



Neue Erkenntnisse zu den Wirkmechanismen von Amygdalin in der Therapie urologischer Tumore

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**Klinik für Urologie
und Kinderurologie**



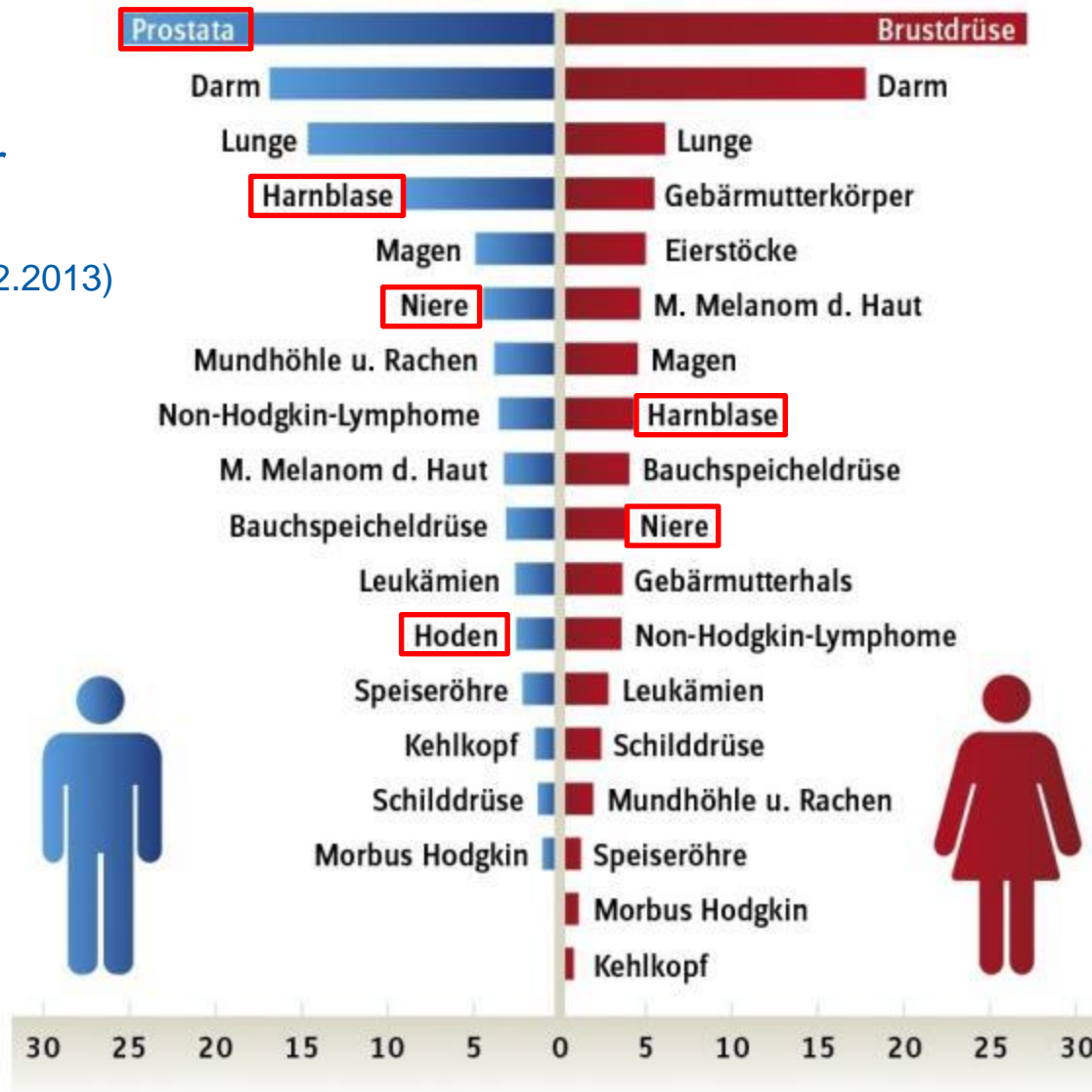
Inzidenz in Deutschland

Risiko:

51% Männer

43% Frauen

(RKI, Stand: 13.12.2013)

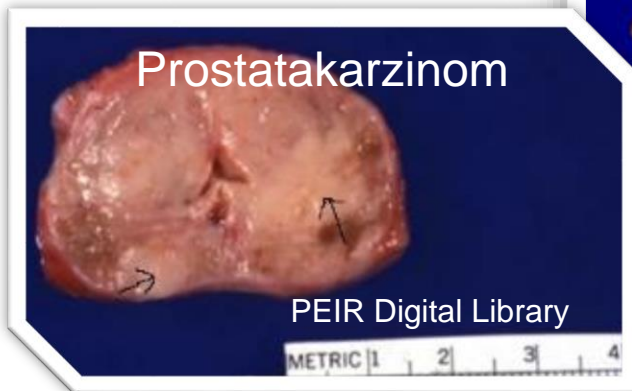




Wie ist die Prognose?

Heilungschance nicht-metastasiertes Stadium

- Prostata: 80 %
- Blase: 50% - 85 %
- Niere: 70 %



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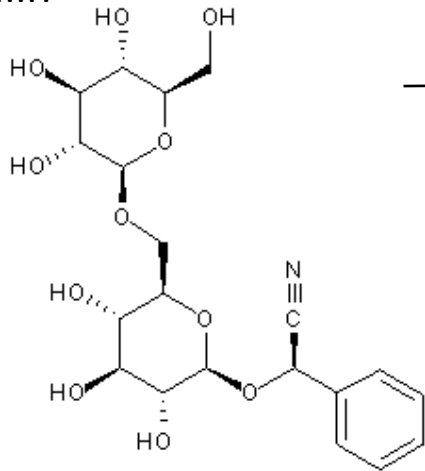
Fortgeschrittene, metastasierte Stadium

