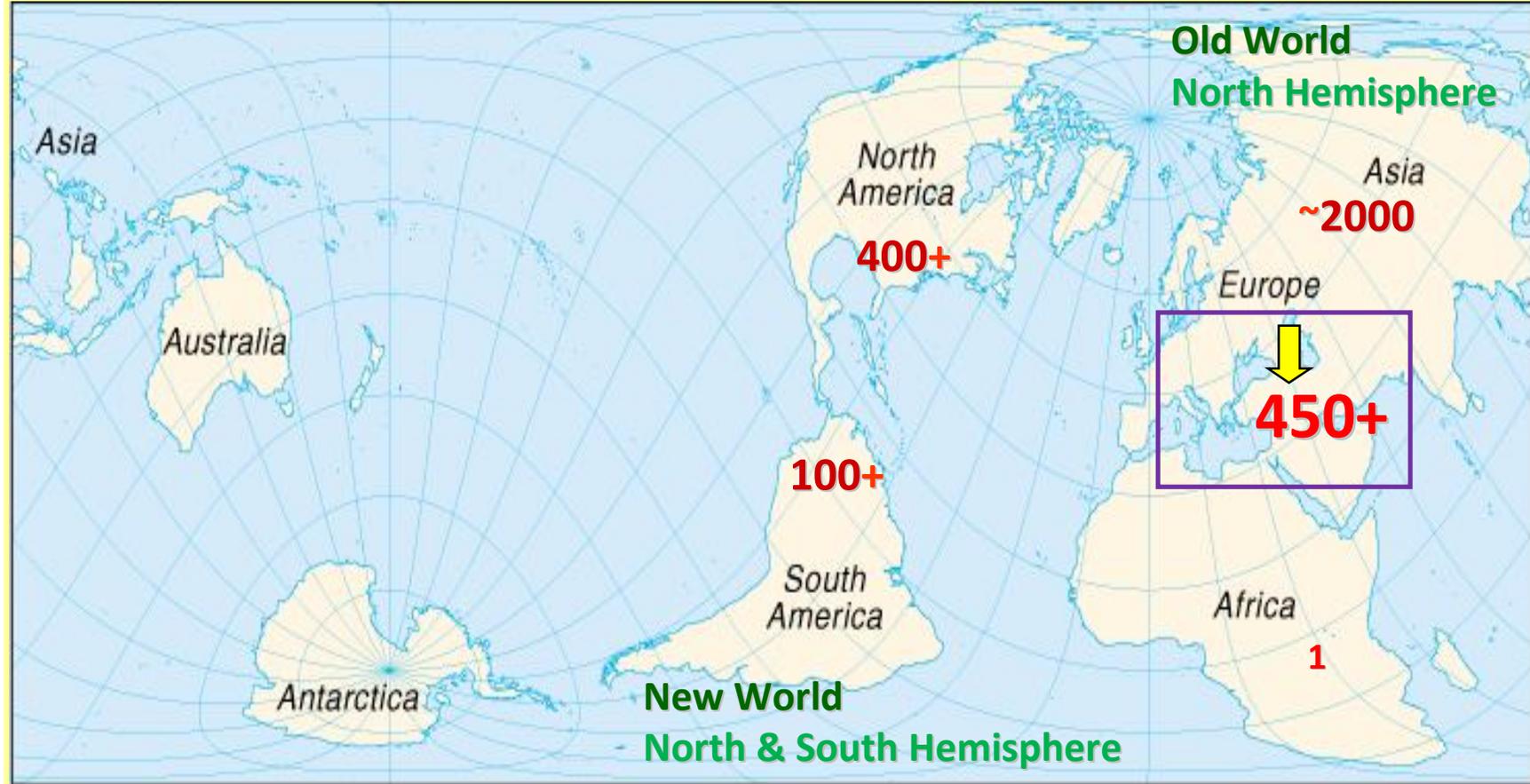
Sikloartanların yayılışı

- **MELIACEAE**
 - *Heynea, Aglaia, Swetenia*
- **ORCHIDACEAE**
 - *Cirrhopetalum, Pholidoda, Cymbidium*
- **PASSIFLORACEAE**
 - *Passiflora*
- **COMBRETACEAE**
 - *Combretum*

- **ARALIACEAE**
 - *Acanthopanax*
- **RANUNCULACEAE**
 - *Thalictrum, Cimicifuga*
- **LEGUMINOSAE**
 - *Astragalus, Abrus*

Yayılıř

134 Section / 3000 tür
Endemizm: Yüksek, %51



Tüm dünyada 3000'den fazla tür bulunmakta,
2000'den fazlası ise Asya'da bulunuyor. **Türkiye'de**
>450

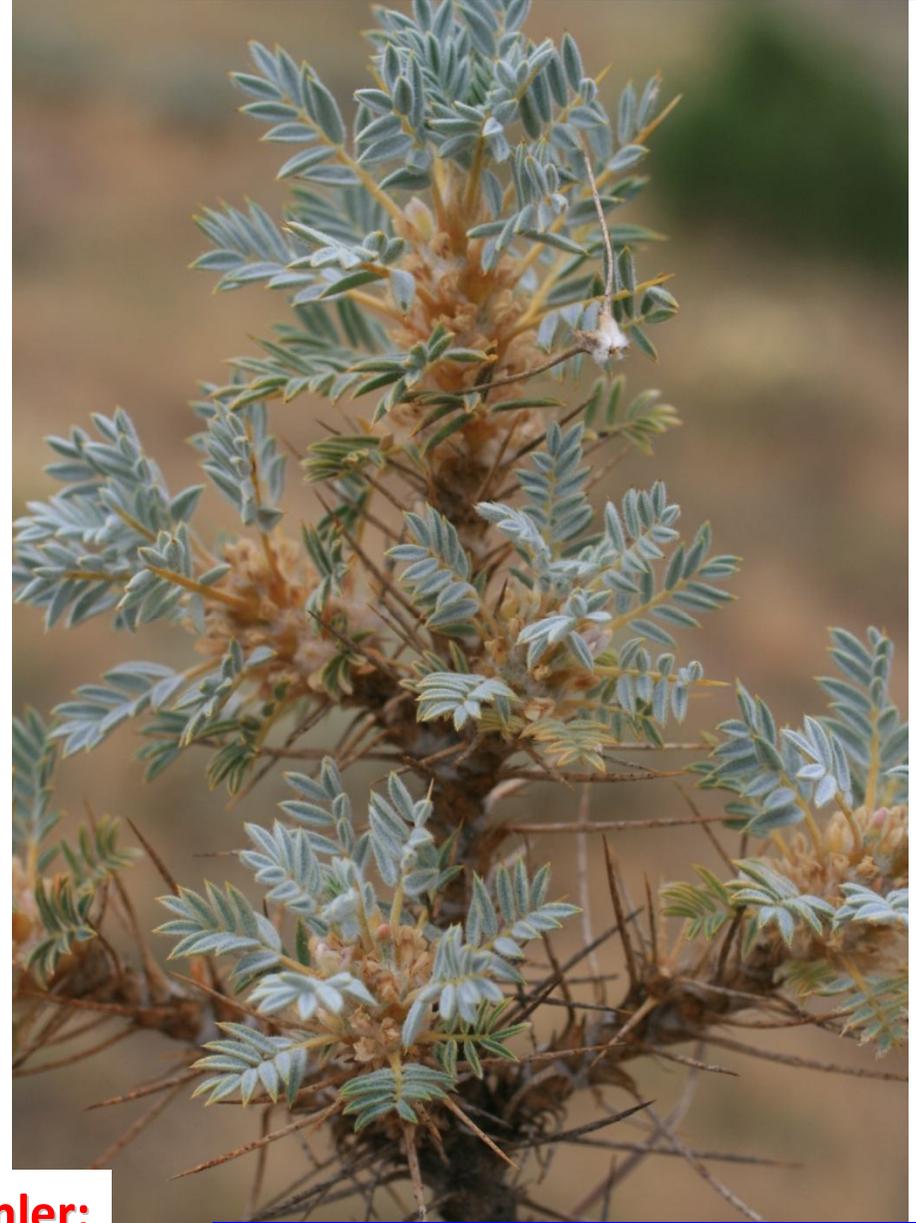
SECT.: CHRISTIANA



Z. Aytaç

Astragalus caraganae

SECT.: RHACOPHORUS



**Resimler:
Z. Aytaç**

Astragalus microcephalus

GUM TRAGACANTH

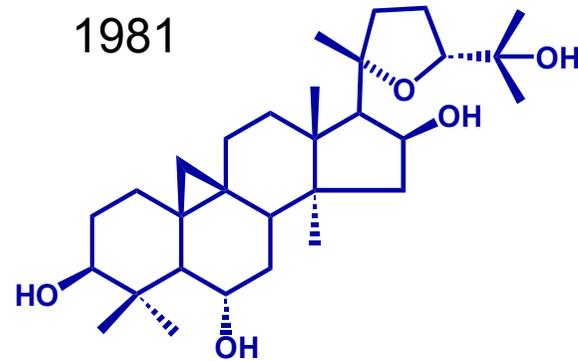
TRAGACANTHA, Kitre

- Birçok *Astragalus* türü GB ve G Asya ülkelerinde “**Kitre Zamkı**” elde etmek amacıyla kullanılıyor.
- ECZACILIK TEKNOLOJİSİ VE KOZMETOLOJİDE:
 - **Viskozite arttırıcı, emülsifiyan**



