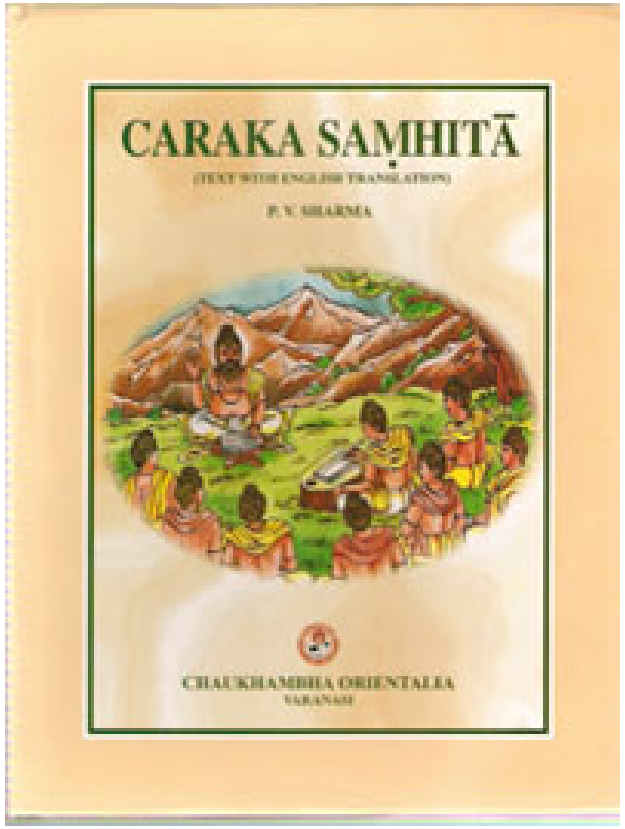
Consumo de hierbas y toxicidad hepática

Raúl J Andrade, MD, PhD, FAASLD
University Hospital, Málaga
On behalf of the Spanish
and LatinAmerican DILI Registries

Use of herbal medicines can be traced back as far as 2100 B.C. in ancient China and India

The first written reports by Caraka date back from 600 B.C. on ancient Indian medicine



Dioscórides a greek physician in I century wrote the most important book on Natural Medicine compilling the curative properties of more than 600 plants and herbs that remained a reference over 15 centuries

REFERENCE BOOK OF HOLISTIC AYURVEDIC MEDICINE

HDS: Agenda

- Current definitions
- Magnitude of the problem
- Which is the worldwide frequency of liver injury?
- Different phenotypes and clinical patterns at presentation
- Difficulties with diagnosis approach and causality assessment
- Future directions

HDS: ***H****erbal and* ***D****ietary* ***S****upplement*

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Herbal and Dietary Supplements nomenclature

WHO traditional medicine strategy (2014-2023)

HERBS

HERBAL MATERIALS

HERBAL PREPARATIONS

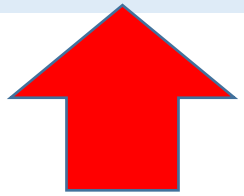
FINISHED HERBAL PRODUCTS

Current definitions

HILI: Herbs **I**nduce **L**iver **I**njury

HDS: Herbal and **D**ietary **S**upplement

“abuse agents” or “hormonal compounds”.



anabolic steroids

Herbal or botanical supplements, products such as vitamins, minerals, amminoacids, and proteins used as diet supplements and performance enhancing supplements (anabolic steroids)

Stricter definitions of HDS, standardization of herbal terminology and HDS categorization are needed

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HDS: ***H****erbal and* ***D****ietetic* ***S****upplement*

Magnitude of the problem

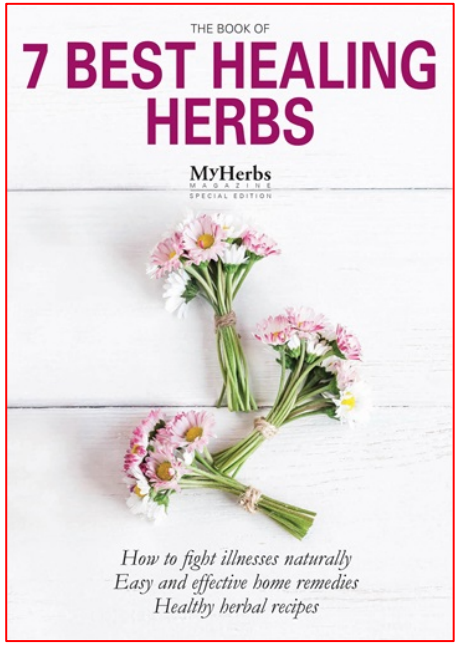
- **Worldwide growing use of HDS**

**Garcia-Alvarez A, et al. PLoS One 2014;9(03):e92265*

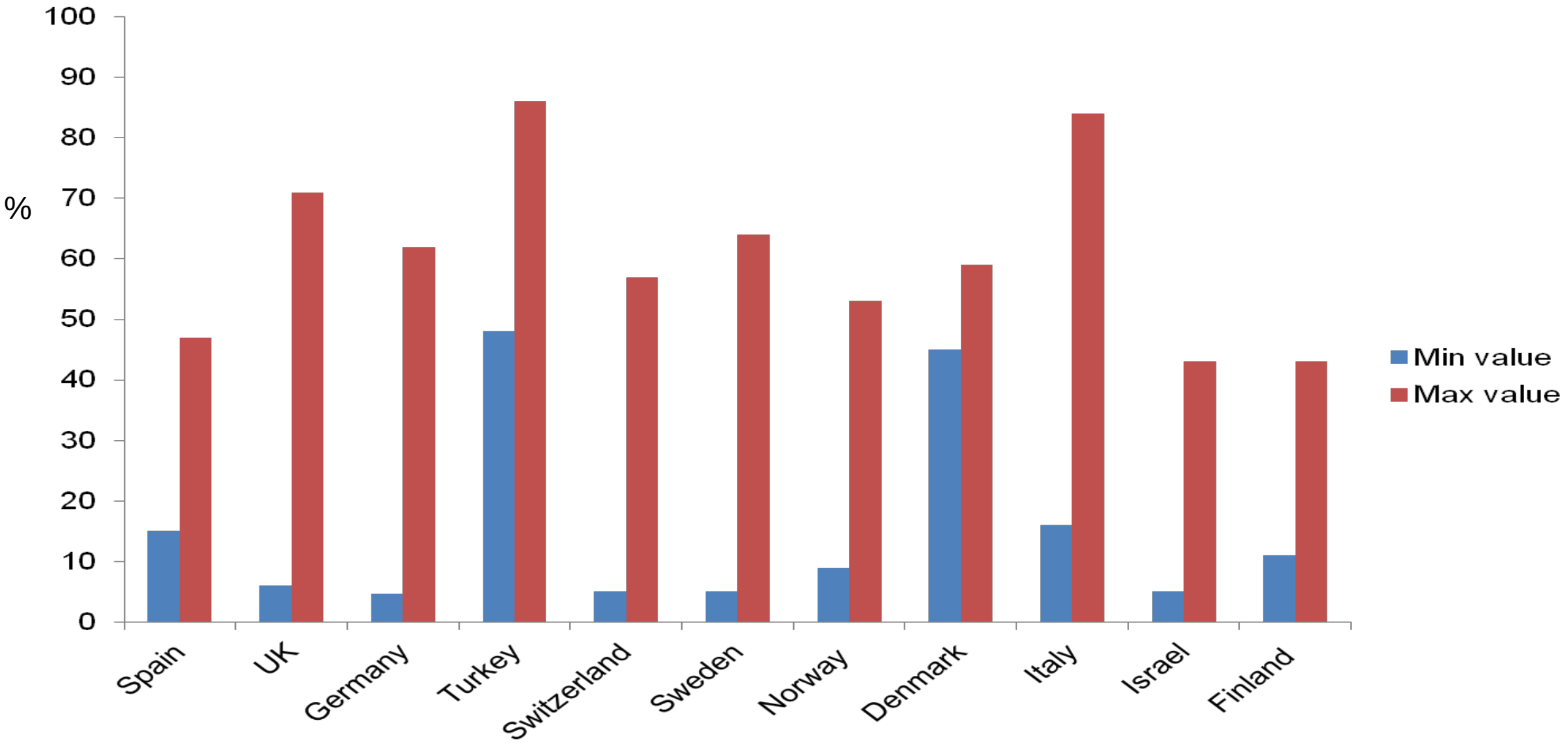
Worldwide growing use of HDS

Main reasons to explain HDS success

- Cultural issue
- **Security Reputation**
- Self-diagnosis and self-medication
- **Lack of specific regulatory control**
- **Easy internet purchase**
- **Disillusionment with traditional medicine**