- Überleben: 14-24 Monate => palliativ

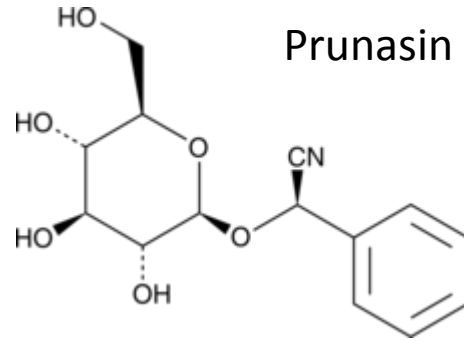


Verstoffwechslung

Amygdalin

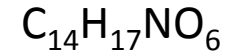


β -glucosidase

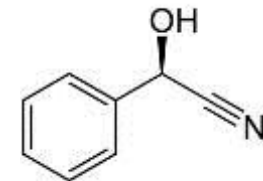


Prunasin

D-mandelonitrile β -D-glucoside

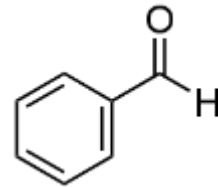
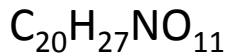


β -glucosidase



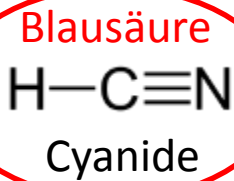
Mandelonitrile

D-mandelonitrile- β -D-gentiobioside



Benzaldehyde

+ Wasser & β -Glucosidase
 \Rightarrow HCN



Cyanide

Rhodanese

Thiocyanate

β -D-glucose



Amygdalin

Diskrepanz

Wissen (toxisches & therapeutisches Potential)

<->

häufige Einnahme durch Karzinompatienten

=> neue Patientendaten fehlen

=> Bewertung BfArM: bedenklich

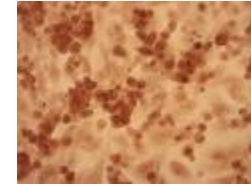


Eigene Projekte zum Amygdalin

- In vitro Zellkulturmodelle

- > Wachstumsverhalten

- > Metastasierungseigenschaften

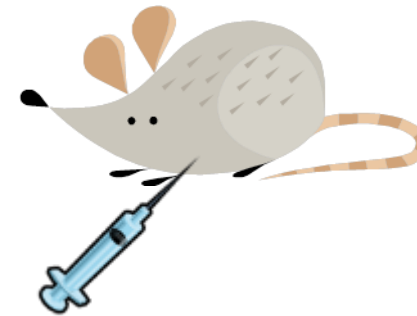


- In vivo Mausmodelle

- > Wachstumsverlauf

- > Gewebe & Serum

- > molekularbiologische Untersuchungen



- Patienten

- > Serum: Cyanid-, Thiocyanat-, Lactat-, K^+ -, Na^+ -, Cl^- -, HCO_3^- Konzentration sowie pH-, Hb- & metHb-Wert

Wirksamkeit & Toxizität?



Studiendesign

Harnblasenkarzinomzellen:
UMUC3, TCCSupp, RT112

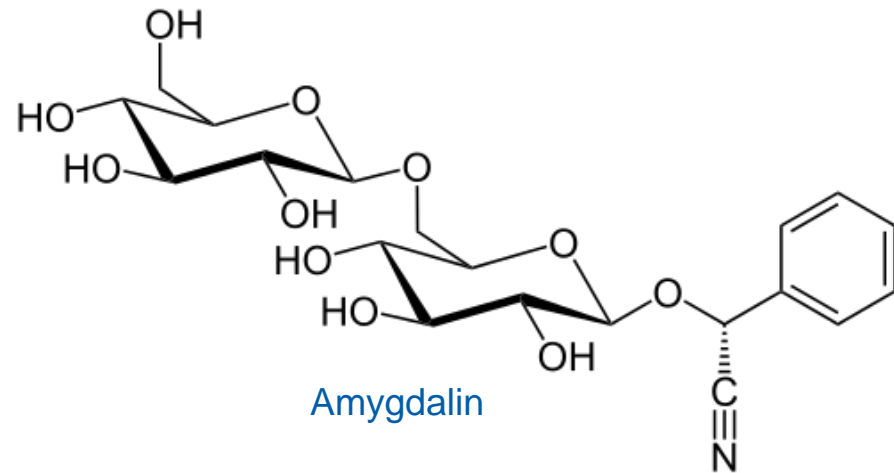
Nierenzellkarzinomzellen:
Caki-1, KTC-26, A498

Behandlung:

Amygdalin [10 mg/ml]
24h oder 2 Wochen



Caki-1





Studiendesign

Wachstum

- Wachstum / Proliferation (MTT / BrdU)
- Zellzyklusphasen (FACS)
- Zellzyklus- & Signalproteine (Western Blot)
- Apoptose (= programmierter Zelltod)



Metastasierung

- Adhäsion an vaskuläres Endothel
- Adhäsion an extrazelluläre Matrixproteine (EZM)
- Migration / Chemotaxis
- Adhäsionsrezeptoren (FACS & Westen Blot)



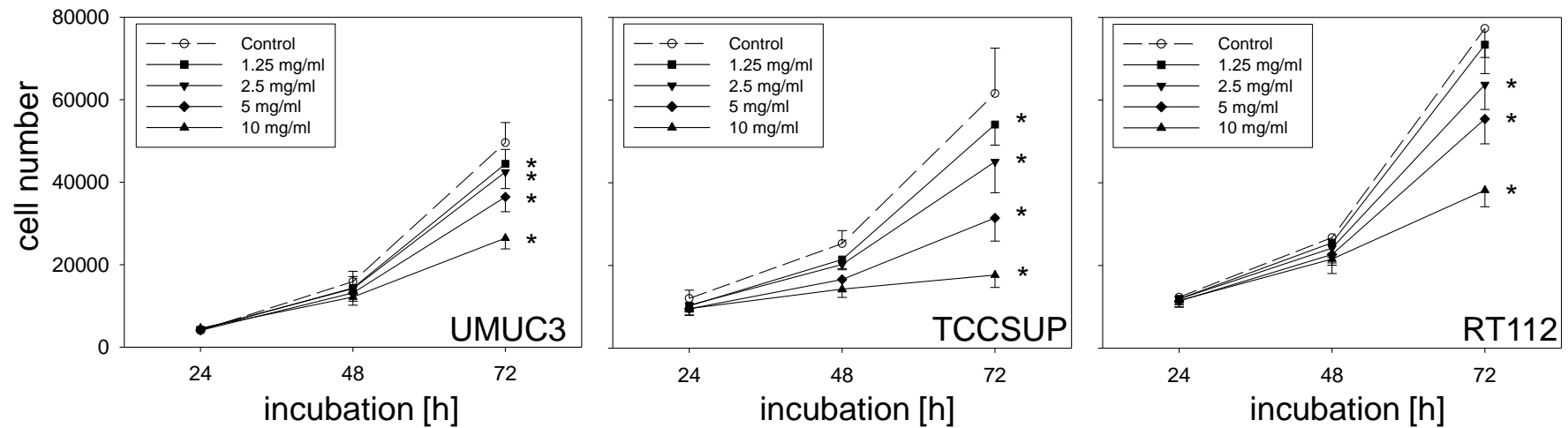
(funktionelle Assays)

