



## Inhibitory mechanisms of two *Uncaria tomentosa* extracts affecting the Wnt-signaling pathway

Carmen Magdalena Gurrola-Díaz<sup>a</sup>, Pedro Macedonio García-López<sup>b</sup>, Krzysztof Gulewicz<sup>c</sup>, Radoslaw Pilarski<sup>c</sup>, Susanne Dihlmann<sup>d,\*</sup>

<sup>a</sup> Instituto de Enfermedades Crónico-Degenerativas, Centro Universitario de Ciencias de la Salud (CUCS), Departamento de Biología Molecular y Genómica, Universidad de Guadalajara, Mexico

<sup>b</sup> Departamento de Botánica y Zoología, Centro Universitario de Ciencias Biológicas y Agropecuarias, Universidad de Guadalajara, Mexico

<sup>c</sup> Phytochemistry Laboratory, Institute of Bioorganic Chemistry, Polish Academy of Sciences, Poznań, Poland

<sup>d</sup> Department of General Pathology, Institute of Pathology, University Hospital Heidelberg, Im Neuenheimer Feld 220/221, D-69120 Heidelberg, Germany

### ARTICLE INFO

#### Keywords:

*Uncaria tomentosa*  
Cat's claw  
Uña de gato  
Wnt-signaling pathway  
cMyc  
Beta-Catenin  
Cancer cells

### ABSTRACT

*Uncaria tomentosa* (“uña de gato”; “cat’s claw”), a woody vine native to the Amazon rainforest, is commonly used in South American traditional medicine to treat a broad spectrum of diseases. Although recent studies have reported anti-inflammatory and anti-proliferative properties of different alkaloids extracted from this plant, the underlying molecular mechanisms of these effects have not been elucidated yet. Our study investigates the inhibitory mechanisms of *Uncaria tomentosa* extracts on the Wnt-signaling pathway, a central regulator of development and tissue homeostasis. A modified cell-based luciferase assay for screening inhibitors of the Wnt-pathway was used for analysis. Three cancer cell lines displaying different levels of aberrant Wnt-signaling activity were transfected with Wnt-signaling responsive Tcf-reporter plasmids and treated with increasing concentrations of two *Uncaria tomentosa* bark extracts. Wnt-signaling activity was assessed by luciferase activity and by expression of Wnt-responsive target genes. We show that both, an aqueous and an alkaloid-enriched extract specifically inhibit Wnt-signaling activity in HeLa, HCT116 and SW480 cancer cells resulting in reduced expression of the Wnt-target gene: c-Myc. The alkaloid-enriched extract (B/S<sub>rt</sub>) was found to be more effective than the aqueous extract (B/W<sub>37</sub>). The strongest effect was observed in SW480 cells, displaying the highest endogenous Wnt-signaling activity. Downregulation of Wnt-signaling by a dominant negative-TCF-4 variant in non-cancer cells rendered the cells insensitive towards treatment with B/S<sub>rt</sub>. B/S<sub>rt</sub> was less toxic in non-cancer cells than in cancer cells. Our data suggest that the broad spectrum of pharmacological action of *Uncaria tomentosa* involves inhibition of the Wnt-signaling pathway, downstream of beta-Catenin activity.

© 2010 Elsevier GmbH. All rights reserved.

### Introduction

The medicinal vine *Uncaria tomentosa* (Rubiaceae), native to the Amazon rainforest and commonly known as “uña de gato” or “cat’s claw” has been traditionally used by indigenous tribes to treat a broad spectrum of mental and physical disorders (Keplinger et al. 1999). Today, it is commonly used in tropical American folk medicine to treat viral infections, arthritis, chronic degenerative diseases, gastric ulcers and cancer. Consequently, it has evoked increasing scientific and commercial interest and is widely promoted as an alternative treatment for these ailments (Heitzman et al. 2005).

Despite a growing number of reports describing the clinical and biological effects of *U. tomentosa* extracts, its pharmacological effectiveness and molecular targets are largely unknown. The most common pharmaceutical forms of *U. tomentosa* are crude water-soluble or ethanol-soluble extracts derived from its bark or roots for oral consumption as infusions (Keplinger et al. 1999). Active components identified in these extracts include different oxindolic alkaloids, indole alkaloids, glycosides (pentacyclic triterpenes with a variety of derivatives such as ursolic acid, quinovic acid glycosides, sterols and procianidins) and tannins the chemical composition of which can vary depending on their geographical origin and seasonal harvesting (Heitzman et al. 2005). Thus, the diverse pharmacological properties of *U. tomentosa* reported in the literature might be ascribed to different types and combinations of these compounds.