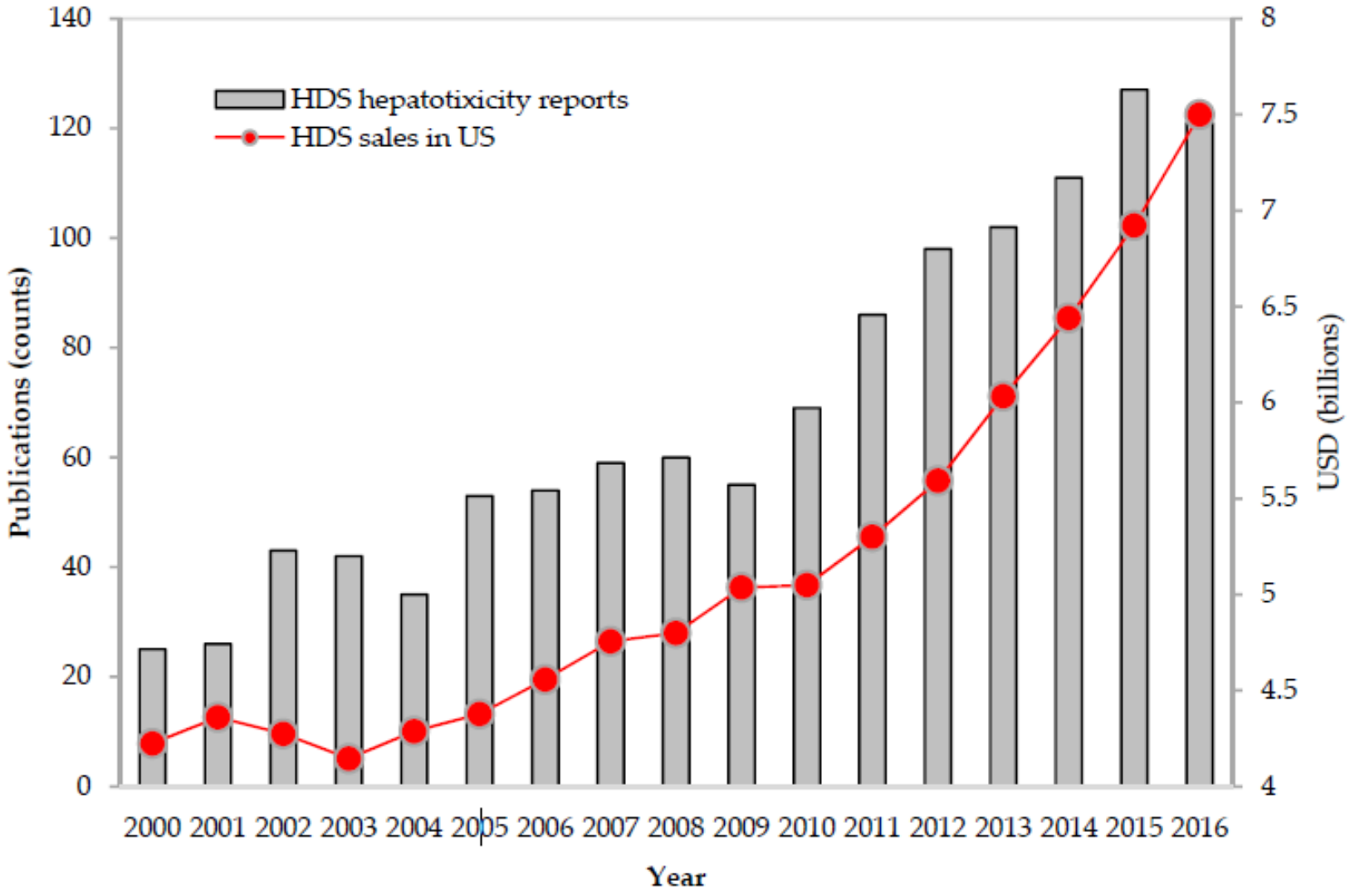


Prevalence of CAM use in Europe



(CAMbrella, WP 4,20)

Increase in herbal dietary supplement (HDS) sale and in publications reporting HDS hepatotoxicity.

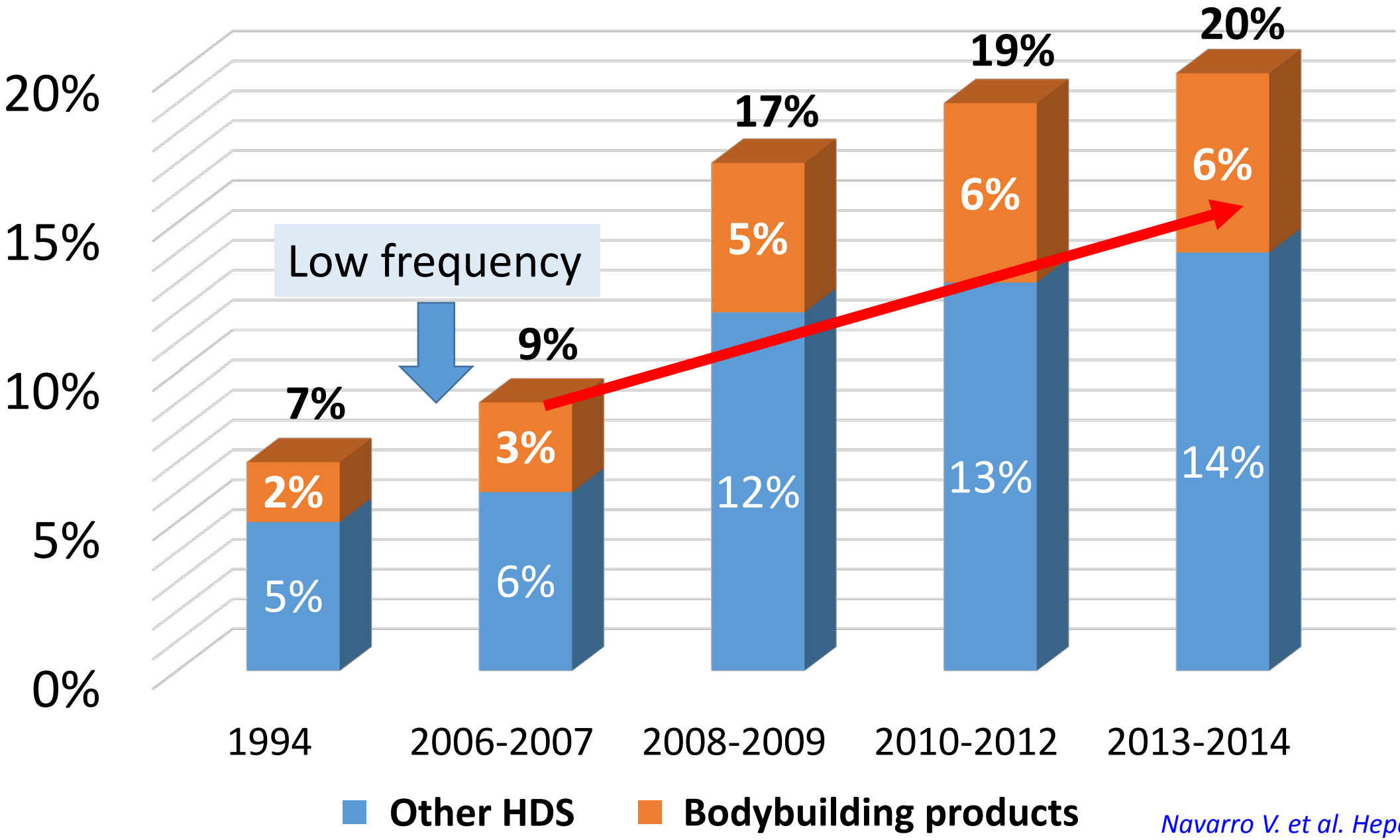


Lindstrom A. Herbal Gram 2014;103:52-56.

Nutrition Business Journal. Supplement Business Report 2015. New York: Penton; 2015.