Blockadestudien -> funktionelle Relevanz Proteine



Tumorzellwachstum - Urothel

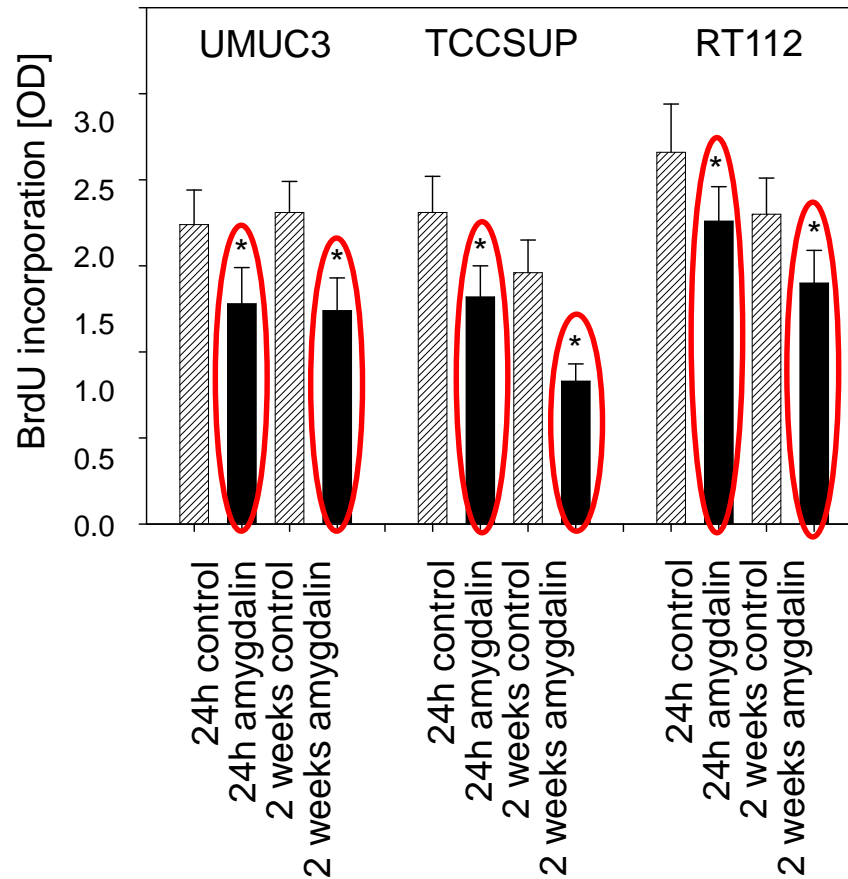
nach 24h Vorbehandlung



24h + Amygdalin => signifikante Inhibition des Wachstums
(analog 2 Wochen + Amygdalin)