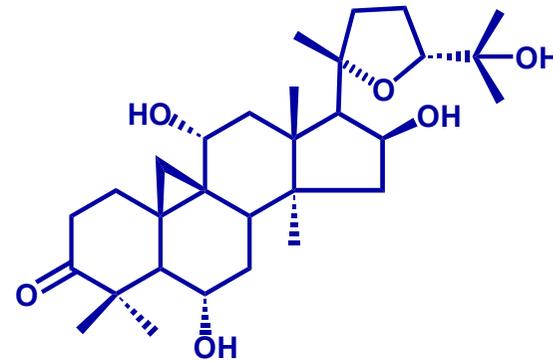
- **TÜRKİYE'de**
- *Astragalus aureus*,
- *Astragalus brachycalyx*
- *Astragalus microcephalus*
- *Astragalus gummifer*

İlk Sikloartanlar (1981)



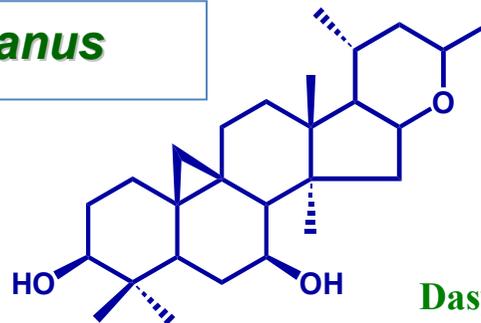
Cyclosieversigenin

A. sieversianus



Cycloasgenin A

A. taschkendicus



Dasyanthogenin

A. dasyanthus

A.N.Svechnikova et al., *Khim. Prir. Soedin.*, No 1, 67-76 (1981)

M.I.Isaev et al., *Khim. Prir. Soedin.*, No 5, 572-581 (1981)

R.I.Eustratova et al., *Khim. Prir. Soedin.*, No 1, 102-103 (1981)

Sikloartan (Cycloartane) Glikozitleri

□ Glikozitler

□ Monodesmozitler

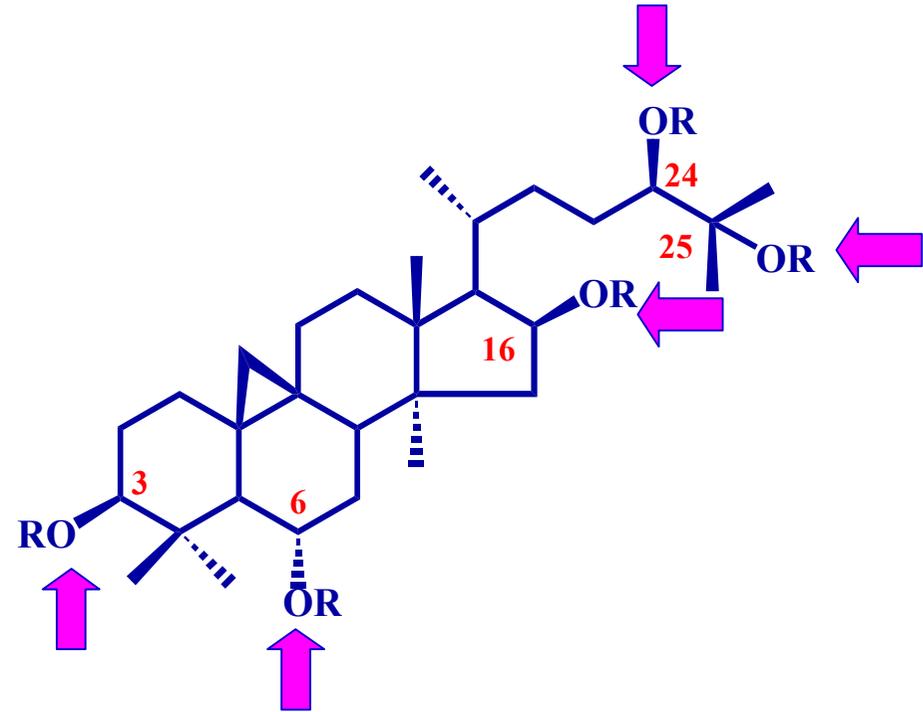
□ Bidesmozitler

□ Tridesmozitler

▪ Şekerler (Monozlar)

- β -D-glukopiranoz
- β -D-ksilopiranoz
- α -L-arabinopiranoz
- α -L-ramnopiranoz
- β -D-apiofuranoz
- β -D-glukuronopiranoz

➔ Glikozidasyon konumları

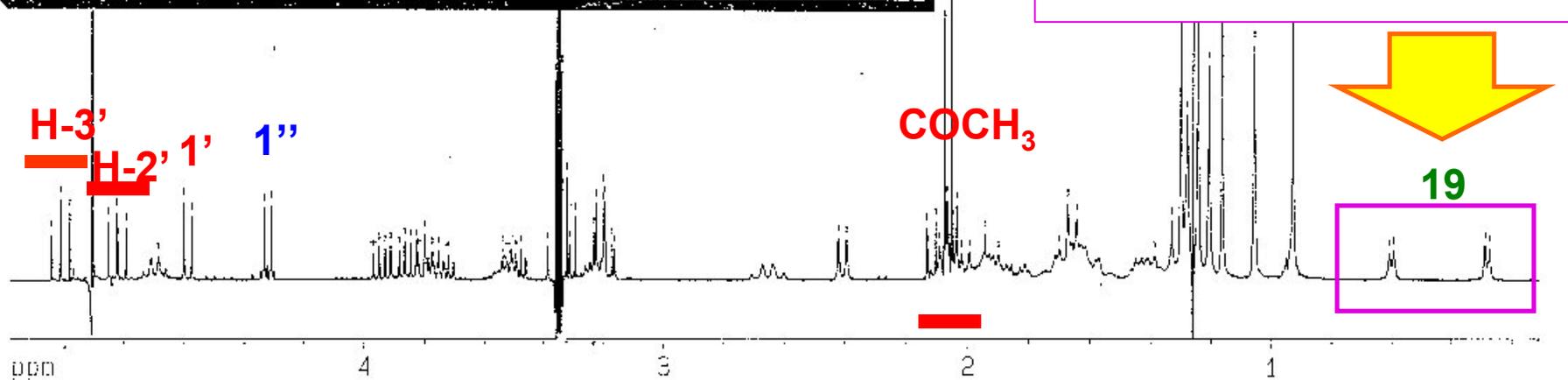
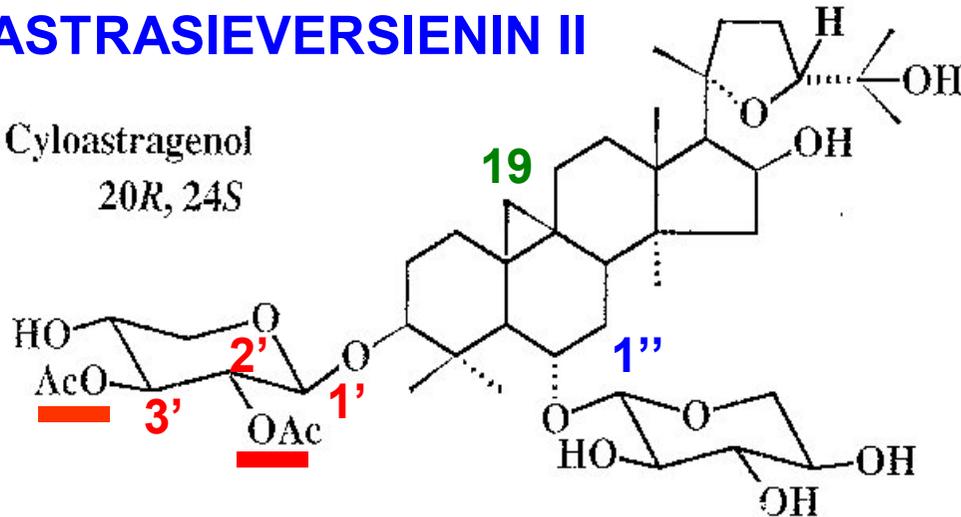


Steroid üzerindeki yapısal farklılıklar:
a.C-17'deki yan zincirde oksidasyon ve epoksidasyona bağlı farklılıklar
b.Steran iskeletindeki hidroksilasyonlar

