

# SAFETY MONITORING OF HERBALS THE MOROCCAN EXPERIENCE

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**Pharmacovigilance of Herbal Medicines Unit**

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# PLAN

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II- Safety Monitoring of Herbals in Morocco

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V- Conclusions

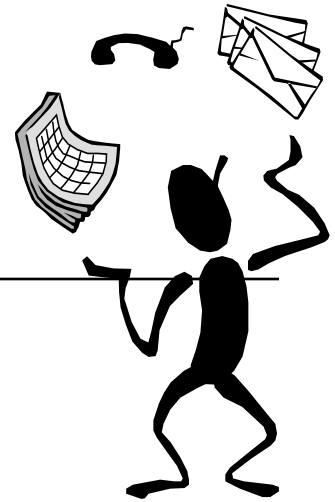
# INTRODUCTION

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- ❖ Herbal medicines are widely used around the world
- ❖ The case in Morocco where HM, as with all medicines, have been shown to have adverse effects, which are related to a variety of causes, essentially in relation to
  - ❖ Self-medication
  - ❖ Quality of HM (contamination, adulteration)
  - ❖ Unlicensed products
  - ❖ Incorrect dosing
  - ❖ Other particular conditions of use

# INTRODUCTION



## Other particular conditions of use

- ❖ Different parts of plant
- ❖ Different methods of preparation
- ❖ Inadequate knowledge by HP and consumers
- ❖ Socioeconomic level
- ❖ Sociocultural level (spiritual interpretation of ARs as a process of healing)
- ❖ Inadequate label
- ❖ Concurrent use of HM & conventional drugs

# SAFETY MONITORING OF HERBALS IN MOROCCO

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## Setting up

- ❖ The safety of Herbals is monitored through the Centre Anti Poison et de Pharmacovigilance du Maroc
- ❖ Pharmacovigilance Department
- ❖ Pharmacovigilance of HM or Phytovigilance Unit
- ❖ Implemented in September 2000
- ❖ Two full time persons

# SAFETY MONITORING OF HERBALS IN MOROCCO

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## Role

- ❖ Assessment of risks and benefits of HM
- ❖ Ultimate aim is to protect patients from herb induced harms

# SAFETY MONITORING OF HERBALS IN MOROCCO


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## Functioning


- ❖ Globally, the same monitoring as conventional drugs both at national and international levels
- ❖ Some adaptation to herbals

# Reporting Form

- ❖ A single reporting form covering all HP
- ❖ Facilitate reporting with an adaptation for HM raw material: part of the herb used, type of extraction and dose  
**(Quality of reports)**
- ❖ Attract the attention of HP **(Quantity of reports)**


 Royaume du Maroc  
Ministère de la Santé

Centre National  
de Pharmacovigilance



**Déclaration des Evénements Indésirables aux  
Médicaments et autres produits de santé**

**Patient :**

Nom et prénom :	Antécédents et terrain :	Localité ou ville :
Age :                      Sexe : M / <input type="checkbox"/> / F / <input type="checkbox"/>		
Poids en Kg :            Si grossesse ; âge gestationnel :		Tél :

**Evénement(s) indésirable(s) :**

Description clinique et para clinique de l'événement indésirable :

Date d'apparition : / /                      Délai d'apparition : Heures / /                      Jours / /                      Mois / /

Diagnostics différentiels éliminés :

Conduite adoptée (précisez : arrêt ou réduction de la dose administrée, traitement correcteur, hospitalisation ou prolongation d'hospitalisation) :

Evolution de l'événement:    Guérison sans séquelles / ☐ / séquelles / ☐ / Sujet non encore rétabli / ☐  
Décès / ☐ / Inconnue / ☐

**Médicaments et autres produits de santé (PS) pris par le patient (par ordre de suspicion décroissant)**

1- Prescription médicale		2- Auto médication		3- Erreur médicamenteuse		4- Produit défectueux			
Nom la spécialité et présentation	Posologie et voie d'administration	Date de début	Date d'arrêt	Indication	Modalités de dispensation		Circonstance de prise		
					1	2	3	4	

Médicament ré administré :    Oui / ☐ / Non / ☐    lequel :

Réapparition de l'événement :    Oui / ☐ / Non / ☐    décrivez :

Si Vaccin : N° de lot :    Nombre de prise :    Lieu de vaccination : Secteur Public / ☐ / Privé / ☐ / Campagne de vaccination / ☐

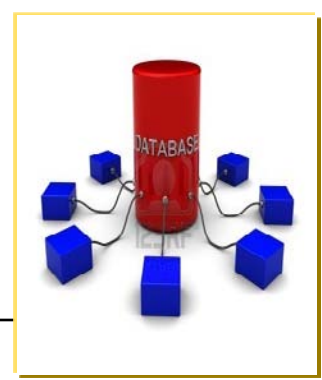
Si Plante médicinale : Dose :    Partie utilisée :    Mode de préparation : infusion / ☐ / Décoction / ☐ / Macération / ☐  
Autres / ☐

Observation relevée le : / / par : Médecin / ☐ / Dentiste / ☐ / Pharmacien / ☐ / Infirmier / ☐ / Patient / ☐ / Autre :    Lieu d'exercice : CHU / ☐ / Public / ☐ / Privé / ☐    Nom,    tel,    Signature