Tumorzellproliferation - Urothel

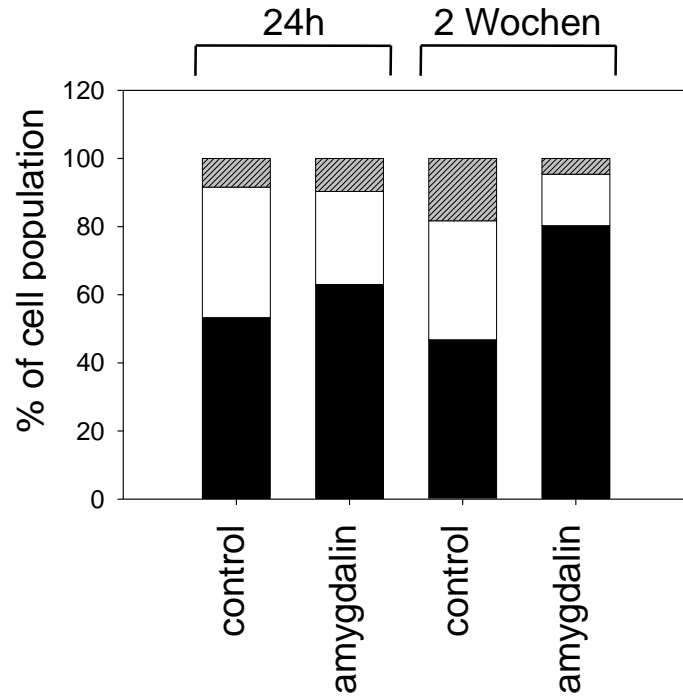


24h & 2 Wochen + Amygdalin
=> signifikante Proliferationshemmung

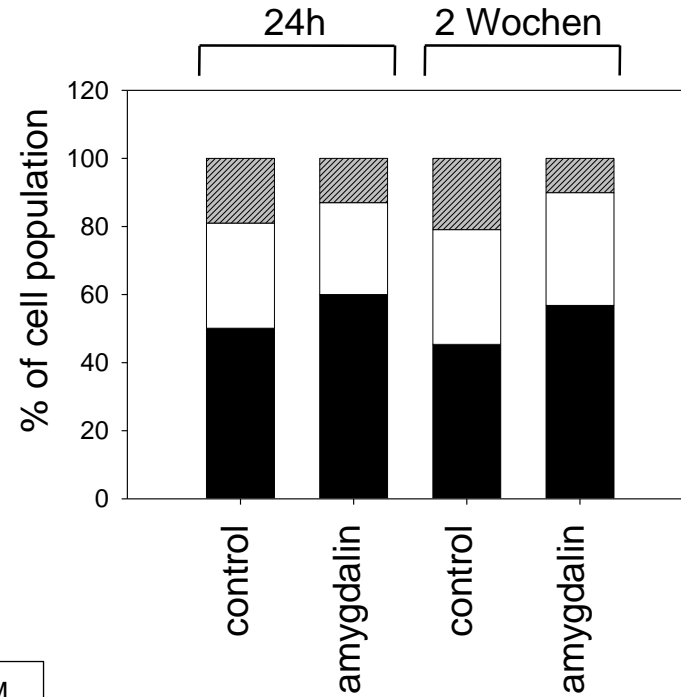


Zellzyklus - Urothel

UMUC3



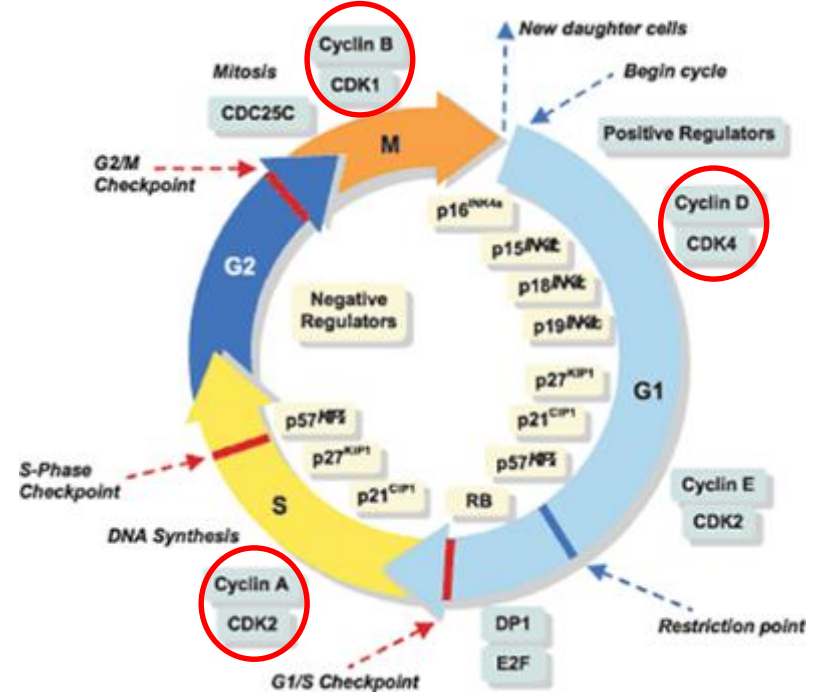
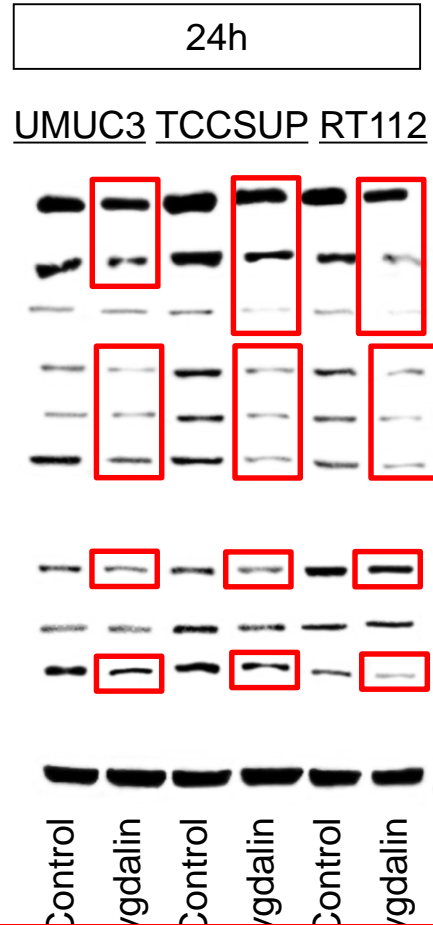
TCCSUP



24h & 2 Wochen + Amygdalin
=> signifikante Inhibition des Zellzyklus



Proteinexpression - Urothel



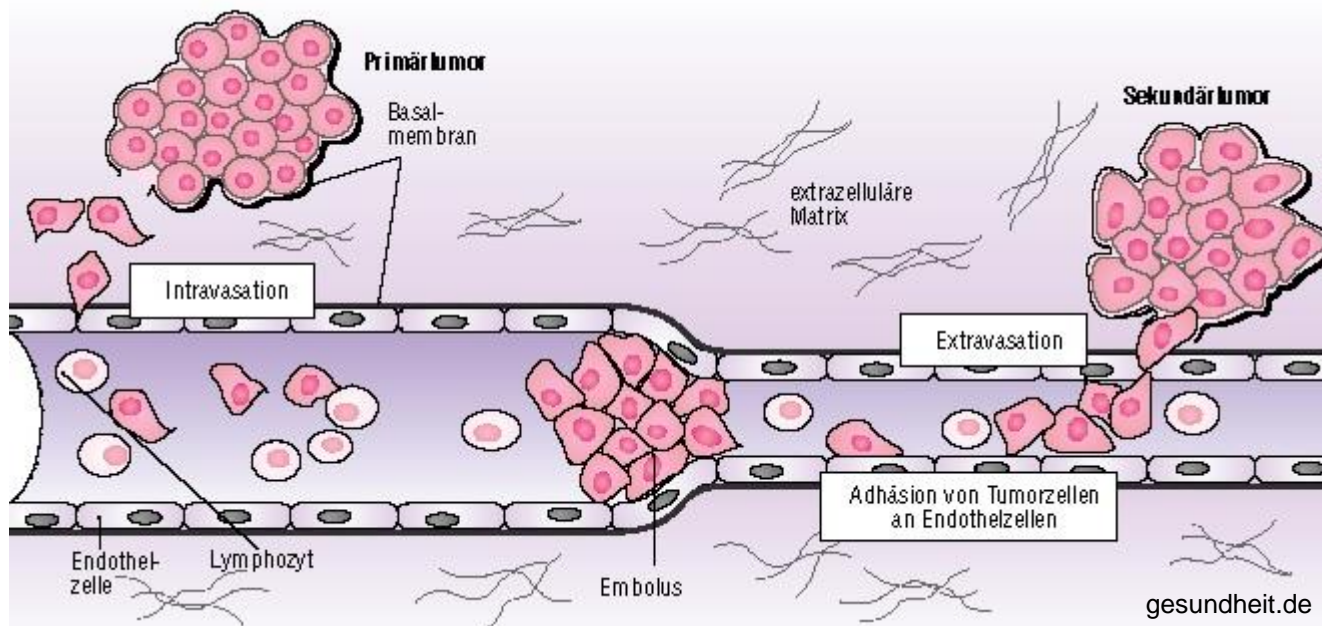
Zellzyklus

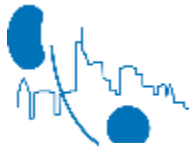
Signal

24h & 2 Wochen + Amygdalin
 ⇒ distinkte Modulationen
 ⇒ Zellzyklus-regulatorischer Proteine & Signalmoleküle