SİKLOARTANLARIN $^1\text{H-NMR}$ Spektrumları

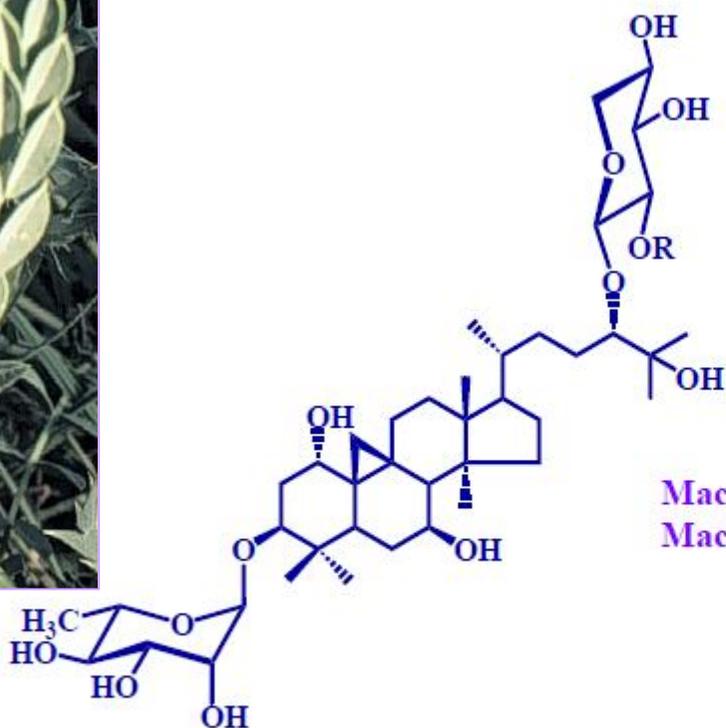
ASTRASIEVERSIENİN II

Cyloastragenol
20R, 24S

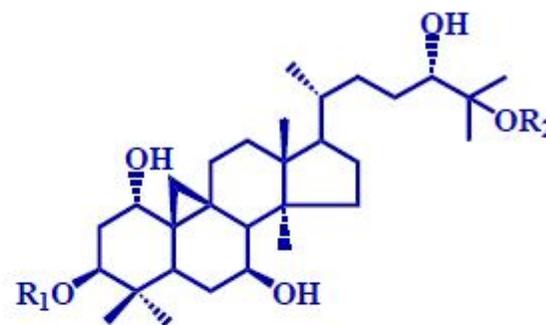


KARAKTERİSTİK ÖZELLİKLERİ: Siklopropan halkasının **metilen** protonları

Astragalus oleifolius (Section: **Macrophyllum**)



Macrophyllisosaponin A: R = Ac
Macrophyllisosaponin B: R = H
Macrophyllisosaponin D: R = Xylose



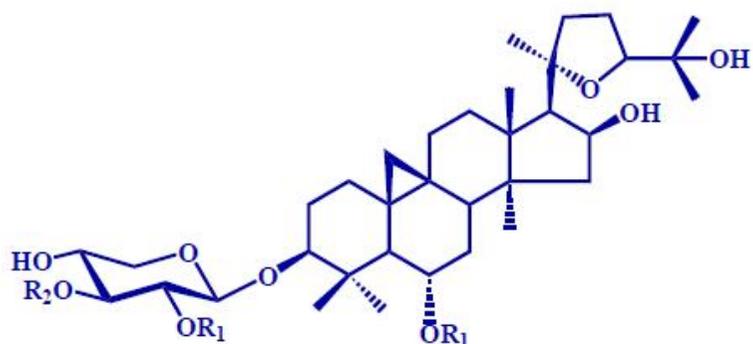
Macrophyllisosaponin C: R₁ = Rhamnose; R₂ = Xylose
Macrophyllisosaponin E: R₁ = R₂ = Glucose



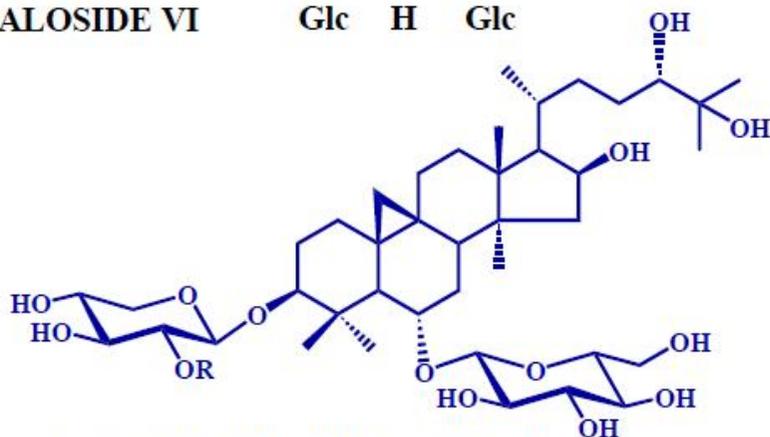
İ.Çalış *et al.*, *J. Nat. Prod.* **59**, 1019-1023 (1996)
E. Bedir *et al.*, *Chem. Pharm. Bull.* **48**, 1081-1083 (2000)

Astragalus melanophrurius

SECTION: CHRISTIANA



ASTRASIEVERSIANIN II	Ac	Ac	Xyl
ASTRASIEVERSIANIN X	H	H	Xyl
ASTRAGALOSIDE I	Ac	Ac	Glc
ASTRAGALOSIDE II	Ac	H	Glc
ASTRAGALOSIDE IV	H	H	Glc
ASTRAGALOSIDE VI	Glc	H	Glc



CYCLOCANTHOSIDE E	R = H
CYCLOCANTHOSIDE G	R = Glc



Biolojik Aktivite - *In vitro* test sistemleri

- **ANTIMALARIAL AKTİVİTE** (*Plasmodium falciparum*)
- **SİTOTOKSİK AKTİVİTE**
 - Cultured Lu1 (human lung)
 - LNCaP (prostate)
 - ZR-75-1 (human breast)
 - P-388, KB and KB-V1 (drug resistant KB)
- **ÖSTROJENİK & ANTI-ÖSTROJENİK AKTİVİTE**
 - (Ishikawa cells)
- **ANTİOKSİDAN**
 - (Colorimetric dye assay)
- **ANTİMUTAJENİK**
 - (*Salmonella typhimurium* strain TM677)
- **PROTEİN KİNAZ C ile Etkileşimleri**
 - (by studying the effect on binding of PDBu)
- **SİKLOOKSGENAZ inhibisyonu**

A. melanophrurius SİKLOARTANLARI

Lenfosit stimulation test:

Her bileşimin insan lenfosit çoğalmasını (proliferasyon) uyardığı saptandı.

Kons. 0.01 – 10 µg/ml.

Daha Yüksek Konsantrasyonlarda:

(100 – 200 µg/ml),

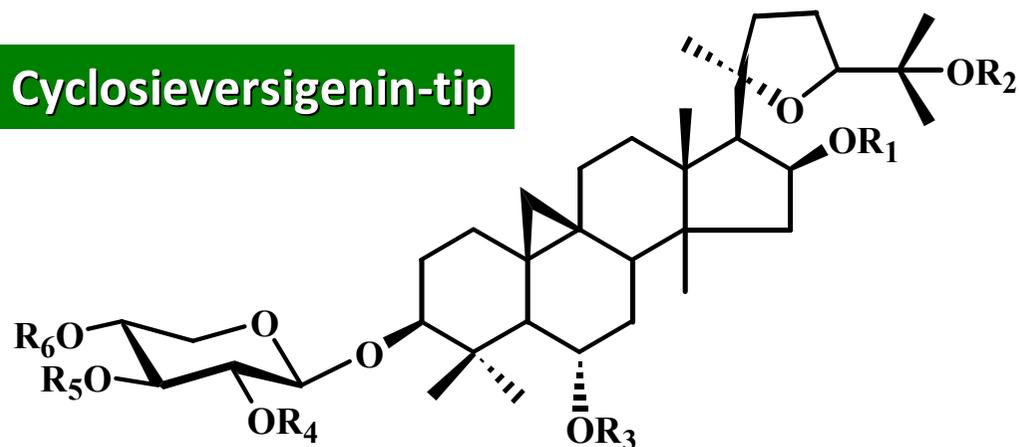
Timidin (thymidine) katımını inhibe ettikleri gözlemlendi.

Astragalus trojanus

Sectio: PTEROPHORUS



Cyclosieversigenin-tip



Trojanoside A

Trojanoside B

Trojanoside H

Trojanoside I

Trojanoside J

Trojanoside K

Astrasiversianin IX

Astrasiversianin XV

R ₁	R ₂	R ₃	R ₄	R ₅	R ₆
COCH ₃	H	β-D-glu	H	H	H
H	β-D-glu	β-D-glu	H	H	H
H	H	β-D-glu	α-L-ara	H	H
COCH ₃	H	β-D-glu	COCH ₃	COCH ₃	H
H	H	β-D-xyl	α-L-ram	COCH ₃	COCH ₃
β-D-glu	H	β-D-glu	H	H	H
H	H	β-D-xyl	α-L-ram	COCH ₃	H
H	H	β-D-xyl	α-L-ram	H	H

E. Bedir *et al.*, *J. Nat. Prod.* **62**, 563-568 (1999)

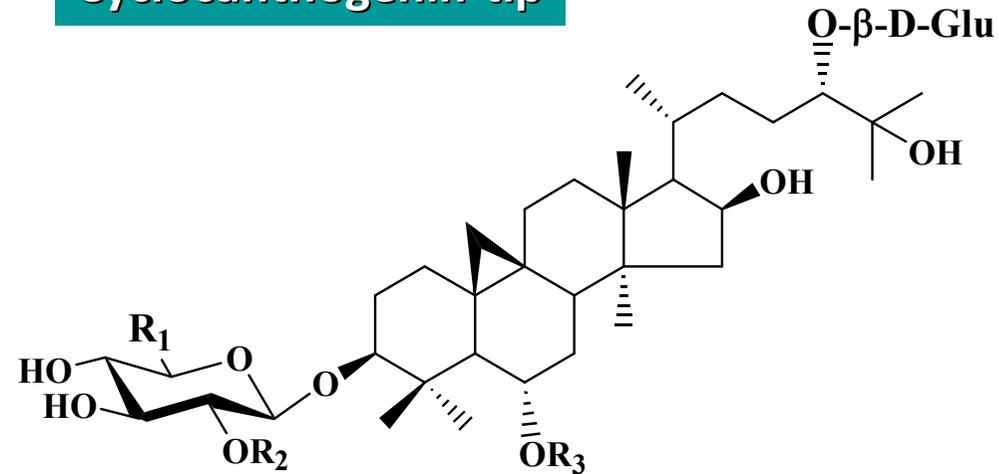
E. Bedir *et al.*, *Phytochemistry* **51**, 1017-1020 (1999)