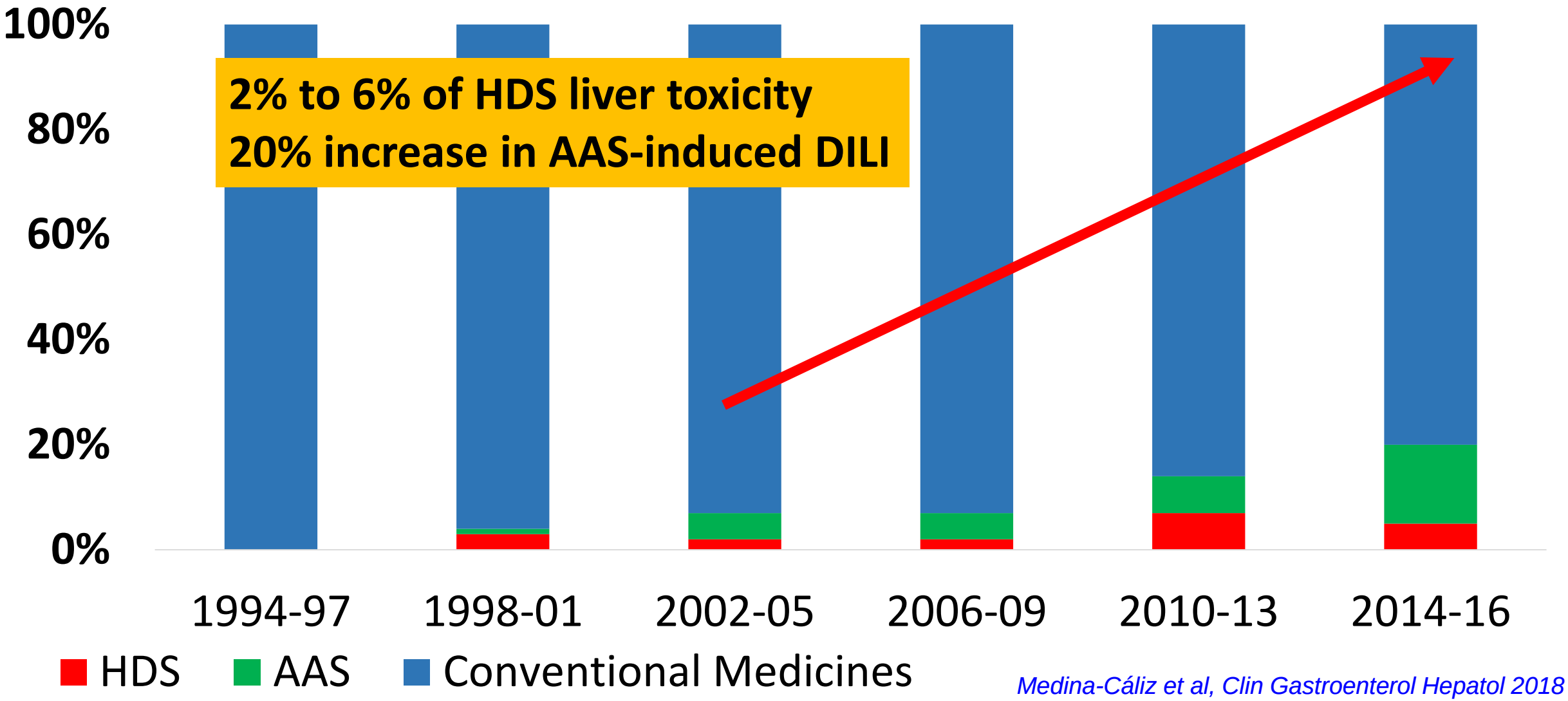
Zhu J. et al . Int J Mol Sci. 2018

Magnitude of the problem : HDS hepatotoxicity



Navarro V. et al. Hepatology 2017

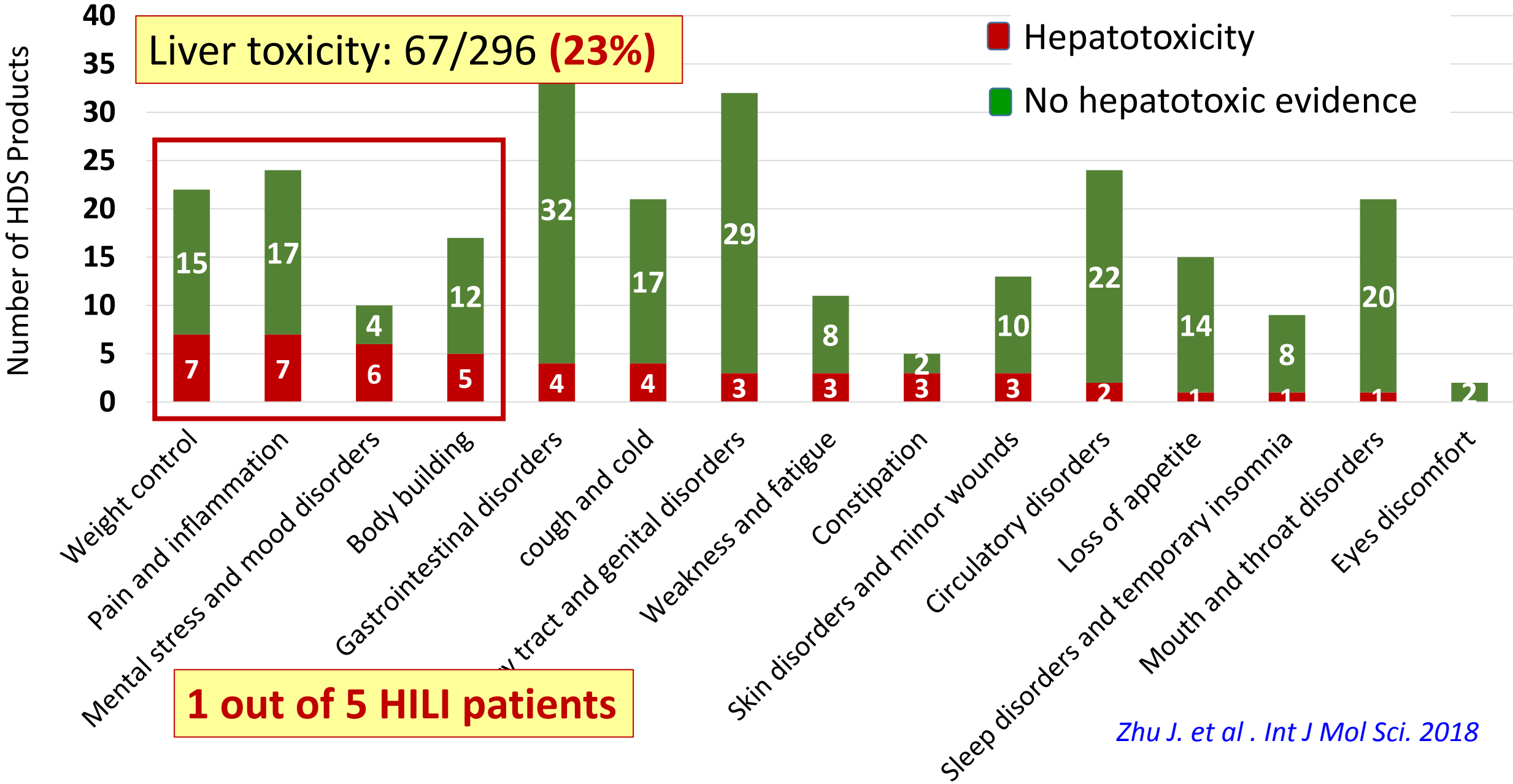
Secular trends in drug-induced liver injury cases enrolled in the Spanish DILI registry from 1994 to 2016



Medina-Cáliz et al, Clin Gastroenterol Hepatol 2018

AAS: Anabolic Androgenic Steroids

The distribution of human use of HDS with and without evidence of DILI



1 out of 5 HILI patients

Zhu J. et al . Int J Mol Sci. 2018

Magnitude of the problem

- Worldwide growing use of HDS

- **Inadecuate regulations on natural remedies**

The complex scenario of HDS regulations

- No requirement by FDA of HDS registration, leaving these products susceptible to inclusion of *unlabeled ingredients* *
- National authorities in Europe have clearer regulation rules

DIRECTIVE 2004/24/EC OF THE EUROPEAN PARLIAMENT AND THE COUNCIL provides the guidelines for the use of herbal medicines in Europe

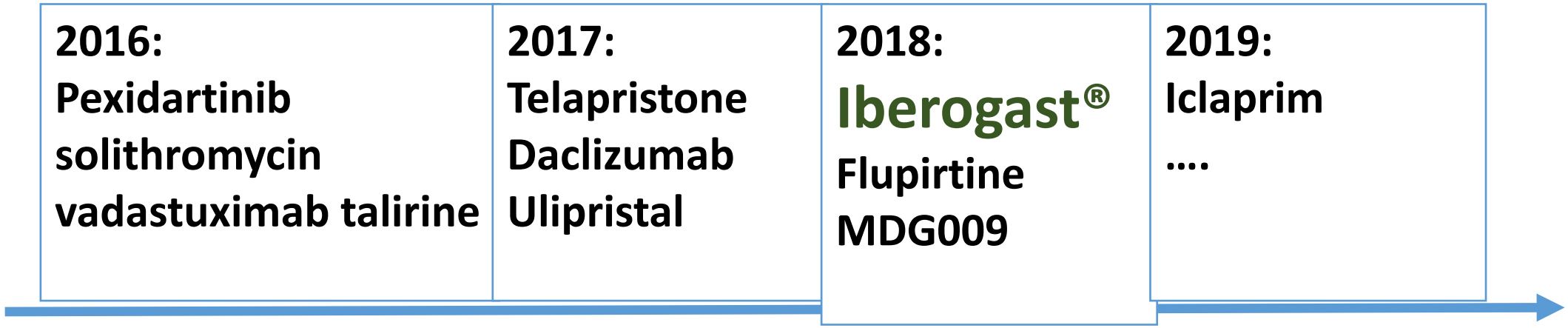
**Cohen PA. N Engl J Med 2012;366:389-391.*

Magnitude of the problem

- Worldwide growing use of HDS
- Inadecuate regulations of natural remedies
- **HDS are usually associated with severe liver damage**

(Usnic Acid, OxyELITE Pro, and Hydroxycut received FDA warnings)

Not Only Drugs are affected by DILI



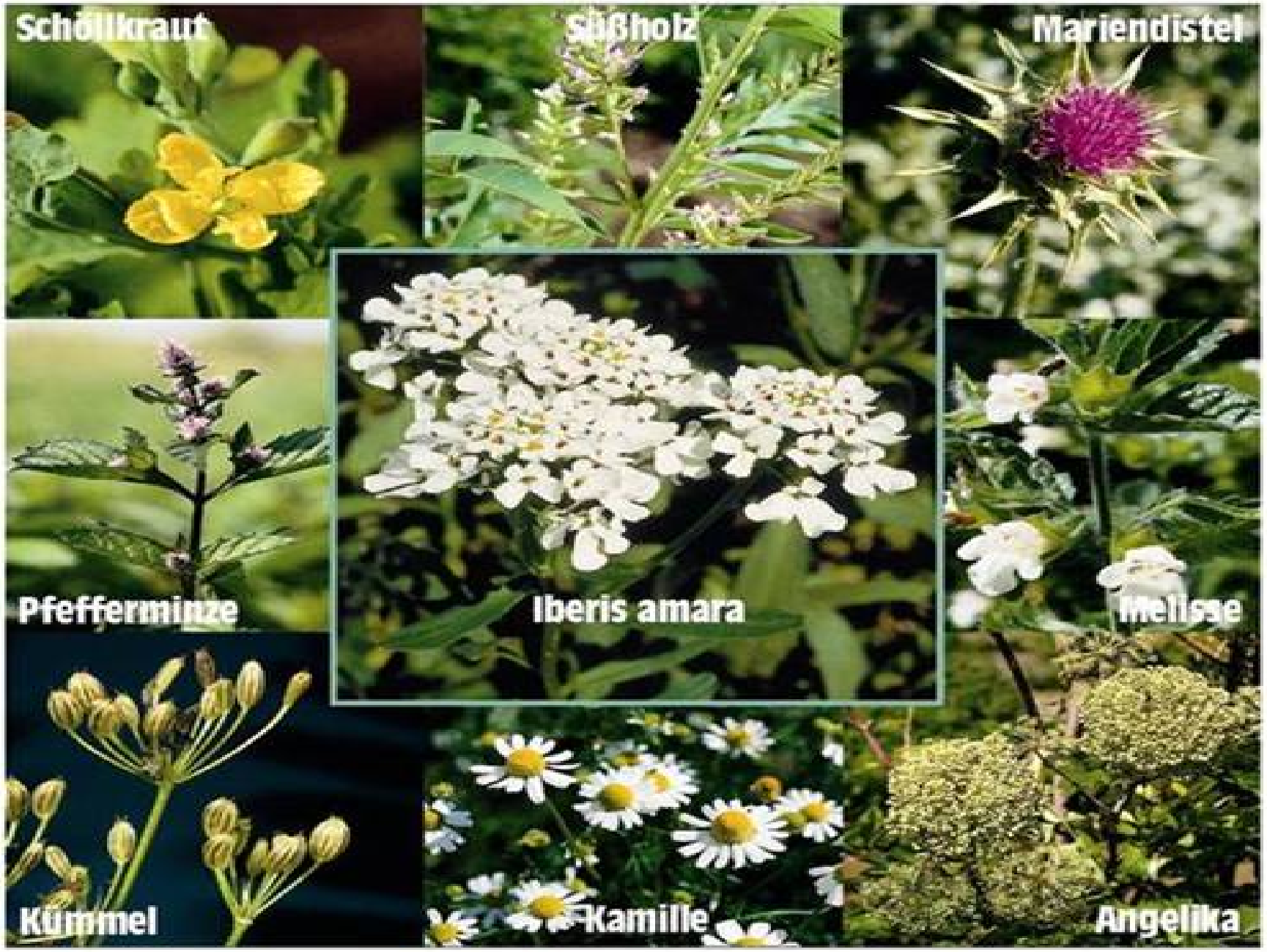
~3 Drugs with regulatory actions due to DILI per year

~1 market withdrawal per year due to DILI

Historic data from 1950s-2013: **~1 withdrawal due to DILI per year**…

Onakpoya et al.; BMC Med. 2016; 14: 10.