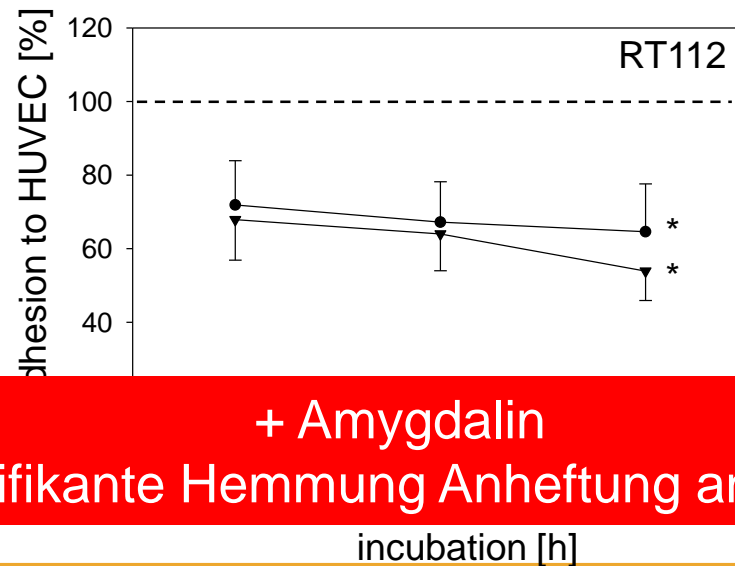
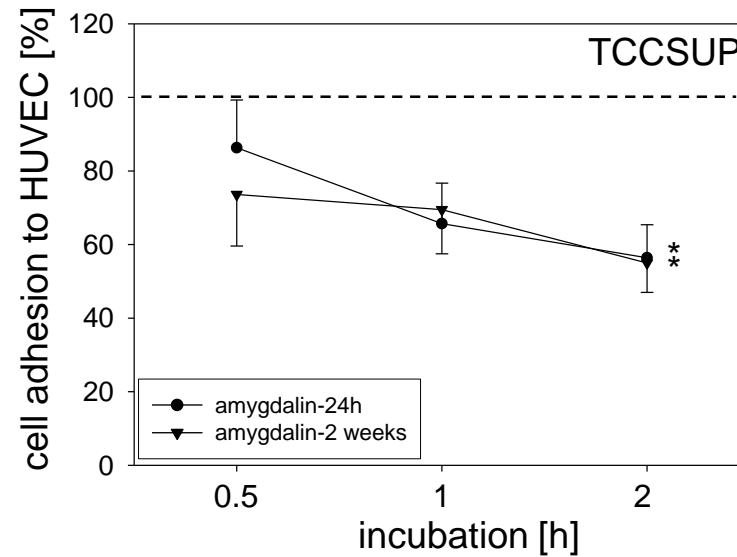
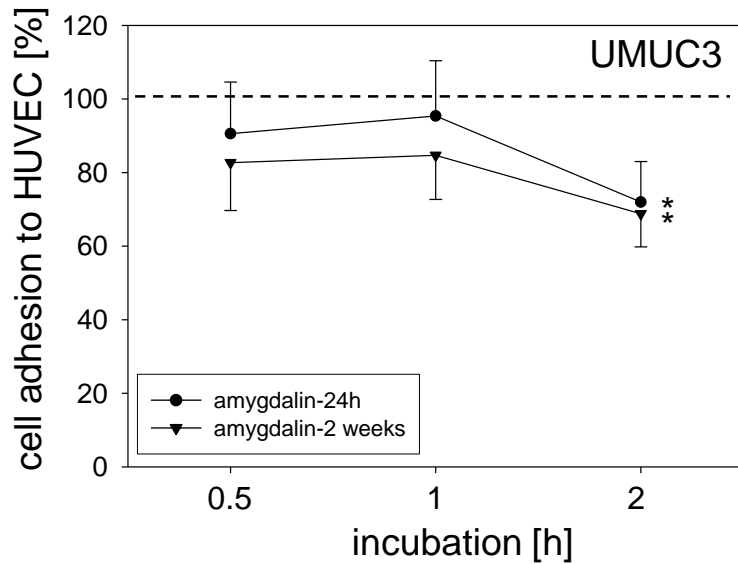


Metastasierung





Adhäsion an Endothel - Urothel



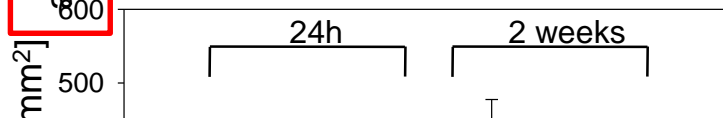
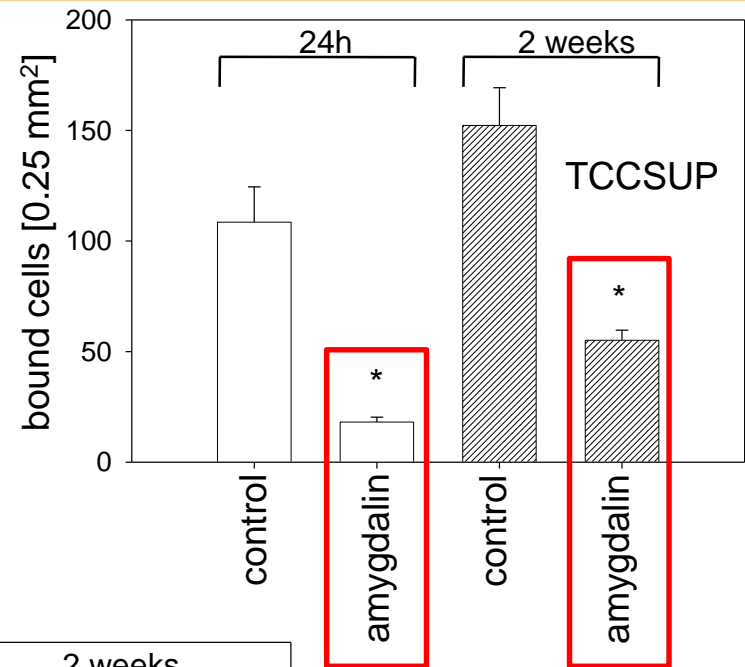
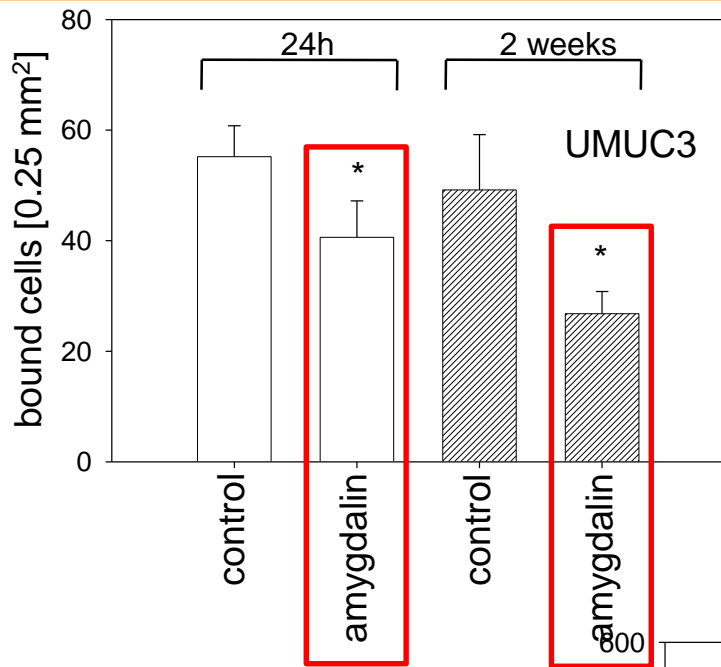
+ Amygdalin