Astragalus trojanus

Sectio: PTEROPHORUS



Cyclocanthogenin-tip



Trojanoside C
Trojanoside D
Trojanoside E
Trojanoside F

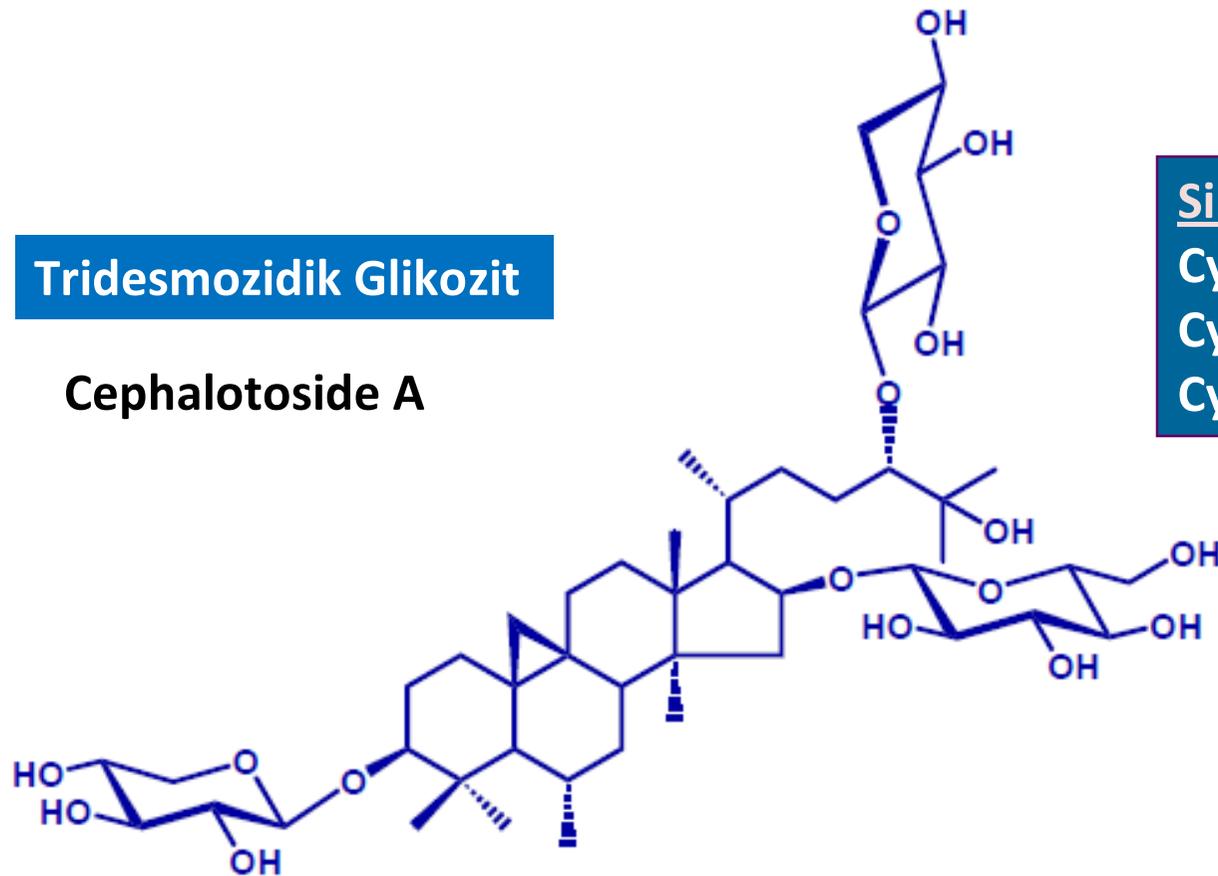
R ₁	R ₂	R ₃
H	α -L-rhamnose	H
CH ₂ OH	H	β -D-glucose
H	α -L-rhamnose	β -D-glucose
H	α -L-arabinose	β -D-glucose

Astragalus cephalotes

Section: Rhacophorus

Tridesmozidik Glikozit

Cephalotoside A



Sikloartanlar:

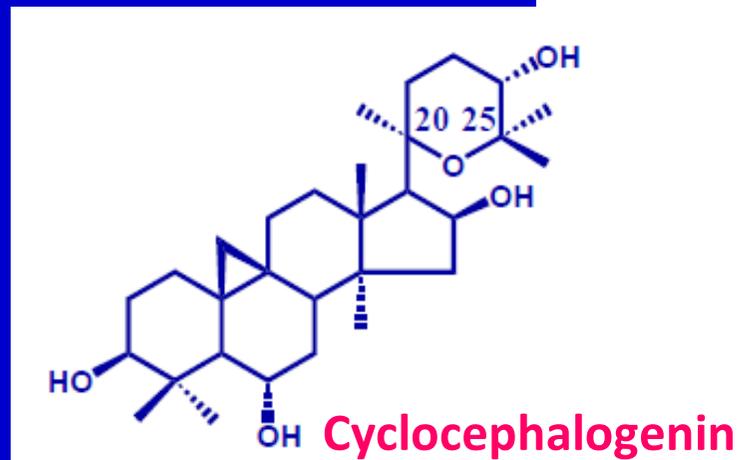
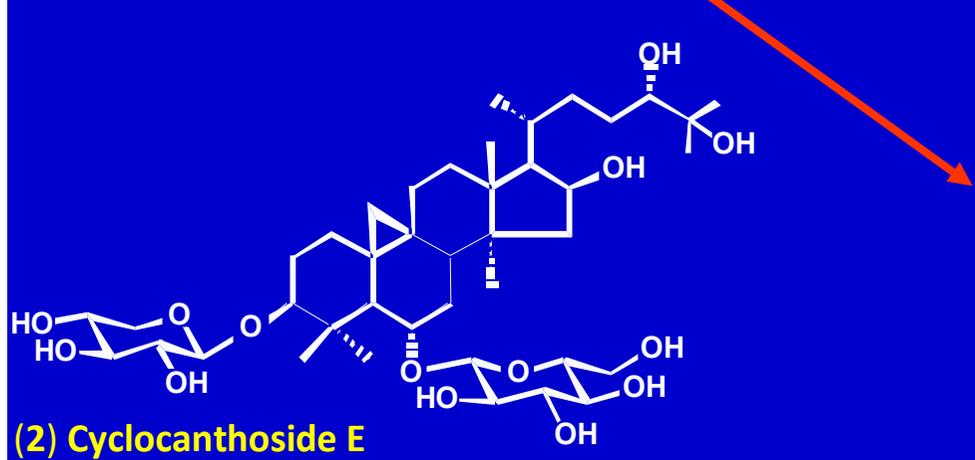
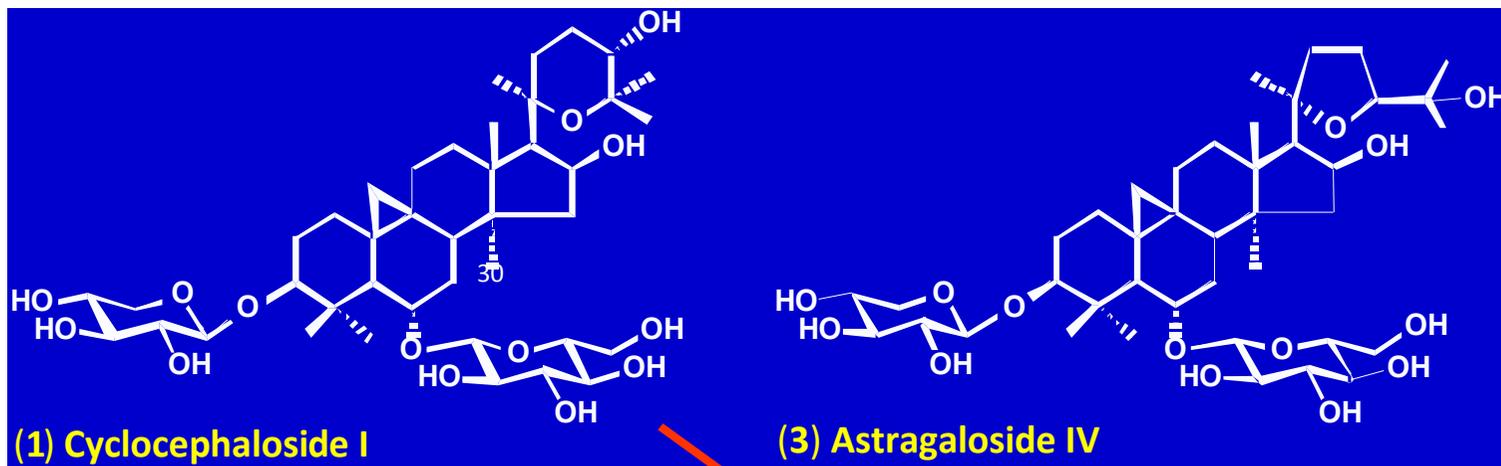
Cyclocanthoside A