IBEROGAST


Schöllkraut
Süßholz
Mariendistel
Pfefferminze
Iberis amara
Melisse
Kümmel
Kamille
Angelika

Talk about HDS in 20 minute: a challenging issue !

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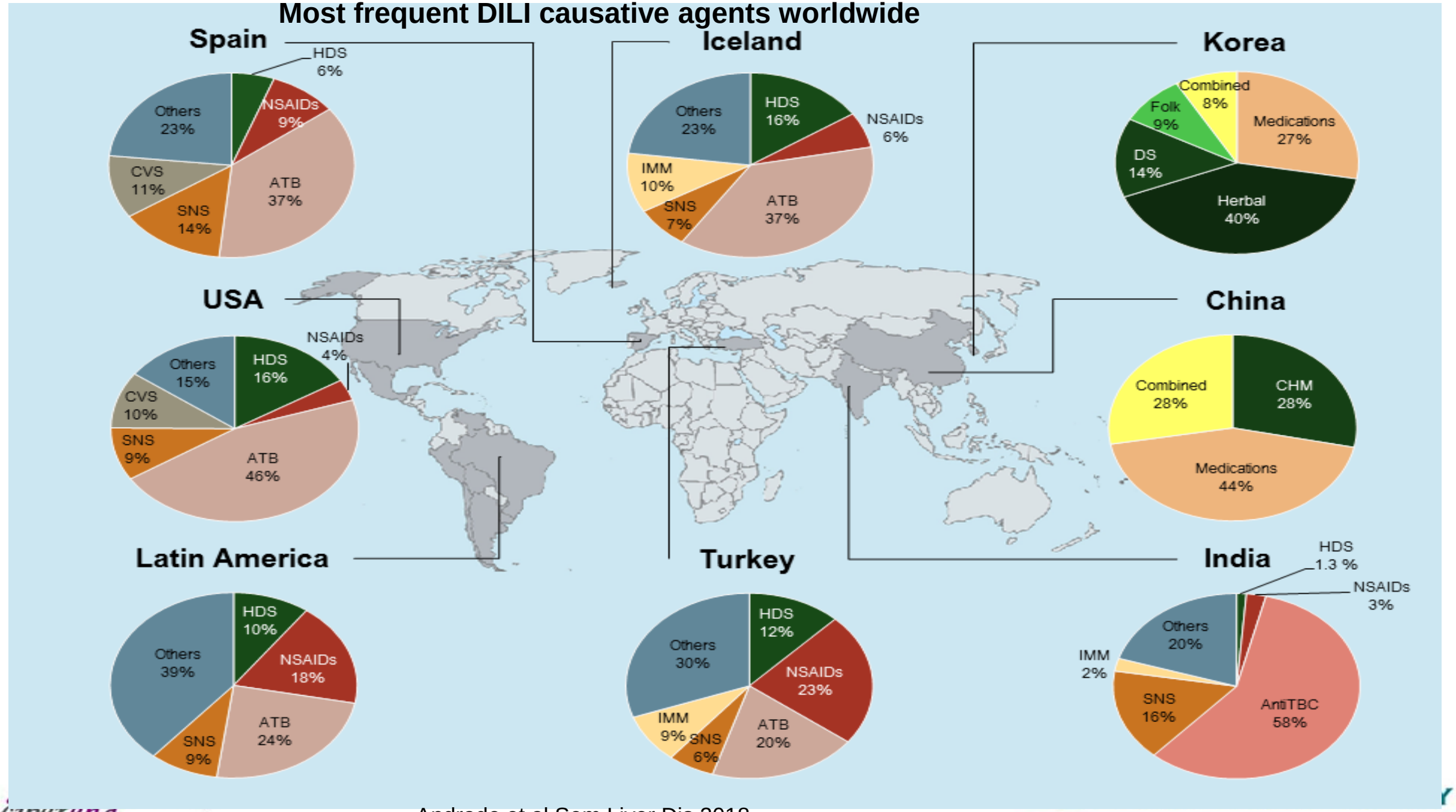
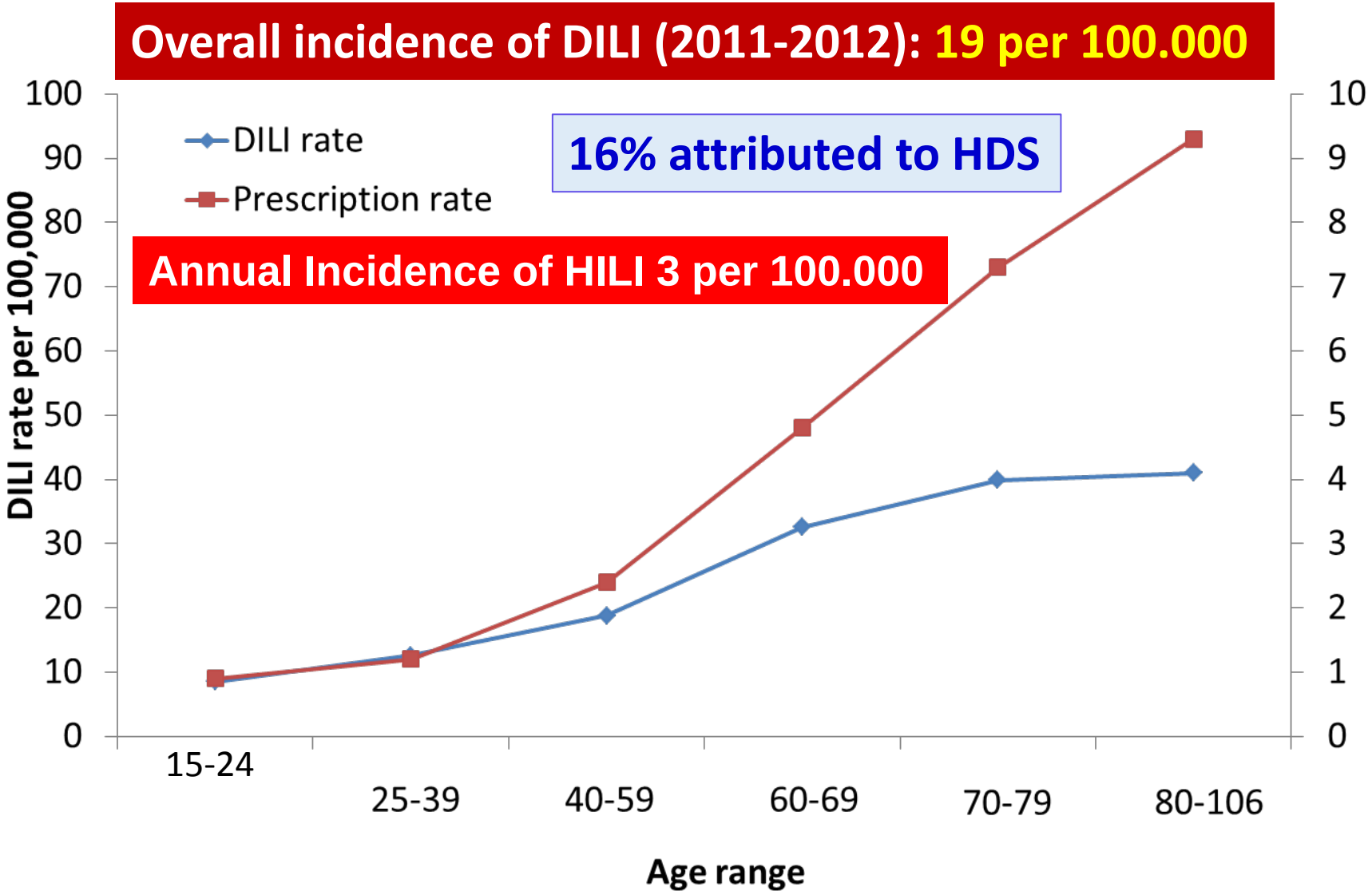


Andrade et al Sem Liver Dis 2018

Epidemiology of drug-induced liver injury in Iceland n=251,860



Björnsson E. et al. Gastroenterology 2013; 144(7):1419-1425

Clinical Gastroenterology and Hepatology 2018;16:1495–1502

Herbal and Dietary Supplement-Induced Liver Injuries in the Spanish DILI Registry

Inmaculada Medina-Caliz,[*] Miren Garcia-Cortes,[*] Andres Gonzalez-Jimenez,[*] Maria R. Cabello,[*] Mercedes Robles-Diaz,[*] Judith Sanabria-Cabrera,[*,‡] Rocio Sanjuan-Jimenez,[*,‡] Aida Ortega-Alonso,[*] Beatriz García-Muñoz,[*] Inmaculada Moreno,[*] Miguel Jimenez-Perez,[§] M Carmen Fernandez,[‖] Pere Ginés,[¶] Martin Prieto,[#] Isabel Conde,[#] Hacibe Hallal,[**] German Soriano,[‡‡] Eva Roman,[‡‡] Agustin Castiella,[§§] Encarnacion Blanco-Reina,[*] Maria R. Montes,[*] Marta Quiros-Cano,[*] Flores Martin-Reyes,[*] M. Isabel Lucena,[*,‡] and Raul J. Andrade,[*] on behalf of the Spanish DILI Registry

- Twenty two year experience in the Spanish DILI Registry
- Trends in HDS-induced liver injury
- Characterization of the phenotype and severity