=> signifikante Hemmung Anheftung an Endothel

incubation [h]

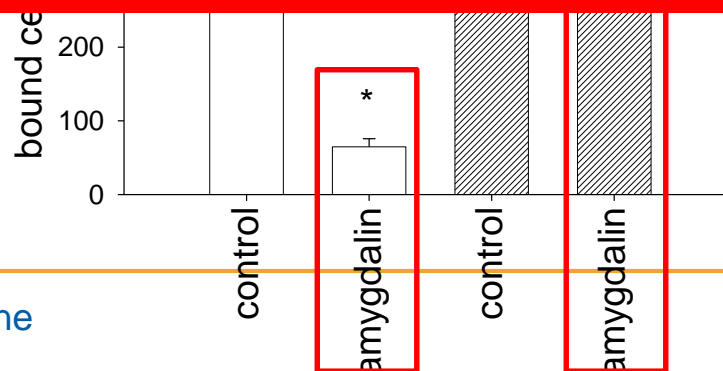


Adhäsion an Kollagen (EZM-Protein) Urothel



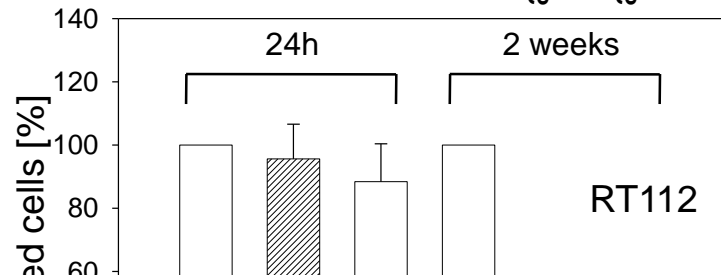
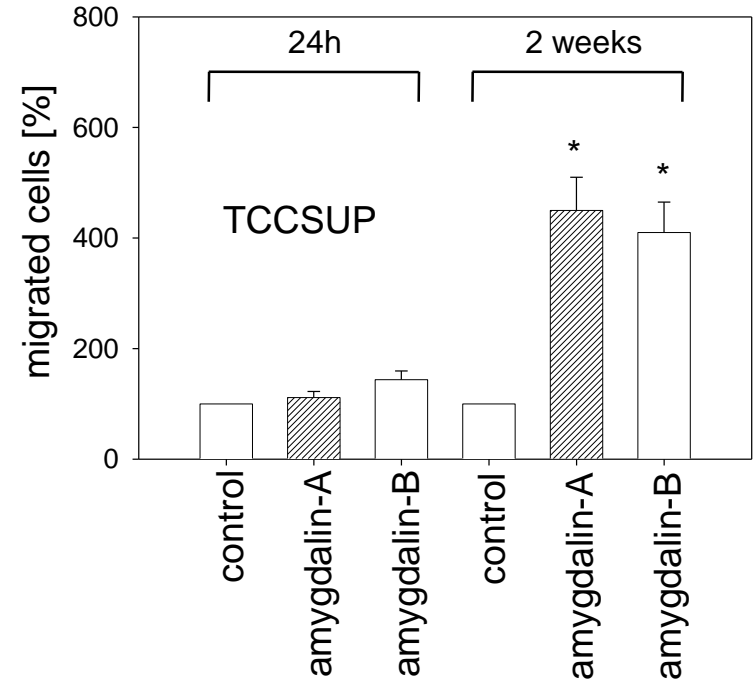
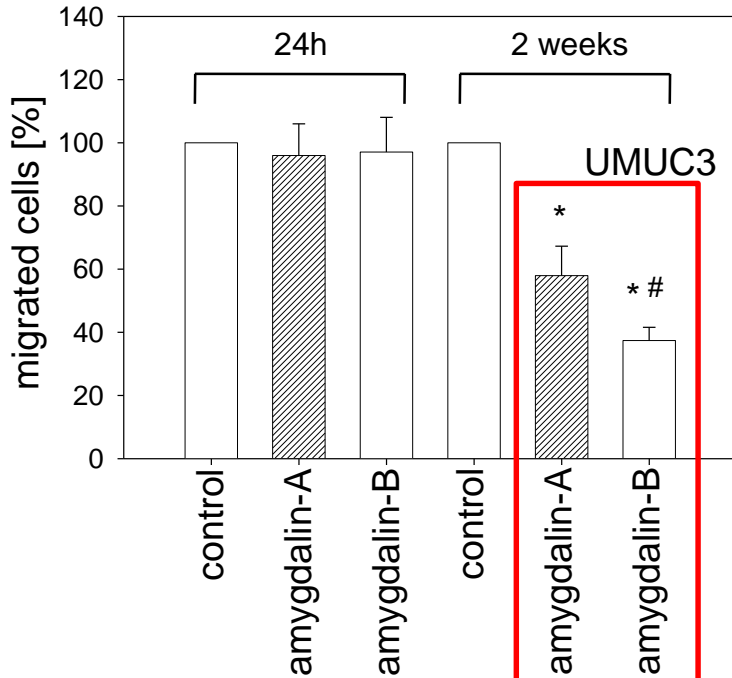
+ Amygdalin