Cyclocanthoside D

Cyclocanthoside E

Astragalus microcephalus

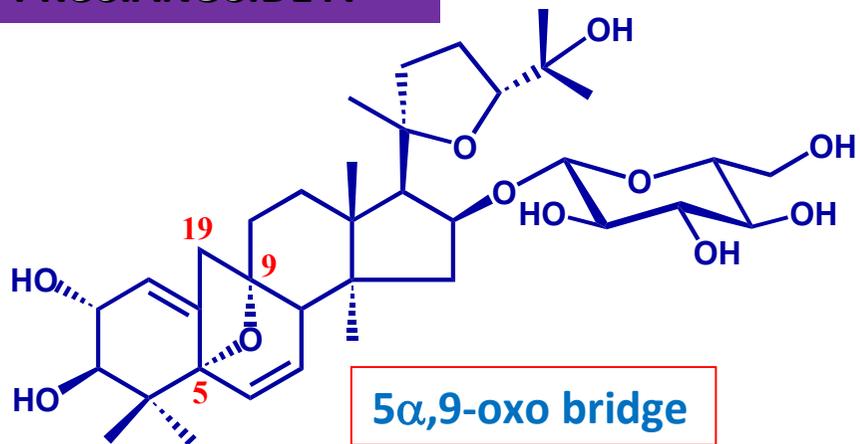
SECTION: RHACOPHORUS



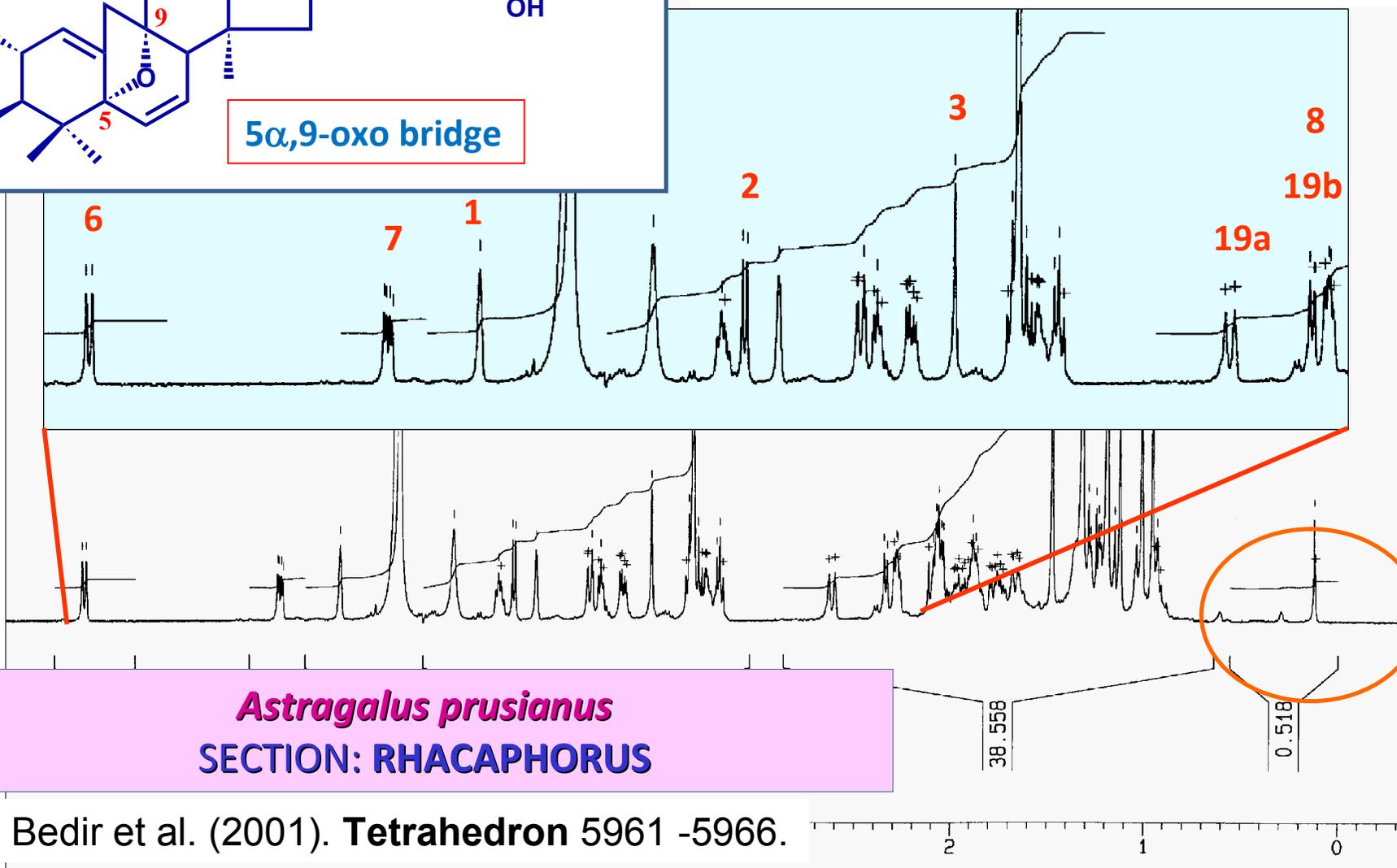
E. Bedir *et al.*, *J. Nat. Prod.* 61, 1469-1472 (1998)

20,25-Epoxycycloartanes*

PRUSIANOSIDE A

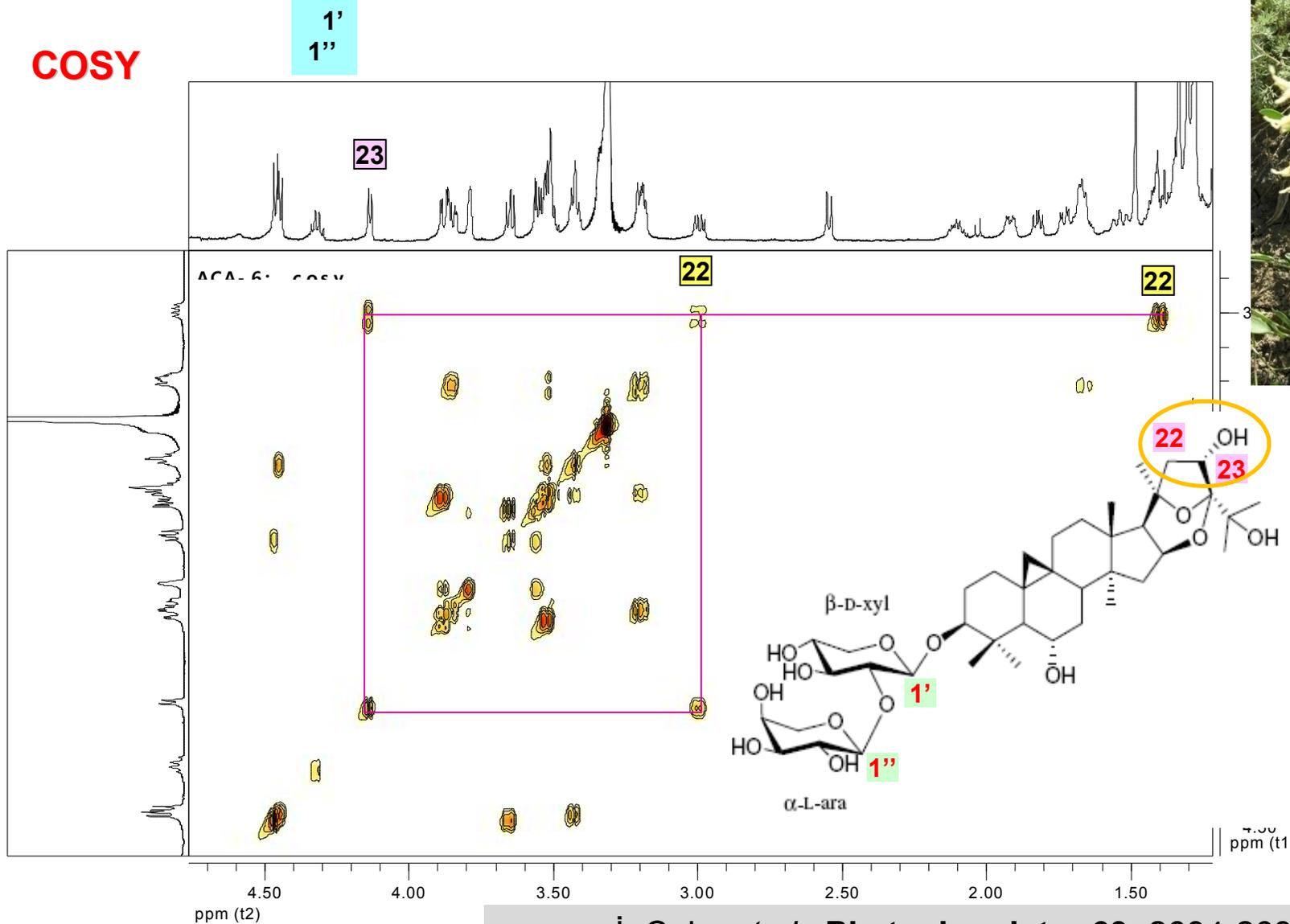


Prusianoside A: ¹H NMR spektrumu



Astragalus campylosema:

3-O-[α -L-ara-(1 \rightarrow 2)- β -D-xyl]-3 β ,6 α ,23 α ,25-tetrahidroksi-16 β ,24;20,24-diepoksisikloartan