Most pharmacological *in vivo*-studies initially investigated how *U. tomentosa* extracts affect anti-inflammatory, immunomodulatory and DNA-repair mechanisms (Akesson et al. 2003; Keplinger

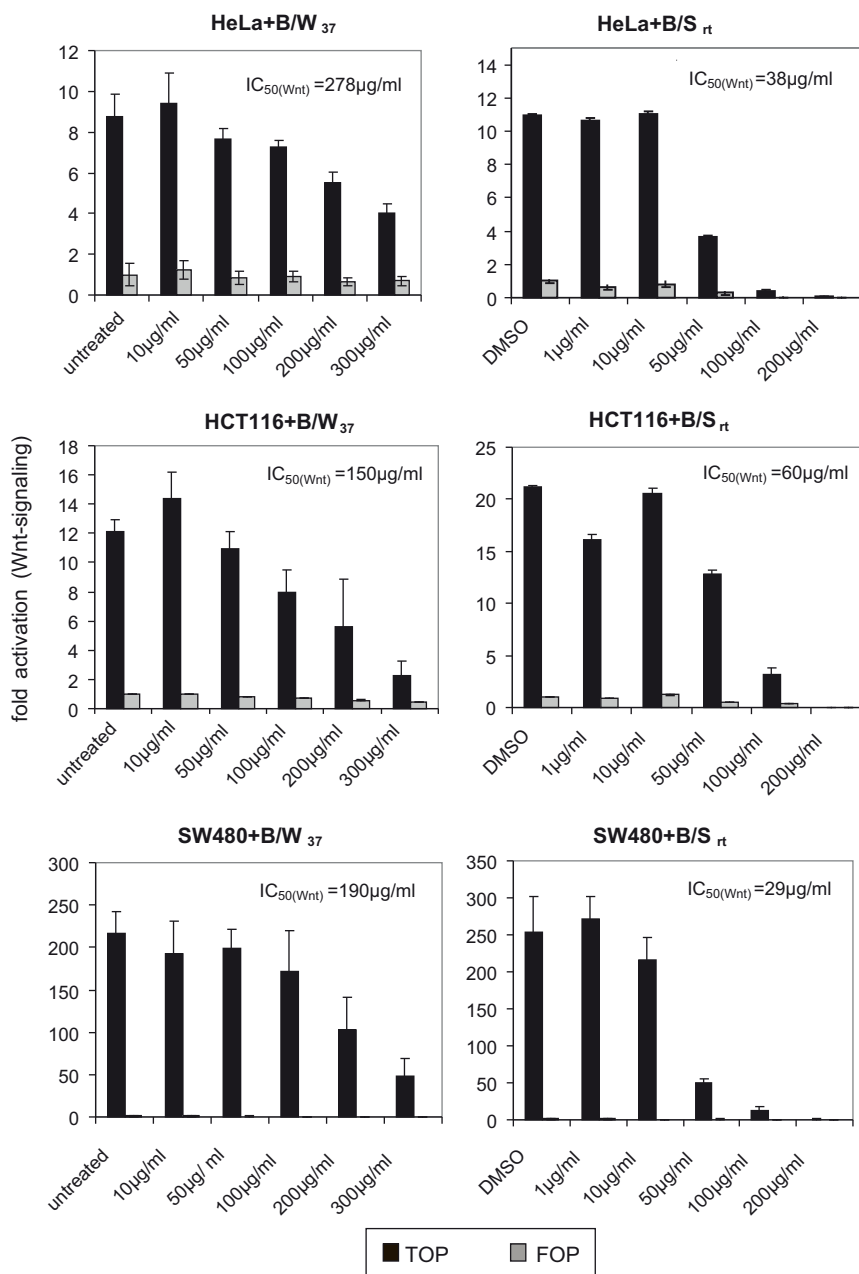
\* Corresponding author. Tel.: +49 6221 5639908.

E-mail address: [susanne.dihlmann@med.uni-heidelberg.de](mailto:susanne.dihlmann@med.uni-heidelberg.de) (S. Dihlmann).

**Table 1**  
TOP/FOP-inhibition ratios of cancer cell lines treated with two different extracts of *Uncaria tomentosa*.

Extract	Cell line	0/DMSO	1 µg/ml	10 µg/ml	50 µg/ml	100 µg/ml	200 µg/ml	300 µg/ml
B/W <sub>37</sub>	HeLa	1.0	–	0.9	1.0	0.8	1.0	<b>0.7</b>
	HCT116	1.0	–	1.2	1.1	0.9	0.8	<b>0.4</b>
	SW480	1.0	–	0.9	1.4	2.1	1.3	1.1
B/S <sub>rt</sub>	HeLa	1.0	1.4	1.2	1.2	1.1	<b>0.0</b>	–
	HCT116	1.0	0.8	0.8	1.1	<b>0.4</b>	<b>0.0</b>	–
	SW480	1.0	0.8	2.2	<b>0.2</b>	<b>0.4</b>	<b>0.0</b>	–
	293T	1.0	1.3	1.3	0.7	0.3	0.0	–

Relative inhibition of Wnt-signaling activity in TOP-luciferase transfected versus FOP-luciferase transfected cells. Ratios, pointing to a specific effect on Wnt-signaling are presented in bold.



**Fig. 1.** Reduction of Wnt-signaling activity in different cancer cell lines upon treatment with *Uncaria tomentosa* extracts B/W<sub>37</sub> and B/S<sub>rt</sub> for 24 h. Fold activation of Wnt-signaling was determined by luciferase reporter assays as described in Section "Materials and methods". Untreated or DMSO-treated cells transfected with FOP-luciferase reporter were set as 1.0. Bars represent the means and standard deviations of six experiments. IC<sub>50</sub>(Wnt) represents the concentration of *Uncaria tomentosa* extracts, that reduces Wnt-signaling activity to 50% of that in untreated or DMSO-treated cells.

Download English Version:

<https://daneshyari.com/en/article/2496942>

Download Persian Version:

<https://daneshyari.com/article/2496942>

[Daneshyari.com](https://daneshyari.com)