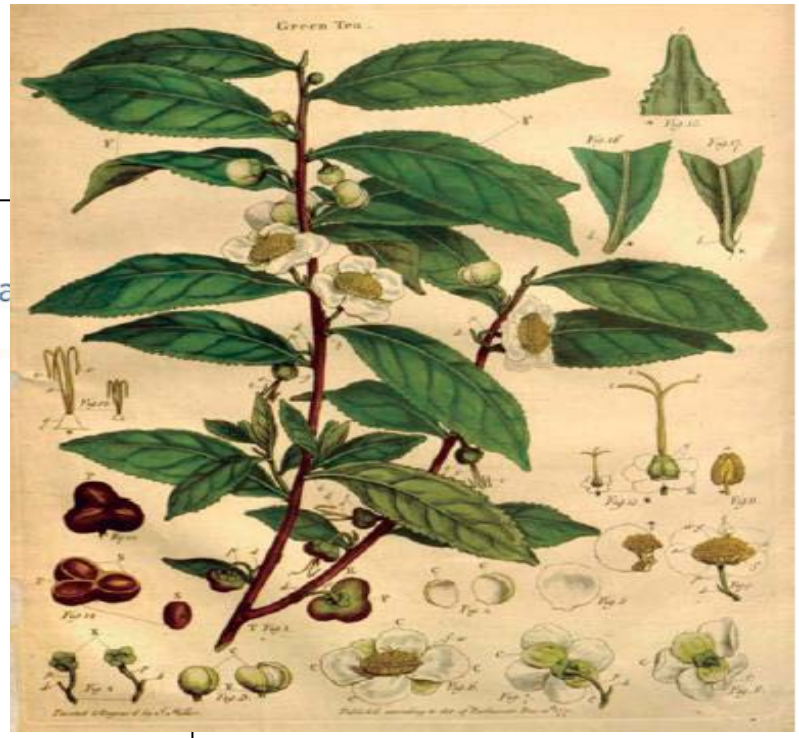
HDS associated with liver injury in the Spanish DILI Registry (n=32)

Camellia sinensis	8
Herbalife products	6
Rhamnus pursiana	2
Valeriana officinalis	2
Phyto soya®	2
Ginkgo Max® *(Ginkgo biloba)*	1
Isoflavones	1
Equisetum arvense	1
Cassia angustifolia	1
Chitosan®	1
Coutarea latiflora (Copalchi)	1
Glycyrrhiza glabra	1
Aesculus hippocastanum	1
Chelidonium majus	1
Serenoa repens	1
Thevetia Peruviana	1
Trim Fast®	1

ALF(n=1)

Self-limited acute hepatitis (n=6)

Medina –Caliz I. et al. Clin Gastroenterol Hepatol 2018



EFSA Journa

SCIENTIFIC OPINION

ADOPTED: 14 March 2018

doi: 10.2903/j.efsa.2018.5239

Scientific opinion on the safety of green tea catechins

EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS),
Maged Younes, Peter Aggett, Fernando Aguilar, Riccardo Crebelli, Birgit Dusemund,
Metka Filipič, Maria Jose Frutos, Pierre Galtier, David Gott, Ursula Gundert-Remy,
Claude Lambré, Jean-Charles Leblanc, Inger Therese Lillegaard, Peter Moldeus,
Alicja Mortensen, Agneta Oskarsson, Ivan Stankovic, Ine Waalkens-Berendsen,
Rudolf Antonius Woutersen, Raul J Andrade, Cristina Fortes, Pasquale Mosesso,
Patrizia Restani, Davide Arcella, Fabiola Pizzo, Camilla Smeraldi and Matthew Wright

Abstract

The EFSA ANS Panel was asked to provide a scientific opinion on the safety of green tea catechins from dietary sources including preparations such as food supplements and infusions. Green tea is produced from the leaves of *Camellia sinensis* (L.) Kuntze, without fermentation, which prevents the oxidation of polyphenolic components. Most of the polyphenols in green tea are catechins. The Panel considered the possible association between the consumption of (-)-epigallocatechin-3-gallate (EGCG), the most relevant catechin in green tea, and hepatotoxicity. This scientific opinion is based on published scientific

HDS associated with liver injury in the SLatinAmerican DILI Registry (n=22)

Herbalife products®	5
Garcinia cambogia	3
Lipodex®	2
Centella asiatica	2
Camellia sinensis	2
Echinacea	1
Monascus pu…	1
Hydroxi…	1
Gi… biloba	1
Peumus boldus	1
Equisetum arvense	1
Chitosan®	1
Kombucha tea	1
Pelargonium sidoides	1

Undereported HILI cases

Chronic hepatitis (n=2)

Self-limited acute hepatitis (n=3)

ELSEVIER

Journal of Hepatology 47 (2007) 521–526

Journal of Hepatology

www.elsevier.com/locate/jhep

Herbal does not mean innocuous: Ten cases of severe hepatotoxicity associated with dietary supplements from Herbalife® products☆

Alain M. Schoepfer[1], Antoinette E
Dominique Criblez[5], Juerg Reichen

[1] University Hospital of Bern,
[2] University Hospital, Depa
[3] Department of General Internal Medicine,
[4] Kantonssp
[5] Department of Gastroente
[6] Department of Clinical Pharmacology, Unive
[7] Department of Pathology,
[8] Medical Offi

See Edito

***Background/Aims*: Herbal agents are popular and per**
cases of toxic hepatitis implicating Herbalife® product

ELSEVIER

Journal of Hepatology 47 (2007) 514–520

Journal of Hepatology

www.elsevier.com/locate/jhep

Association between consumption of Herbalife® nutritional supplements and acute hepatotoxicity☆

Eran Elinav[1], Galia Pinsker[4], Rifaat Safadi[1], Orit Pappo[2], Michal Bromberg[4], Emilia Anis[4], Lital Keinan-Boker[4], Efrat Broide[5], Zvi Ackerman[3], Dorit Nitzan Kaluski[4], Boaz Lev[4], Daniel Shouval[1,*]

[1] Liver Unit, Hadassah-Hebrew University Medical Center, Ein-Kerem, P.O. Box 12000, Jerusalem 91120, Israel
[2] Department of Pathology, Hadassah-Hebrew University Medical Center, Jerusalem, Israel
[3] Department of Medicine, Hadassah-Hebrew University Medical Center, Jerusalem, Israel
[4] Ministry of Health, Israel
[5] Institute of Gastroenterology, Assaf Harofeh Medical Center, Zerifin, Israel

See Editorial, pages 444–446

***Background/Aims*: Nutritional supplements are frequently considered to be harmless but indiscriminate use of unlabelled ingredients may lead to significant adverse reactions.**

***Methods*: In 2004, identification of four index cases of acute hepatitis associated with Herbalife® intake led to a ministry of health investigation in all Israeli hospitals. Twelve patients with acute idiopathic liver injury in association with consumption of Herbalife® products were investigated.**

* These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure or prevent any disease. * Estas declaraciones no han sido evaluadas por la Administración de Alimentos y Medicamentos. Este producto no tiene la intención de diagnosticar, tratar, curar o prevenir ninguna enfermedad.

HERBALIFE®

Cell Activator®

Mitochondrial and Nutrient Absorption Support*

Apoya la función mitocondrial y la absorción de nutrientes*

DIETARY SUPPLEMENT
SUPLEMENTO DIETÉTICO

60 CAPSULES | CÁPSULAS

Supplement Facts
Datos del Suplemento

Serving Size • Porción: 1 capsule • cápsula
Servings Per Container • Porciones por Envase: 60

Amount Per Serving • Cantidad por Porción		% DV • % VD
Alpha Lipoic Acid • Ácido Alfa Lipoico	150 mg	†
Purified Aloe Vera Concentrate (Whole Leaf) • Concentrado Purificado de Sábila (Hoja Entera)	52 mg	†
Shiitake Mushroom • Hongo de Shiitake	15 mg	†
Pomegranate Rind Extract • Extracto de Cáscara de Granada	11 mg	†
Rhodiola Root Extract • Extracto de Raíz de Rhodiola	10 mg	†
Pine Bark Extract (Pycnogenol®) • Extracto de Corteza de Pino (Pycnogenol®)	2 mg	†
Resveratrol • Resveratrol	0.9 mg	†

† Daily Value (DV) not established • Valor Diario (VD) no establecido

OTHER INGREDIENTS: Microcrystalline Cellulose, Gelatin, Potassium Citrate, Silicon Dioxide and Magnesium Stearate.
OTROS INGREDIENTES: Celulosa Microcristalina, Gelatina, Citrato de Potasio, Dióxido de Silicio y Estearato de Magnesio.

Formula 3 Cell Activator® is formulated with alpha-lipoic acid, which helps regenerate antioxidant activity‡ within the cells. It also has aloe vera, which may support the body's absorption of micronutrients.*
‡Glutathione and vitamin C.
RECOMMENDED USE: Take one capsule twice a day with shakes or meals.
Herbalife Also Recommends: Use with Formula 1 shake and Formula 2 Multivitamin Complex, to complete the Herbalife® Core Cellular Nutrition program.
30-day money-back guarantee. This exclusively formulated product is only available through Herbalife Independent Distributors.
Pycnogenol® is a registered trademark of Horphag Research Ltd. protected by one or more of U.S. patents #5, 720, 956/#6, 372, 266 and other international patents.

Formula 3 Cell Activator® está formulado con ácido alfa lipoico, que ayuda a regenerar la actividad antioxidante‡ dentro de las células. También contiene sábila, la cual apoya al cuerpo en la absorción de micronutrientes.*
‡Glutatión y vitamina C.
USO RECOMENDADO: Tome una cápsula dos veces al día con los batidos o las comidas.
Herbalife También Recomienda: Use con Fórmula 1 batido y Fórmula 2 Multivitamin Complex, para completar el programa básico Herbalife® de Nutrición Celular.
Garantía de reembolso por 30 días. Este producto de formulación exclusiva solo está disponible a través de los Distribuidores Independientes de Herbalife.
Pycnogenol® es una marca registrada de Horphag Research, Ltd. protegido por una o más de los patentes de EUA #5, 720, 956/#6, 372, 266 y otras patentes internacionales.

Formulated and distributed exclusively by • Formulado y distribuido exclusivamente por:
HERBALIFE INTERNATIONAL OF AMERICA, INC., 800 W. Olympic Blvd., Suite 406, Los Angeles, CA 90015, USA
Made in USA with US and imported ingredients • Hecho en EUA con ingredientes estadounidenses e importados

3123US
L3123US-06 SKU3123

HERBALIFE®

Thermo complete®

Complemento alimenticio con vitamina C, té verde y yerba mate
Alto contenido en vitamina C

Contiene cafeína. No recomendado para niños ni mujeres embarazadas (164 mg / 2 tabletas)

Nº de lote y consumir preferentemente antes del: Ver base del envase

90 TABLETAS
CANTIDAD NETA: 78,9 g

Thermo complete® contiene vitamina C que contribuye al metabolismo energético normal y a la protección de las células frente al estrés oxidativo. También contiene una mezcla especialmente seleccionada de ingredientes botánicos incluyendo té verde y yerba mate.