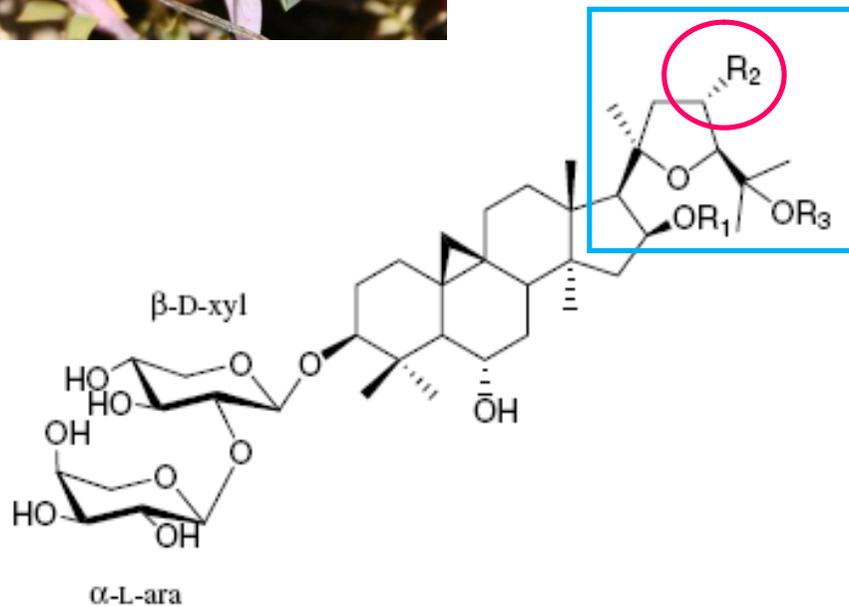
İ. Çalış et al., *Phytochemistry* 69, 2634-2638 (2008)



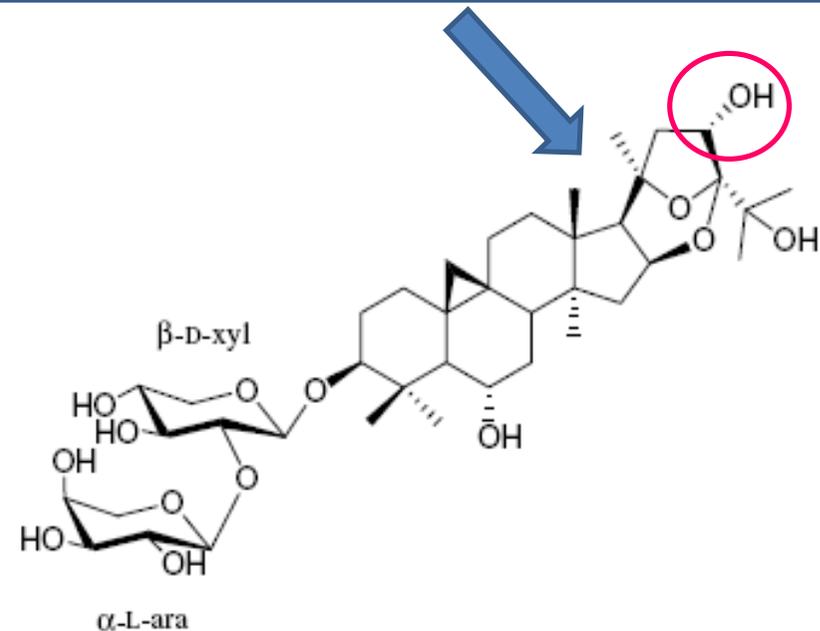
Astragalus campylosema

SECTION: PROSELIUS

16 β ,24;20,24-diepoksisikloartan Glikozitleri



- 1 $R_1 = R_3 = H; R_2 = OH$
- 2 $R_1 = COCH_2OH; R_2 = OCOCH_3; R_3 = H$
- 3 $R_1 = R_2 = H; R_3 = \beta$ -D-glucopyranose



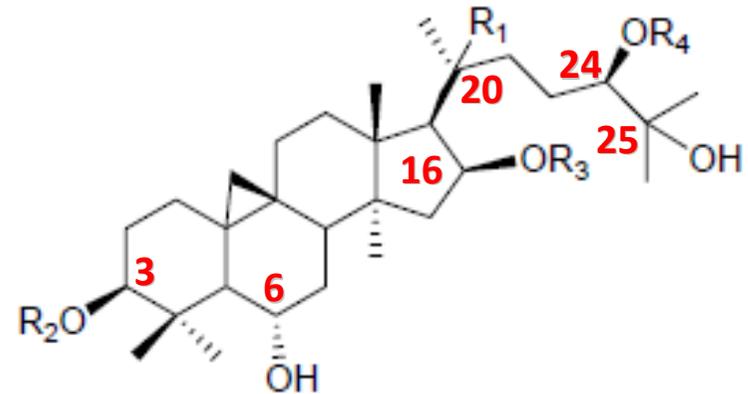
3 β ,6 α ,23 α ,25-tetrahydroxy-
20(R),24(R)16 β ,24;20,
24-diepoxycycloartane
Glycosides



Astragalus stereocalyx

SECTION: STEREOCALYX

- **Altı yeni** sikloartan-tip triterpen glikozit.
- Sitotoksik Aktivite
- Sadece bir bileşikte **Hela** (human cervical cancer) hücrelerine karşı aktivite gözlemlendi.
 - $IC_{50} = 10 \text{ mM}$.
- **$3\beta,6\alpha,16\beta,20(S),24(R),25$ -hekzahidroksisikloartan glikozitler**



C-20 Hidroksilasyon

F.N. Yalçın et al., (2011). *Phytochemistry Lett.* (in press).

Çalışılan *Astragalus* Türleri (8/60 Sectio; 14/450 tür)*

- **MACROPHYLLIUM**
 - *A. oleifolius* (2)
 - *A. isairiucs* (devam ediyor..)
- **CHRISTIANA**
 - *A. melanophrurius*
- **ALOPECIAS**
 - *A. macrocephalus*
- **RHACOPHORUS**
 - *A. microcephalus*
 - *A. cephalotes*
 - *A. zahlbruckneri*
 - *A. prusianus*
- **PTEROPHORUS**
 - *A. brachypterus*
 - *A. trojanus*
 - *A. baibutensis*
- **PROSELIUS**
 - *A. elongatus*
 - *A. campylosema*
- **STEREOCALYX**
 - *A. Stereocalyx*
- **VULNERARIA**
 - *A. vulneraria*

*450 *Astragalus* türü 60 grupta toplanmıştır

Sonuçlar

- >70 sekonder metabolit:
- 38 Novel ve/veya yeni sikloartan glikoziti
- 22 bilinen sikloartan glikoziti
- 3 sikloartan
- 1 oleanan,

Astragalus türleri sikloartanlar için iyi bir kaynak

Rhacophorus (dikenli çalılar) sikloartanlarca en zengin seksiyon

Astragaloside IV en çok karşılaşılan glikozit.

İmmunomodulatör, kolesterol düşürücü, antistres, antioksidan, hepatoprotektif aktiviteleri kanıtlanmış.

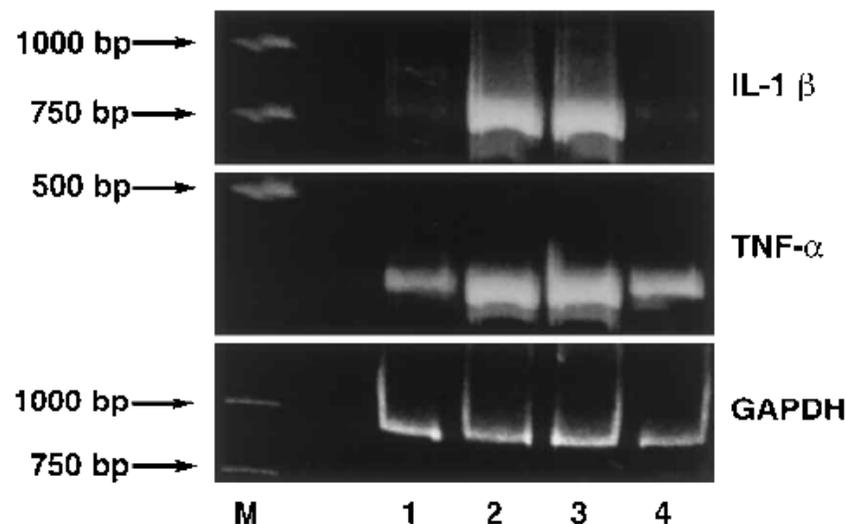
Birçok yeni aktivite çalışması devam ediyor

Örnekler

Immunostimulatory Effects of Cycloartane-Type Glycosides from *Astragalus Species*

Bedir *et al.*, *Biol. Pharm. Bull.* 23, 834—837 (2000)

- Nineteen cycloartane glycosides isolated in our studies have been studied for their **immunostimulant effects** and **expression of inflammatory cytokines**.