=> signifikante Inhibition Adhäsion an Kollagen





Migration - Urothel



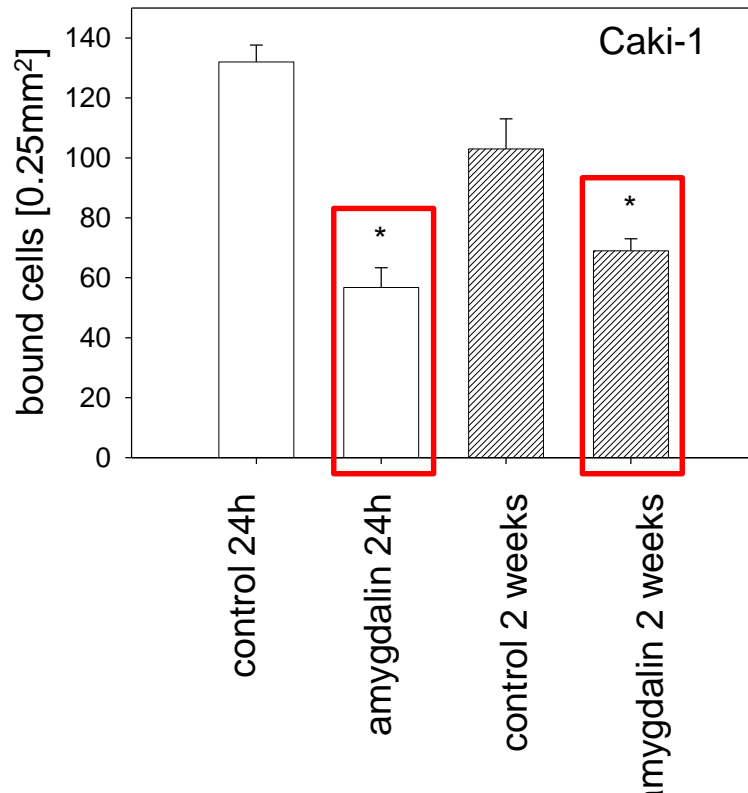
Amygdalin A =
keine Weiterbehandlung im Versuch (24h)

+ 2 Wochen Amygdalin
=> in 2 von 3
signifikante Reduktion Migration

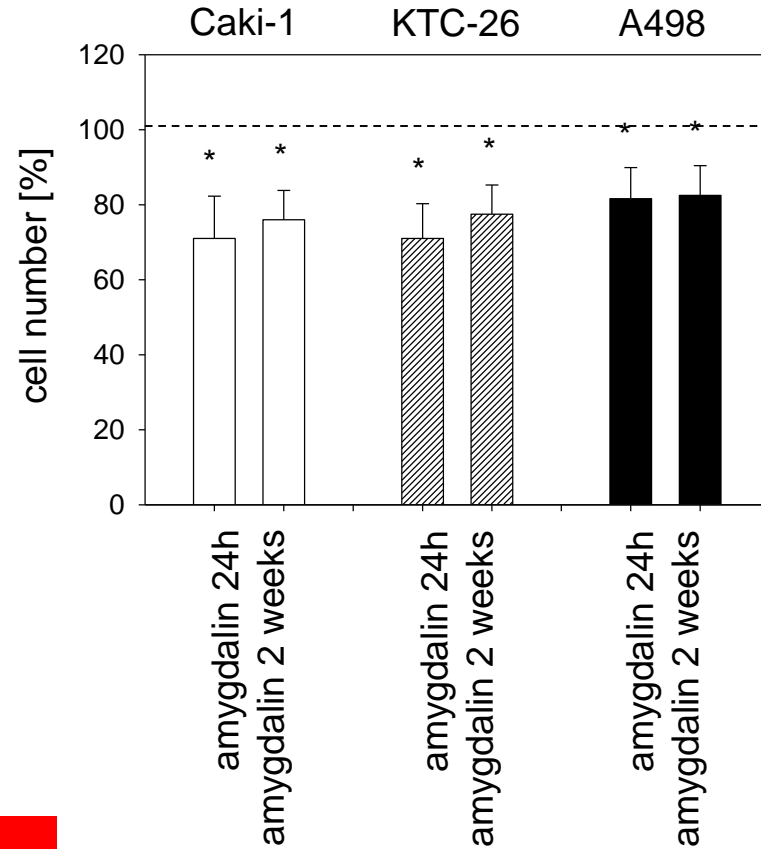


Metastasierungseigenschaften - Niere

Adhäsion an Kollagen (EZM):



Chemotaxis:

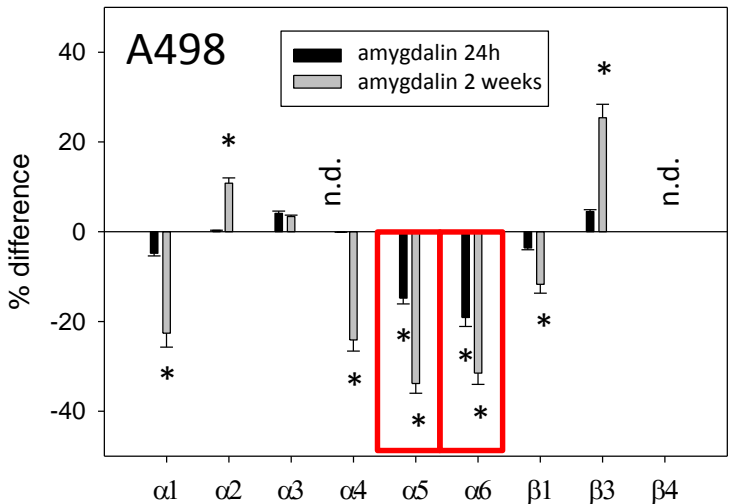
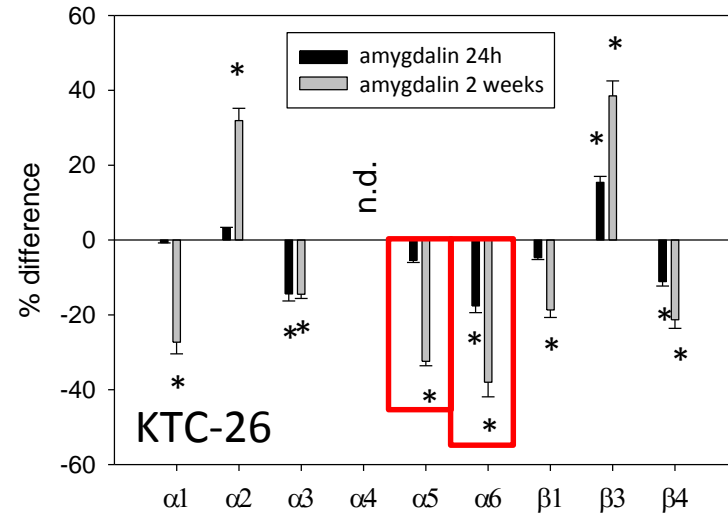
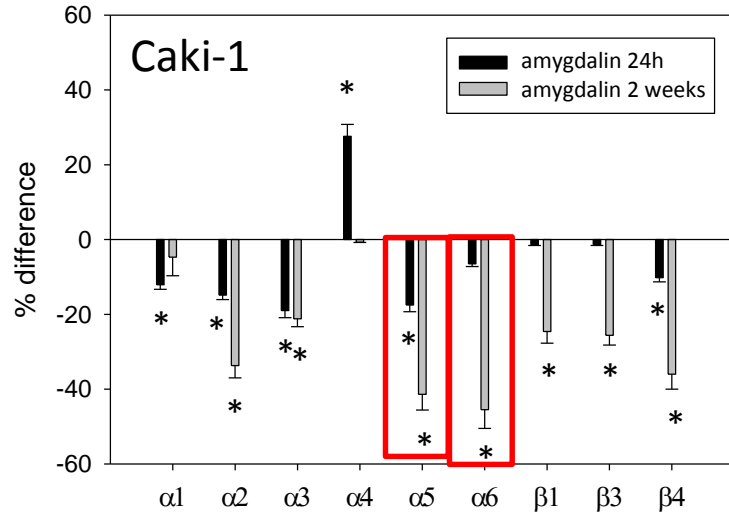


Amygdalin
-> Reduktion Adhäsion
-> Reduktion Chemotaxis

Kontrolle = 100%



Oberflächenexpression Integrin-Subtypen (Adhäsionsrezeptoren) - Niere



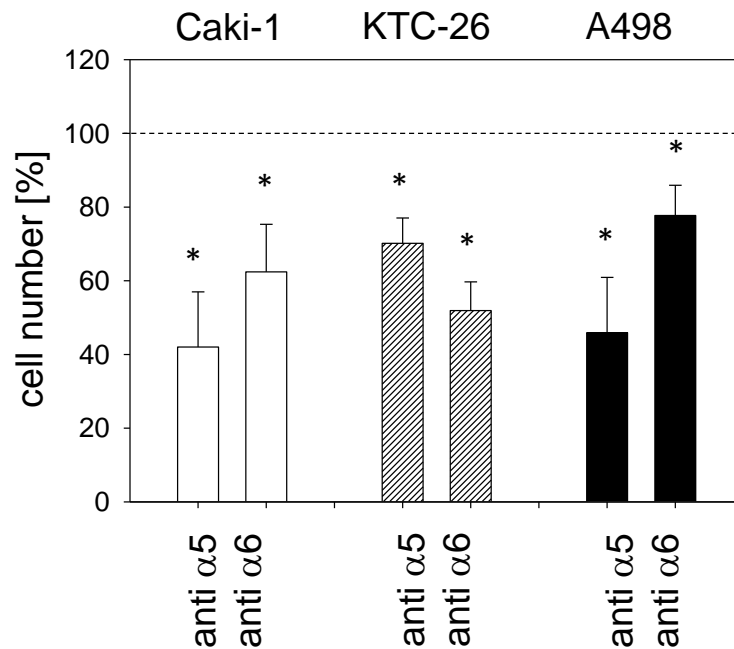
Angaben: %-Differenz zur Kontrolle

Amygdalin
-> signifikante Modulation
Integrine ($\alpha 5$ & $\alpha 6$)



Blockadestudie - Urothel

Chemotaxis:



Kontrolle = 100%

Blockade Integrin $\alpha 5$ & $\alpha 6$
-> Reduktion Chemotaxis
=> involviert



Zusammenfassung

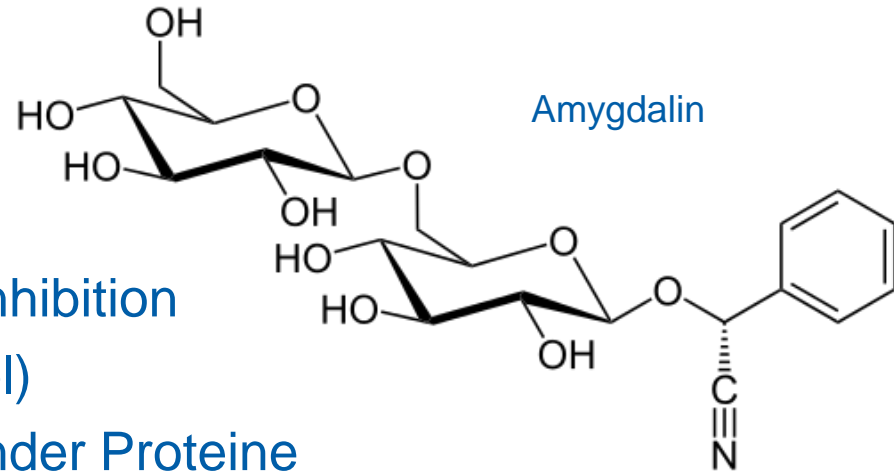
+ Amygdalin

Wachstum:

- Proliferations- & Wachstumsinhibition
- Zellzyklusarrest in G1 (Urothel)
- Reduktion zellzyklusaktivierender Proteine

Metastasierung:

- Inhibition der Anheftung an Endothel und Kollagen
- Hemmung der Migration (2 von 3, Urothel) / Chemotaxis (Niere)
- Modulation Adhäsionsrezeptoren
- Beteiligung Integrin $\beta 1$ und $\beta 4$ -> Adhäsion & Migration (Urothel)
- Beteiligung Integrin $\alpha 5$ und $\alpha 6$ -> Chemotaxis (Niere)





Schlussfolgerung

Amygdalin

⇒ antitumorale Aktivität

in vitro



Acknowledgments

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