USO RECOMENDADO: Tome una tableta dos veces al día, por la mañana y por la tarde. Conservar el producto bien cerrado y en lugar fresco y seco.

Garantía de devolución de 30 días. Este producto, de formulación exclusiva, está disponible únicamente a través de Distribuidores Independientes de Herbalife.

ADVERTENCIA: Se recomienda no superar la dosis diaria expresamente recomendada. Los complementos alimenticios están destinados a complementar la dieta y no deben utilizarse como sustitutivos de una dieta variada y un estilo de vida saludable. Mantener el producto fuera del alcance de los niños más pequeños. Las personas con hipertensión o problemas cardiovasculares, deben consultar a su médico antes de utilizar este producto.

Información nutricional

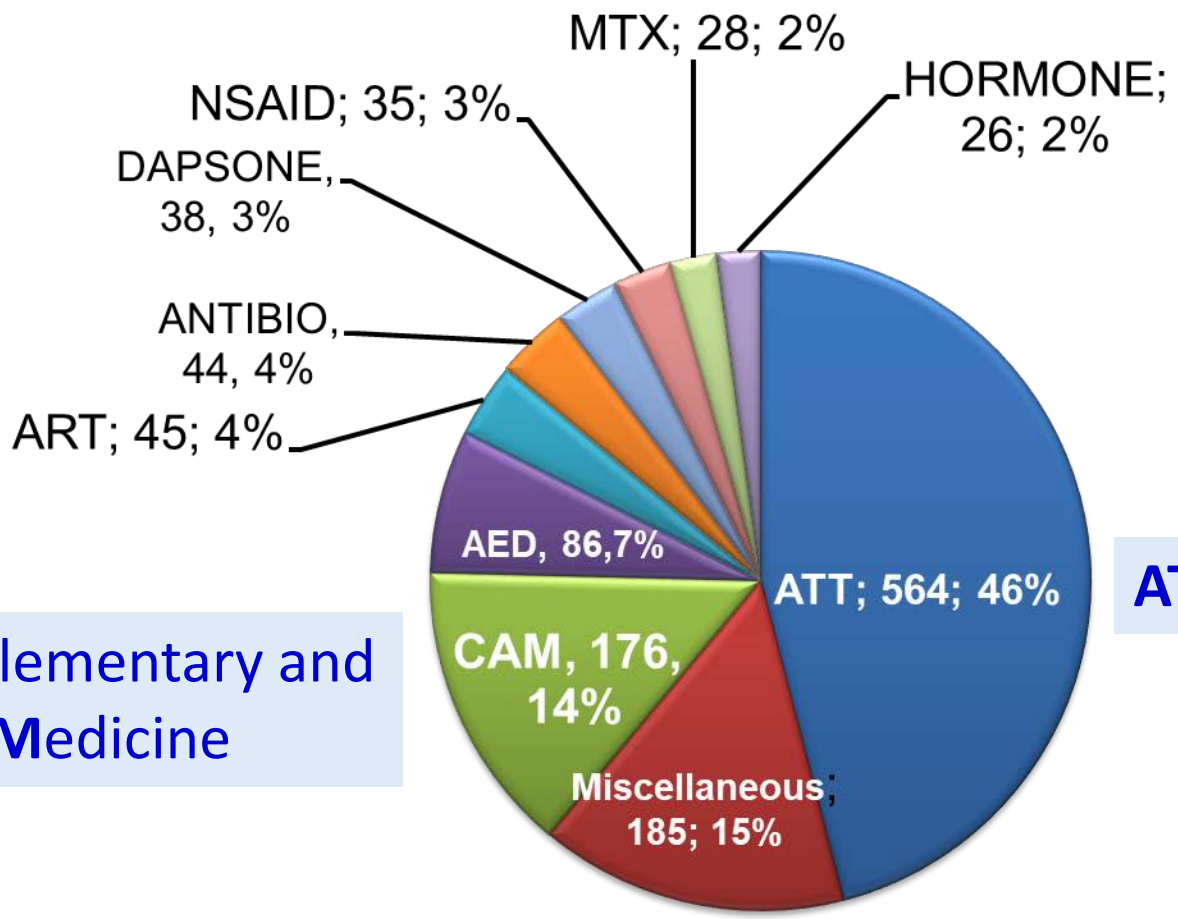
Valores medios	Por 2 tabletas	% VRN*
Vitamina C	40 mg	50 %
Cafeína	143 mg	
Extracto de té verde	300 mg	
del cual: cafeína	9 mg	
Extracto de yerba mate	150 mg	
del cual: cafeína	12 mg	

* Valores de referencia de nutrientes

INGREDIENTES: Agentes de carga (carbonato cálcico, celulosa microcristalina), extracto de té verde (*Camellia sinensis*), almidón de maíz, extracto de cacao (*Theobroma cacao*, 9 %), extracto de yerba mate (*Ilex paraguariensis*), cafeína en polvo, canela en polvo (*Cinnamomum zeylanicum*, 6 %), antiaglomerantes (dióxido de silicio, ácidos grasos, sodio carboximetilcelulosa, sales magnésicas de ácidos grasos), semillas de **apio** en polvo (*Apium graveolens*, 3 %), hojas de perejil en polvo (*Petroselinum crispum*, 3 %), ácido L-ascórbico, hoja de alfalfa en polvo (*Medicago sativa*, 2 %), semillas de hinojo en polvo (*Foeniculum vulgare*, 3 %), recubrimiento de la tableta [agentes de recubrimiento (carboximetilcelulosa sódica), dextrina, dextrosa, emulgente (lecitina de **soja**)], raíz de regaliz en polvo (*Glycyrrhiza glabra*, 1 %). Consejos para alergias: para los alérgenos, ver los ingredientes en **negrita**.

Distribuido por: HERBALIFE INTERNATIONAL LUXEMBOURG S.à R.L.
c/o HERBALIFE EUROPE LIMITED, The Atrium, 1 Harefield Road, Uxbridge, Middlesex UB8 1HB, U.K.
Representante en España: HERBALIFE INTERNATIONAL ESPAÑA S.A., Calle Velázquez, nº 149. 28002, Madrid, España

INDILI Drugs Implicated (N=1227)



CAM: Complementary and **A**lternative **M**edicine

ATT: **A**ntituberculosis **T**herapy

AED, anti-epileptic drugs; ART, antiretroviral treatment; MTX, methotrexate; NSAID, Nonsteroidal anti-inflammatory drugs

Courtesy H. Devarbhavi

Traditional and complementary medicines as cause of DILI in Asia

Traditional medicines are often integrated into healthcare system in ASIA

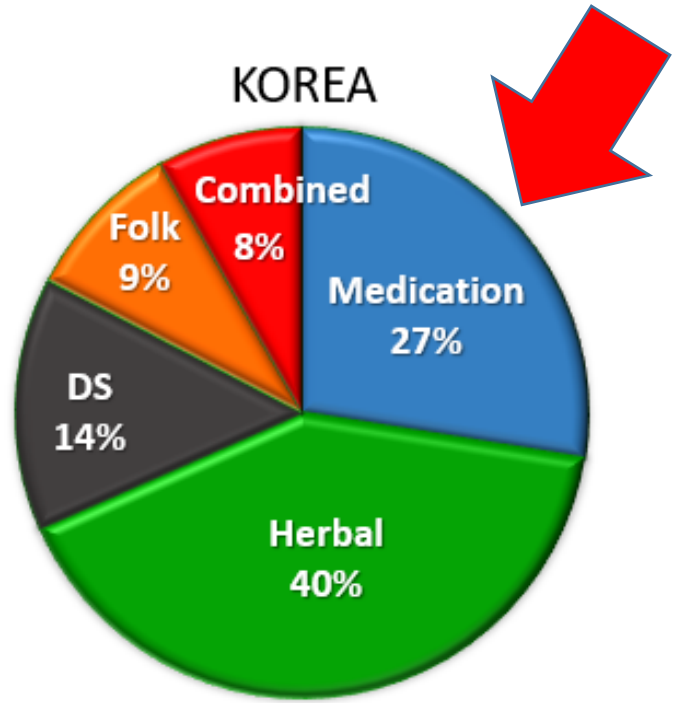
Singapore 71%

South Korea 42% → **73%**

China 18% → **28%**

Japan 17%

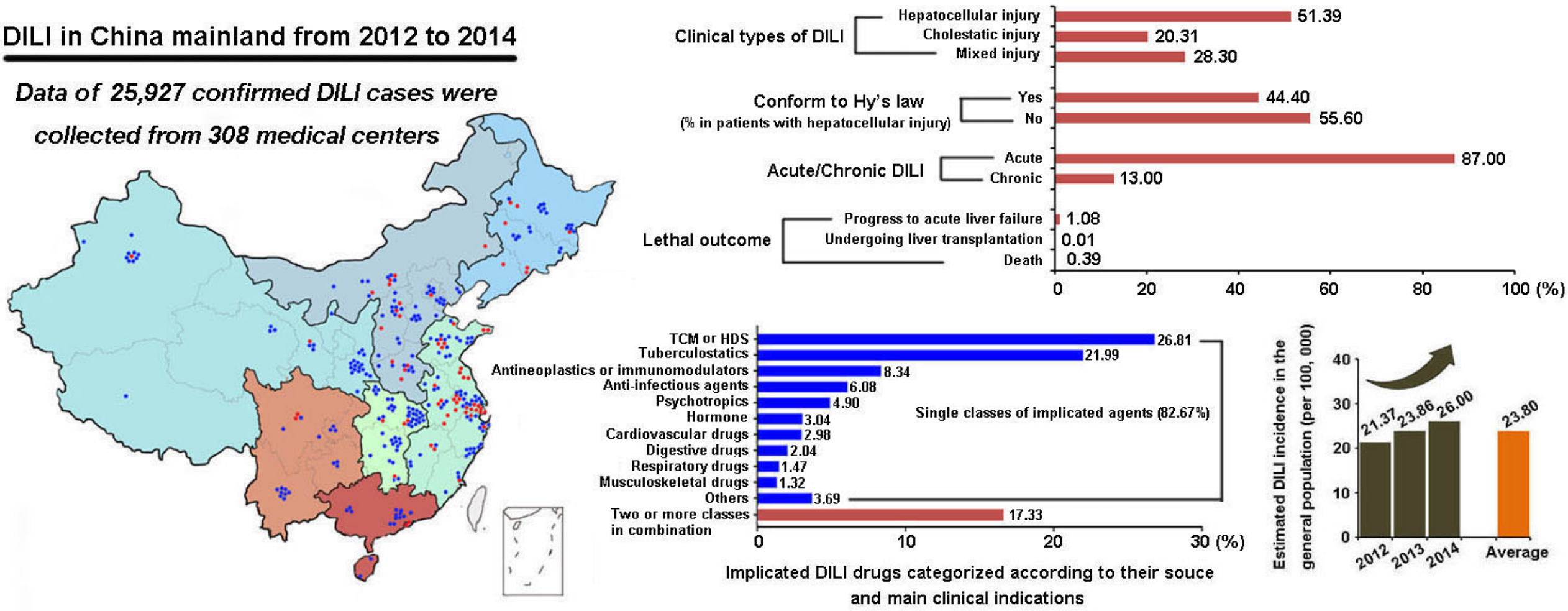
India 2% → **8%**



Suk K et al. AJG 2012;107:1380

Liv Int 2007;27:465. Kor J Hpatol 2004;10:125; Eur J Gastro Hepatol 2013;25:825; Hep Res 2009;39:427; JGH 2016;31:1476