Astragaloside I enhances cytokine production

RT-PCR Results for IL-1 β mRNA, TNF- α mRNA and GAPDH mRNA in THP-1

↑ Cells at 2 h: (M) PCR Marker, (1) Control, (2) LPS at 10 mg/ml, (3) **Astragaloside I** at 200 mg/ml, and

***Interleukin 1, beta (IL1B)**, is a cytokine protein which is an important mediator of the inflammatory response, and is involved in a variety of cellular activities, including cell proliferation, differentiation, and apoptosis.*

Effects of triterpene saponins from *Astragalus* species on in vitro cytokine release

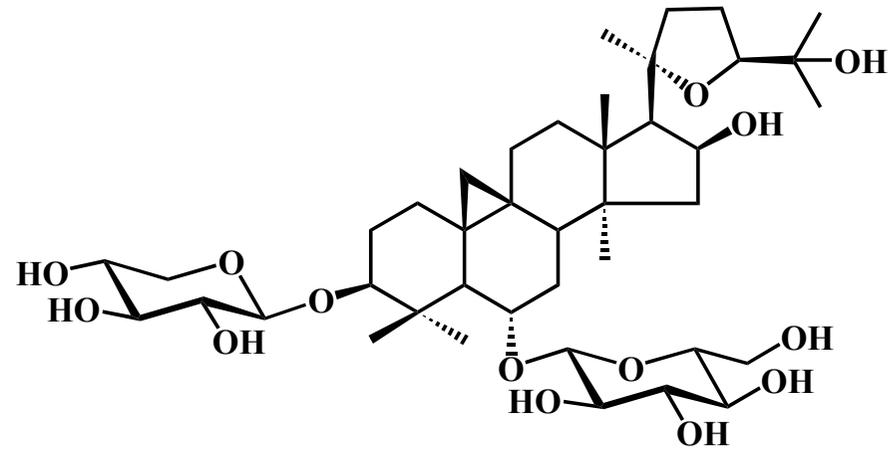
- **Selected glycosides** (13 cycloartane and one triterpene glycosides), **MeOH extracts** of the *Astragalus* roots were studied for their effects on cytokine release.
- The cycloartane type saponins had a prominent **Interleukin-2 (IL-2)** inducing activity between 35.9% and 139.6%. Among the extracts the highest score was obtained for ***Astragalus oleifolius*** (141.2%). Among the cycloartane glycosides, especially the activity of **Astragaloside VII**, a tridesmosidic glycoside of cycloastragenol, was the most remarkable (139.6%).

Interleukin-2 (IL-2) is an interleukin, a type of cytokine immune system signaling Molecule. IL-2 mediates its effects by binding to IL-2 receptors, which are expressed by lymphocytes, the cells that are responsible for immunity.

Yesilada et al., **Journal of Ethnopharmacology** 96,71–77 (2005).

Gastroprotective effect of Astragaloside IV: role of prostoglandins, sulfhydrils and nitric oxide

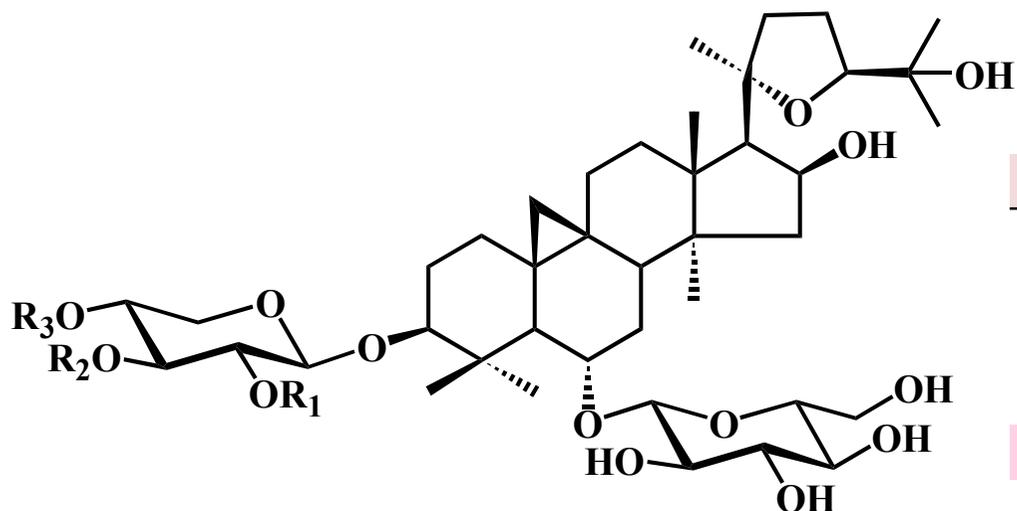
- **Astragaloside IV** suspended in Tween 80 at 3, 10 and 30 mg/kg, showed 15, 37 and 52% **gastroprotection**, resp..
- The effect was dose dependent.



Astragaloside IV
Astragalus zahlbruckneri

Glycyrrhizic acid, aescine and momordin Ic are some examples of saponins with antiulceractivity

Antiprotozoal Saponosides from the Roots of *Astragalus baibutensis* var. *brevicalyx*



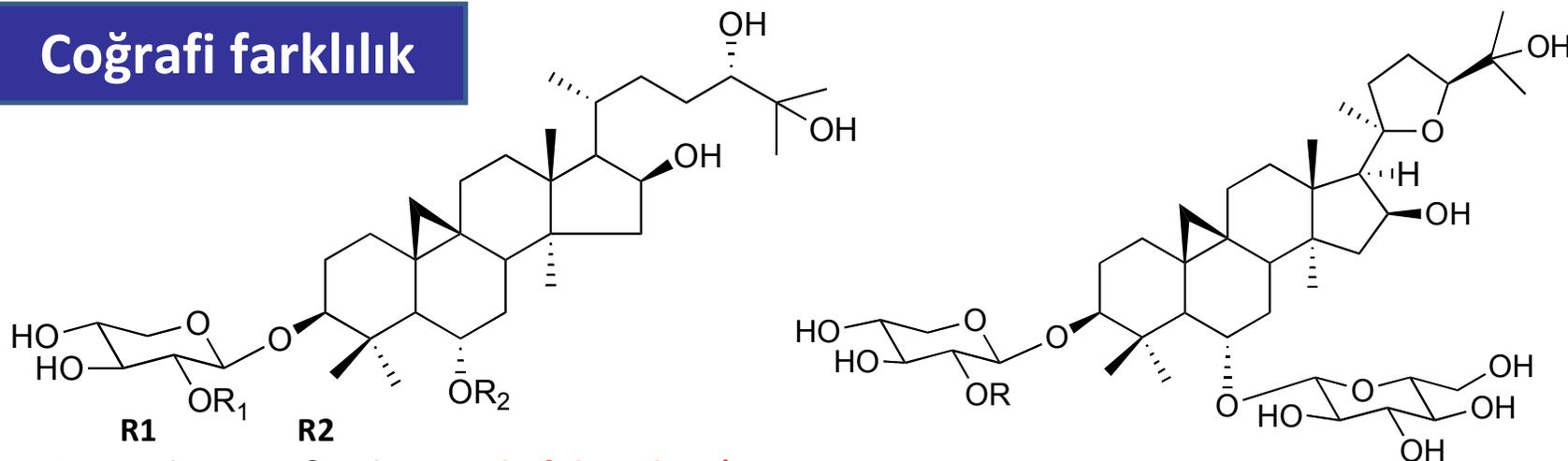
		R ₁	R ₂	R ₃
1	Acetylastragaloside I	Ac	Ac	Ac
2	Astragaloside I	Ac	Ac	H
3	Astragaloside II	Ac	H	H
4	Astragaloside IV	H	H	H
5	Baibutoside	Apiose	H	H

Compound	<i>T. b. rhodesiense</i>	<i>T. cruzi</i>	<i>L. donovani</i>	<i>P. falciparum</i>	L6 cell cytotox.
Reference	0.00295 ^a	0.31 ^b	0.152 ^c	0.002 ^d	0.00186 ^e
(1) Ac-Astragaloside I	9.5 (2.5)	5.0	>30	>20	24.2
(2) Astragaloside I	57.6	>30	>30	>20	>90
(3) Astragaloside II	64.8	>30	25.9	>20	>90
(4) Astragaloside IV	46.9	>30	28.9	>20	>90
(5) Baibutoside	>90	>30	>30	>20	>90

IC50 values in µg/ml. Reference compounds: ^amelarsoprol, ^bbenznidazole, ^cmiltefosine, ^dchloroquine, ^ephodophyllotoxin

Antiprotozoal activity of the Saponosides of the Roots of *Astragalus oleifolius* (Şırnak: Uludere–Habur, Hakkari)

Coğrafi farklılık



- 1** α -arabinose β -xylose **Oleifolioside A***
2 α -arabinose β -glucose **Oleifolioside B***
3 H β -glucose **cyclocanthoside E**

- 4 R:** Ac Astragaloside II
5 R: H Astragaloside IV

Compound	<i>T. b. rhodesiense</i>	<i>T. cruzi</i>	<i>L. donovani</i>	<i>P. falciparum</i>	Cytotoxicity L6 cells
Reference	0.0032 ^a	0.50 ^b	0.087 ^c	0.086 ^d	0.008 ^e
1	>90	>30	13.2	>50	>90
2	>90	>30	13.7	>50	>90
3	85.2	>30	14.1	>50	>90
4	66.6	>30	21.3	>50	>90
5	>90	>30	>30	>50	>90

IC50 values in $\mu\text{g/ml}$. References: ^amelarsoprol, ^bbenznidazole, ^cmiltefosine, ^dchloroquine, ^ephodophyllotoxin

Tyrosinase inhibition studies of cycloartane and cucurbitane glycosides and their structure–activity relationships

Aim: To discover a lead molecule for the development of new medications of several skin diseases related with the **over-expression of the enzyme tyrosinase***, like hyperpigmentation.