DILI in China: almost 26.000 cases identified¡



Shen et al Gastroenterology 2019

Talk about HDS in 20 minute: a challenging issue !

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HDS: different phenotypes and clinical pattern at presentation

- More frequent among young women, and associated with hepatocellular injury and high transaminase levels [1,2,3]
- HDS-induced liver injury most commonly developed ALF and required liver transplant [1,2,3]

1. Navarro V. Hepatology 2017
2. Medina –Caliz I. et al. Clin Gastroenterol Hepatol 2018
3. Hillman et al. Am J Gastroenterol. 2016 ;111: 958–965

Outcomes of HDS Associated Liver Injury

136 patients with HDS-induced liver injury (2003-2012)

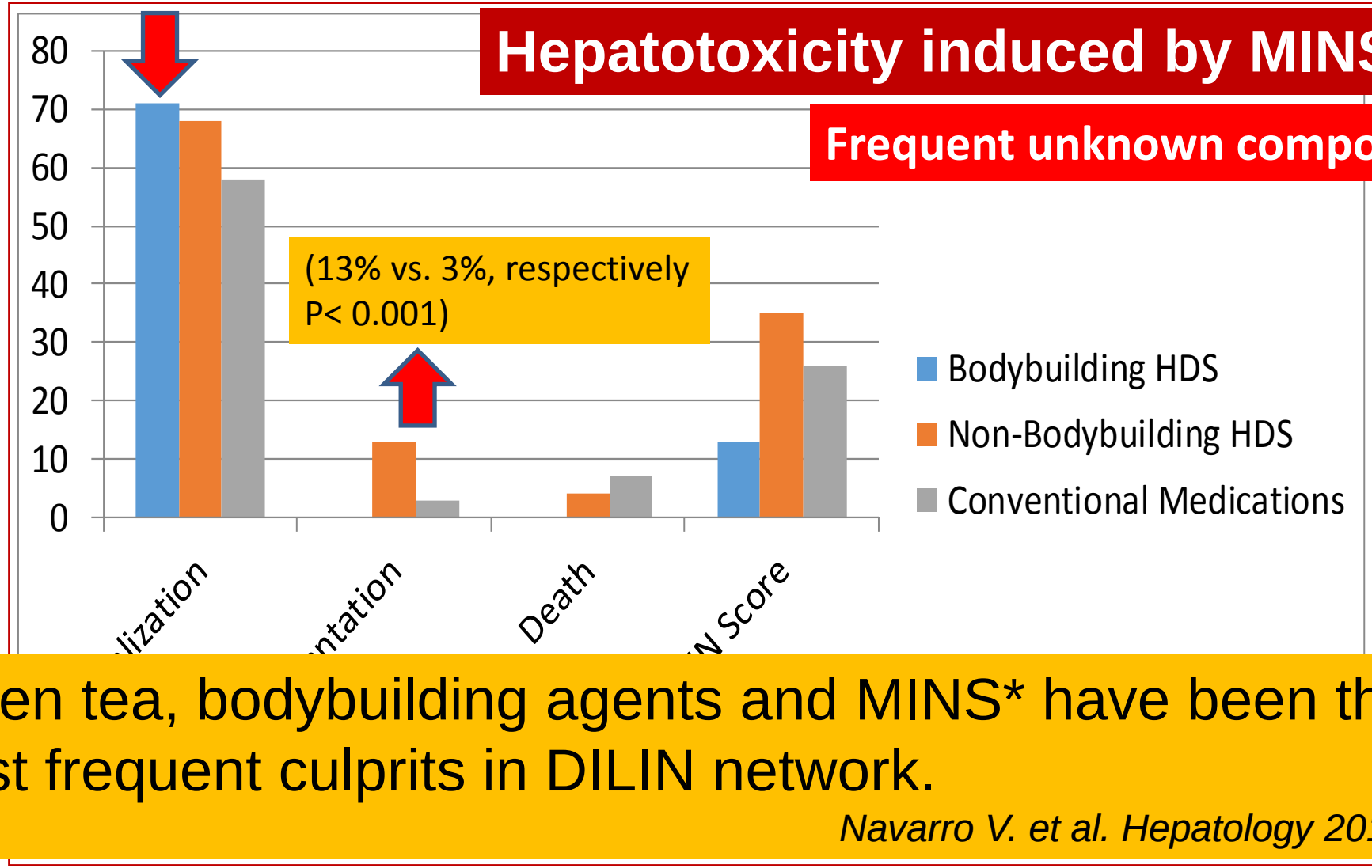
n=839

HDS: 16%

HDS:20%

Hepatotoxicity induced by MINS : 68%

Frequent unknown components



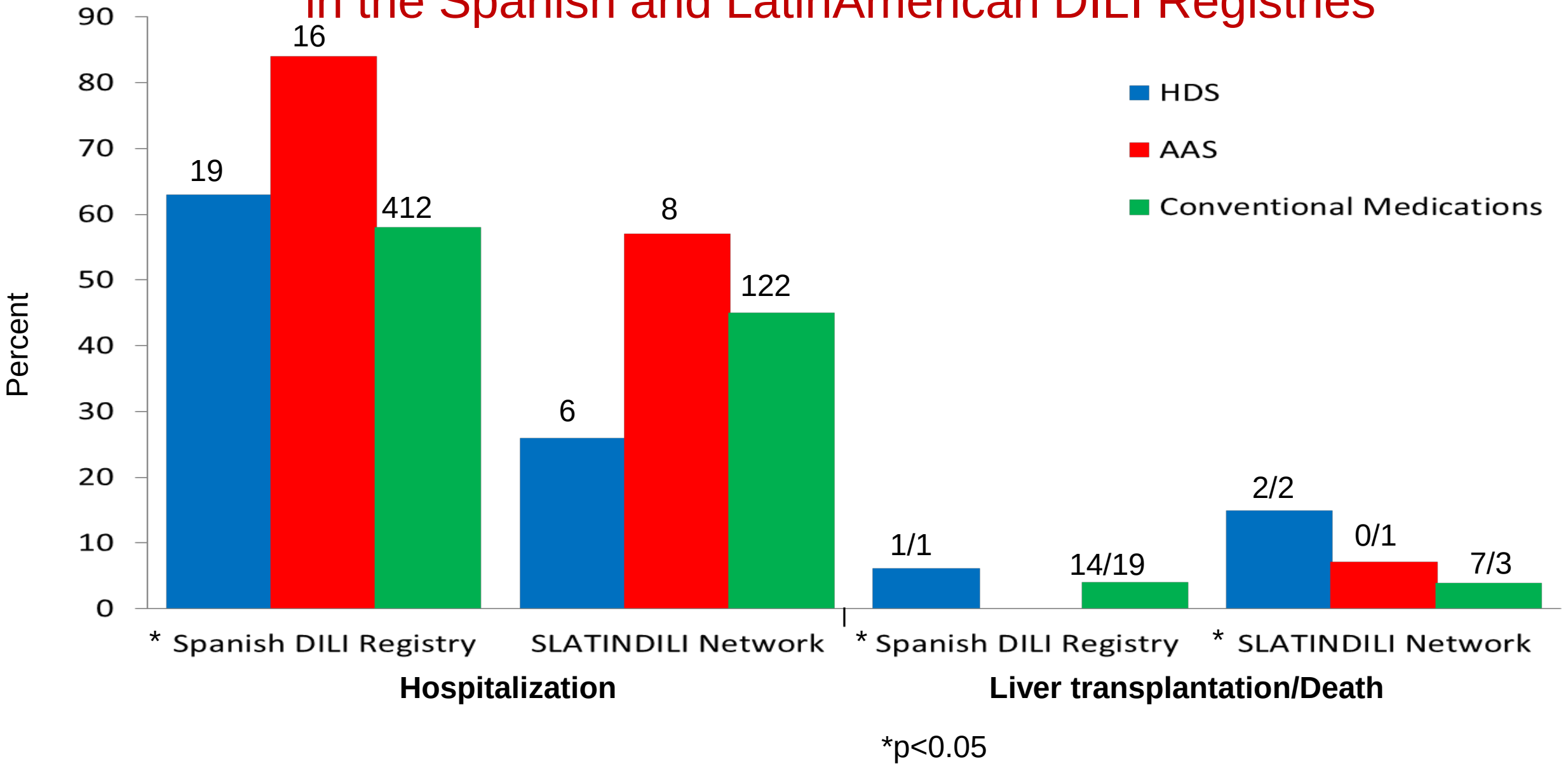
Green tea, bodybuilding agents and MINS* have been the most frequent culprits in DILIN network.

Navarro V. et al. Hepatology 2017

Navarro V, et al. Hepatology 2014;60:1399-1408

*MINS: ***M****ultiple* ***I****ngredients* ***N****utritional* ***S****upport*

Outcomes of HDS-induced liver injury in the Spanish and LatinAmerican DILI Registries



*p<0.05

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- **Difficulties with diagnosis approach and causality assessment**
- Future directions

HDS: ***H****erbal and* ***D****ietetic* ***S****upplement*

How to Approach Diagnosis of HDS-Induced Liver Injury?

- HDS may contain multiple and even **undeclared ingredients**
- Herbal terminology varies across countries, thus limiting identification of the active ingredient(s)
- **Physicians should obtain and save the product packaging**

JAMA®

Online article and related content current as of July 22, 2009.

Lead, Mercury, and Arsenic in US- and Indian-Manufactured Ayurvedic Medicines Sold via the Internet

Robert B. Saper; Russell S. Phillips; Anusha Sehgal; et al.

JAMA. 2008;300(8):915-923 (doi:10.1001/jama.300.8.915)

- One-fifth of Ayurvedic medicines purchased via the Internet contain detectable lead, mercury, or arsenic (19.5%-21.7%)
- 95% were sold by US Web sites and 75% claimed GMP (good manufacturing practise)

Courtesy H. Debvarhavi

Case Report

JOURNAL OF CLINICAL AND EXPERIMENTAL HEPATOLOGY

Slimming to the Death: Herbalife®-Associated Fatal Acute Liver Failure—Heavy Metals, Toxic Compounds, Bacterial Contaminants and Psychotropic Agents in Products Sold in India

Cyriac A. Philips [*], Philip Augustine [*], Sasidharan Rajesh [*], Solomon K. John [*], Gopakumar C. Valiathan [*], Jos Mathew [*], Sameer Phalke [†], Kuruveetil L. Antony [‡]

[*] *The Liver Unit, The Cochin Gastroenterology Group, Emakulam Medical Centre, Kochi, Kerala 682028 India,* [†] *Medgenome Labs, Narayana Health City, Bommasandra, Bengaluru, Karnataka 560099 India and* [‡] *Envirodesigns Ecolabs, Eco Tower, Palarivattom, Kochi, Kerala 682025 India*

Pro and cons of causality assessment in HILI

- RUCAM/CIOMS scale is challenging in the domain “previous hepatotoxicity potential”.

- Serum biomarkers:
  - New assay to assess **pyrrole-protein adduct** [1]
  - Detection of **autoantibodies*** in serum of patients with HILI induced by germander [2,3]

- **Chemical composition studies are very useful but not available yet in clinical practice**

* Antimicrosomal epoxide hydrolase autoantibodies

1. Lin G. et al. J Hepatol 2011;54(04):666–673
2. Larrey D. et al. Ann Intern Med 1992;117:129–132
3. Larrey D. et al. J Hepatol 2011; 54: 599–601

HDS: Agenda

- Current definition and magnitude of the problem
- Whichis the worldwide frequency of liver injury?
- Potential mechanistic pathways
- Different phenotypes and clinical pattern at presentation
- Difficulties faced with diagnosis approach and causality assessment
- **Future directions**

HDS: ***H****erbal and* ***D****ietetic* ***S****upplement*

What we should improve in the future?

- **Efforts should be made to achieve worldwide regulatory requirements**
- Identifying the chemical composition of HDS is a key step in determining the responsible ingredients.
- Improved methods of causality assessment are needed.
- Pharmacogenetics studies are crucial to better known HILI risk

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EDITORIAL

WILEY Liver INTERNATIONAL

Herbal-induced liver injury: The price to pay for a healthier life?

See Article on Page 389

Liver toxicities related to the use of herbs and dietary supplements (HDS) are a growing health concern although this rising burden is less well acknowledged than the risk posed by conventional drugs.[1] In the current issue of Liver International, Wang et al[2] from China present their long-term experience with the hepatotoxicity induced by He Shou Wu (*Polygonum multiflorum* Thunb), an ancient anti-ageing Chinese herb claimed to have benefits on a number of conditions such alopecia and greying of hair, cancer, diabetes, atherosclerosis, sleep disorders and neurodegenerative diseases.

The potential of this herb to cause liver injury is well known. Indeed, *Polygonum multiflorum* was the major implicated Chinese herbal medicine in the largest series of drug-induced liver injury cases published to date from China, either as a single agent or as a preparation containing this compound.[3]

However, this and other studies did not go into details when reporting the hepatotoxicity of this herb. Thus, the study by Wang et al[2] have the merit to compile consistent clinical and pathological data on 29 patients from a single centre over a 13-year period providing detailed information of the clinical presentation and outcome of liver injury induced by He Shou Wu. Hence, clinicians facing a new potential case will find this data very valuable. The majority of the patients (75%) were of female gender. The phenotype was consistently (100% of the cases) hepatocellular at presentation with markedly elevated levels of transaminases and total bilirubin. In addition, one patient was rechallenged with the product, one patient died of liver failure, and three had a chronic outcome. This characteristic presentation and outcome of *Polygonum multiflorum*-induced liver no less than a 10% of the cases in DILI Registries, with female sex[6] and Asian Race[7] identified as independent risk factors that predict fulminant liver failure and death within 6 months after DILI onset respectively. Of note, the relative contribution of herbs and dietary supplements to the cases of toxic acute liver failure in the Acute Liver Failure study group experience has increased in the past decade from 12% to 20%.[8] Most importantly, herbal and dietary supplement-induced acute liver failure has been shown to have a poorest prognosis than that of prescription medicines with higher transplantation rates (56% vs 32%) and only 17% spontaneous survival vs 34% of recovery in cases attributed to conventional drugs.[9] Because herbal consumption is often overlooked, clinician's awareness of this specific HILI phenotype is important to enquire about consumption of herbal and dietary supplements and could help refine causality assessment methods. Indeed, the widely used RUCAM scale yielded lower scores when it was used to assess suspected herbal hepatotoxicity as compared to prescription medicines[3] in part because RUCAM was developed specifically for drugs and one of the domains (information in the summary of product characteristics) does not apply to herbs.[1] The diagnostic approach for HILI is actually similar to that of DILI although more potential pitfalls need to be taken into account when herbs are suspected causes of liver injury (Figure 1).

The study by Wang et al[2] also highlights the issue of distinguishing herbal (or drug)-induced liver injury f
atitis (AIH); 26% of cases had high titre
(ANA), and one patient required steroids
laboratory abnormalities. The differentia
iopathic) AIH and drug-induced AIH or "
injury remains an open unresolved ques
duced" AIH is the absence of significant

Raúl J. Andrade

Unidad de Gestión Clínica de Aparato Digestivo, Instituto de Investigación Biomédica de Málaga-IBIMA, Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas CIBERehd, Hospital Universitario Virgen de la Victoria, Universidad de Málaga, Málaga, Spain

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DRUG-INDUCED LIVER INJURY

WILEY Liver INTERNATIONAL

Clinicopathological features of He Shou Wu-induced liver injury: This ancient anti-aging therapy is not liver-friendly

Yan Wang[1] | Lan Wang[1] | Romil Saxena[2] | Aileen Wee[3] | Ruiyuan Yang[1] | Qiuju Tian[1] | Jiping Zhang[4] | Xinyan Zhao[1] | Jidong Jia[1]

[1]Liver Research Center, Beijing Friendship Hospital, Capital Medical University, Beijing Key Laboratory on Translational Medicine on Cirrhosis, National Clinical Research Center for Digestive Disease, Beijing, China

[2]Department of Pathology, Indiana University School of Medicine, Indianapolis, Indiana

[3]Department of Pathology, Yong Loo Lin School of Medicine, National University of Singapore, National University Hospital, Singapore, Singapore

[4]Department of Pathology, Guangzhou Kingmed Center for Clinical Laboratory, Guangzhou, China

Correspondence: Xinyan Zhao, MD, PhD, Jidong Jia, MD, PhD, Liver Research Center, Beijing Friendship Hospital, Capital Medical University, Beijing Key Laboratory on Translational Medicine on Cirrhosis, National Clinical Research Center for Digestive Disease, 95 Yong An Road, Xi Cheng District, Beijing, China (zhao_xinyan@ccmu.edu.cn; jia_jd@ccmu.edu.cn).

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Abstract

Background & Aims: *Polygonum Multiflorum* Thumb (PMT), an ancient anti-aging Chinese herb known traditionally as He Shou Wu, has side effects of liver toxicity. To determine the main clinical and pathological characteristics of liver toxicity induced by PMT and the clinical course after its cessation.

Methods: Data of patients, diagnosed as drug-induced liver injury and hospitalised in Beijing Friendship Hospital from August 2005 to August 2017, were retrospectively reviewed. Clinical, pathological data and outcome after cessation of He Shou Wu were obtained and analysed. Kruskal-Wallis and Chi-square (χ^2) tests were performed.

Results: Twenty-nine patients with He Shou Wu-induced liver injury were enrolled. The median age was 53 years (range 15-74) and 75.9% (22/29) were women. The most common symptom was jaundice (79.3%, 23/29). Of nine patients with liver biopsies, six showed acute cholestatic hepatitis, two acute, and one chronic hepatocellular injury pattern. The latency, liver chemistries and outcomes were comparable between pure He Shou Wu (5 patients) and its compounds (24 patients). Twenty-five of 29 patients (86.2%) had normal serum alanine aminotransferase levels after 45 days (range: 10-138 days) and total bilirubin of 46 days (range: 0-551 days). One patient was rechallenged with He Shou Wu and two developed autoimmune features. One patient died of liver failure and three had chronic persistent liver injury.

Conclusions: The main clinicopathological injury pattern of He Shou Wu-induced liver injury is moderate to severe hepatitis with or without cholestasis. Most patients recover completely; however, chronic disease and death do occur.

KEYWORDS

clinical course, drug-induced liver injury, He Shou Wu, *Polygonum Multiflorum* Thumb

Alternative Medicine — The Risks of Untested and Unregulated Remedies

"It is time for the scientific community to stop giving alternative medicine a free ride... There cannot be two kinds of medicine — conventional and alternative.

There is only medicine that has been adequately tested and medicine that has not, medicine that works and medicine that may or may not work.

Once a treatment has been tested rigorously, it no longer matters whether it was considered alternative at the outset. If it is found to be reasonably safe and effective, it will be accepted."

The NEW ENGLAND JOURNAL of MEDICINE

Angell & Kassirer N Engl J Med 1998;339:839-41.

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