**) Tyrosinase is known to be a key enzyme for melanin biosynthesis in plants and animals.*

Table 1. Tyrosinase inhibitory activities of the compounds, as compared with the reference inhibitors

Compounds	IC ₅₀ ± SEM	Refs.
Cycloalpioside D (1)	NA	5
Cyclocarposide (2)	102.39 ± 0.26367	6
Cyclosieversioside F (3)	95.25 ± 0.21487	7
Askendoside D (4)	48.92 ± 0.08231	8,9
Askendoside B (5)	13.95 ± 0.56159	8,10
Cycloorbicoside A (6)	NA	12,15
Cycloorbicoside G (7)	54.64 ± 0.29424	13,15
Askendoside G (8)	NA	11
Cucurbitacin L (9)	NA	14
Bryoamaride (10)	85.01 ± 0.07679	14
Kojic acid (KA) ^a	16.67 ± 0.519	3
L-Mimosine (LM) ^a	3.68 ± 0.02234	4

^aReference inhibitors.

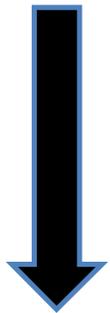
Cancer chemopreventive effects of cycloartane- type and related triterpenoids

- Forty-eight **natural** and **semisynthetic cycloartane-type** and related triterpenoids have been evaluated for their inhibitory effects on **Epstein-Barr virus early antigen (EBV-EA)** activation induced by the tumor promoter 12-*O*-*tetradecanoylphorbol*-13-acetate (TPA) in **Raji cells** as a primary screening test for anti-tumor promoters.

It has been found that **cycloartane-type and related triterpenoids**, especially those **with a hydroxy group at C-24** in the side chain, are valuable as **chemopreventive agents** in chemical carcinogenesis.

Sonuç

- Yeni ilaç molekülleri veya lider, model olarak kullanılabilen bileşik araştırma programlarında (**Drug Discovery**), **doğal bileşikler ve dolayısıyla steroidal yapıli bileşikler**, potansiyel bir grup olarak yerlerini koruyacaktır.



SONUÇ

Antikanser İlaçlar

1940s-06/2006, (N **175**).

N: Doğal Bileşik

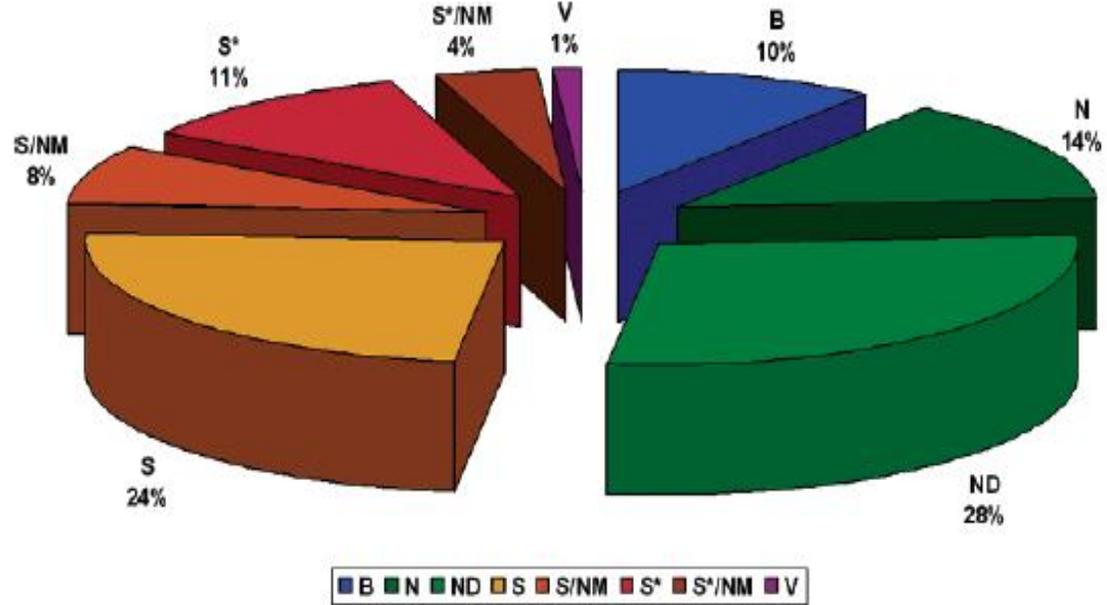
ND: DB-Yarısentetik türevi

S: Sentetik

S*: DB Model alınarak Üretilmiş Sentetik

V: Viral

B: Biyolojik



Total: 175

- **B**: 18; %10

- **V**: 2; %1

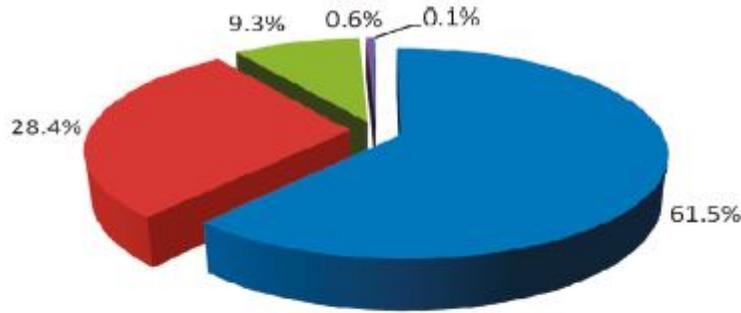
175 - 18 - 2 =: 155

Doğal Kaynaklıların Oranı: %72.9
(N, ND, S*/NM, S*, S*/NM) = 113 /
155

SONUÇ

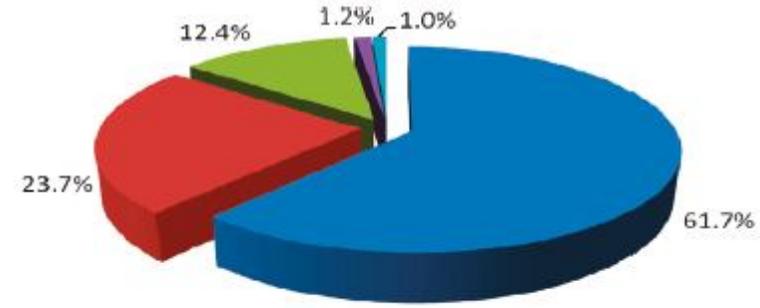
The Relevance of Higher Plants in Lead Compound Discovery Programs

Kinghorn AD *et al.* (2011). *J. Nat. Prod.* 74, 1539–1555



2001

2001'de 1142 DB



2010

2010'da 1369 DB

- Plant (%)
- Marine/aquatic (%)
- Terrestrial microbial/fungi (%)
- Terrestrial animal (%)
- Unspecified organism (%)

2001 – 2010 yılları arasında JNP'de yayınlanan doğal bileşiklerin (DB) elde edildikleri canlı organizmalar yönünden karşılaştırılması

SONUÇ

The Relevance of Higher Plants in Lead Compound Discovery Programs

Kinghorn AD *et al.* (2011). *J. Nat. Prod.* 74, 1539–1555

Table 1. Plant Natural Products and Derivatives Approved by the U.S. FDA from 2001 to 2010^a

year approved	generic name	Natural Lead Comp.	trade name	indication
2001	galanthamine	★ galanthamine	Razadyne	dementia associated with Alzheimer's disease
2002	nitisinone ^b	leptospermone	Orfadin	hereditary tyrosinemia type 1
2003	miglustat ^b	1-deoxynojirimycin	Zavesca	type 1 Gaucher disease
2004	tiotropium ^b bromide	atropine	Spiriva	COPD and exacerbation of COPD
2004	tropium ^b chloride	atropine	Sanctura	overactive bladder
2004	solifenacin ^b	quinine	VESIcare	overactive bladder
2005	paclitaxel (protein-bound)	★ paclitaxel (taxol)	Abraxane	breast cancer
2006	sinecatechins ^c	green tea phenols	Veregen	genital warts
2006 ^d	nabilone ^b	Δ^9 -tetrahydrocannabinol	Cesamet	chemotherapy-induced nausea
2008	methylnaltrexone ^b bromide	morphine	Relistor	opioid-induced constipation
2008	tetrabenazine ^b	emetine	Xenazine	Huntington's-associated cholera
2009	artemether ^b and lumefantrine	★ artemisinin	Coartem	malaria
2009	colchicine	★ colchicine	Colcrys	gout
2010	cabazitaxel ^b	★ paclitaxel (taxol)	Jevtana	hormone-refractory metastatic prostate cancer
2010	dextromethorphan and quinidine	★ morphine and quinidine	Nuedexta	pseudobulbar affect
2010	capsaicin	★ capsaicin	Qutenza	postherpetic neuralgia

Teşekkürler

- ***Astragalus***
 - M. Zor
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 - F.N. Yalçın
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- ***Primula***
 - A.Yürüker
- ***Ajuga***
 - P. Akbay
- ***Phlomis***
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 - (Chicago, USA)
- Dr. Z. Aytaç
- Dr. H. Duman
- Dr. A.A. Dönmez



TUBİTAK

SBAG-1233 (CYCLAMEN)

SBAG-1688 (ASTRAGALUS)

SBAG-2304 (PHLOMIS)