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# DATA MANAGEMENT

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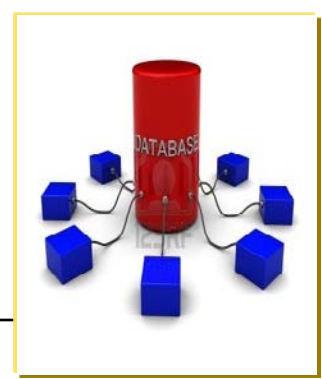


## Data Storage

- ❖ Database that collates all case reports of suspected AEs in relation with HM was developed
- ❖ Database includes case reports submitted through the spontaneous reporting system and intensive monitoring programmes (surveys, prevalence studies)

# DATA MANAGEMENT

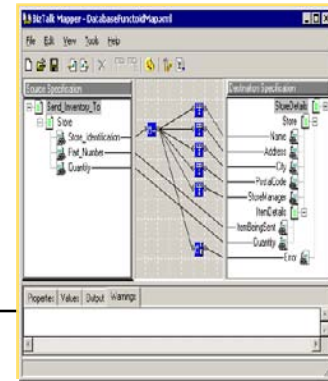
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## Data Quality

- ❖ An additional requirement identifying at least:
  - ❖ part of the herb used
  - ❖ type of extraction
  - ❖ indication
  - ❖ dose
- ❖ Data elements of reports are complete as possible

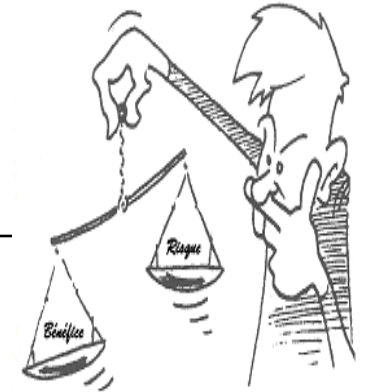
# RECORDING AND CODING THE IDENTITY OF HERBALS



## Unlike Drugs ...

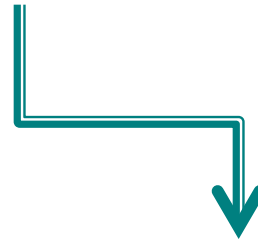
- ❖ *HATC classification is not used*
- ❖ The binomial nomenclature (part used if specified)
- ❖ HM contain multiple ingredients and it is not always possible to identify them all
- ❖ HATC classification for the whole plant but not for a given part (or else several places in the HATC classification)
- ❖ Mixture of several HM
- ❖ HM from other countries

# CAUSALITY ASSESSMENT



## Data Analysis

- ❖ To analyze the causes of AEs, many causality assessment methods are available
- ❖ They have been developed for conventional drugs
- ❖ These can be applied with difficulty to HM



**Many Challenges!!**

# CAUSALITY ASSESSMENT CHALLENGES

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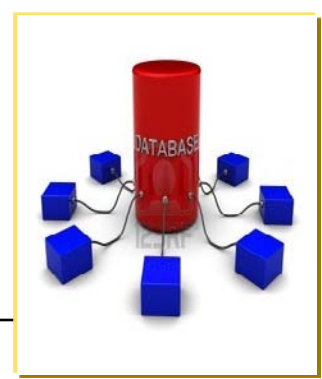


## Data Analysis

- ❖ HM identification
- ❖ A lack or quality of information, example dose/quantity: handle, pinch, tablespoon, herbal infusion
- ❖ Incompatible time criteria: regularly, quite a few times, frequently
- ❖ Limited literature data (knowledge of some HM and their medicinal use has not been documented)

# DATA MANAGEMENT

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## Analysis of the Global WHO database

- ❖ Since 2004, Moroccan AEs of HM reports are sent to UMC via VigiFlow (irregular activity)
- ❖ Daily routine
- ❖ First quarter 2013, HM data analysis was made from WHO database

# SIGNAL DETECTION ON REPORTS FOR HERBALS

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- ❖ As for now UMC don't perform any specific herbal signal detection, but the herbal reports are included in the **general signal detection work**
- ❖ The challenge in detecting such signals is not due to the technical process, but due to the **underreporting** of such reactions and the fact that HM have their own **specificities not found for drugs**

# HERBALS SIGNAL DETECTION

## EXAMPLE: CADE OIL



Dataset date: 2013-05-05  
 Number of combinations in result: 4  
 Total number of reports: 8 073 388

		<a href="#">preferred base</a>	<a href="#">preferred term</a>	<a href="#">critical</a>	<a href="#">Ncomb</a>	<a href="#">IC</a>	<a href="#">IC025</a> ▼	<a href="#">Ndrug</a>	<a href="#">Nadr</a>	<a href="#">Ncountry</a>	<a href="#">Nderhall</a>	<a href="#">Nreerhall</a>	<a href="#">Nfatal</a>
<a href="#">details</a>	<a href="#">reports</a>	Juniperus oxycedrus	Dyspnoea		6	2.08	0.71	33	253 219	1	0	0	0
<a href="#">details</a>	<a href="#">reports</a>	Juniperus oxycedrus	Renal failure chronic	Yes	3	2.44	0.39	33	35 604	1	0	0	0
<a href="#">details</a>	<a href="#">reports</a>	Juniperus oxycedrus	Hypoaesthesia		3	2.24	0.19	33	58 825	1	0	0	0
<a href="#">details</a>	<a href="#">reports</a>	Juniperus oxycedrus	Coma	Yes	3	2.15	0.10	33	70 082	1	0	0	0

A positive IC value indicates that a particular *Juniperus oxycedrus* oil- ADR pair is reported more often than expected, based on all the reports in the database



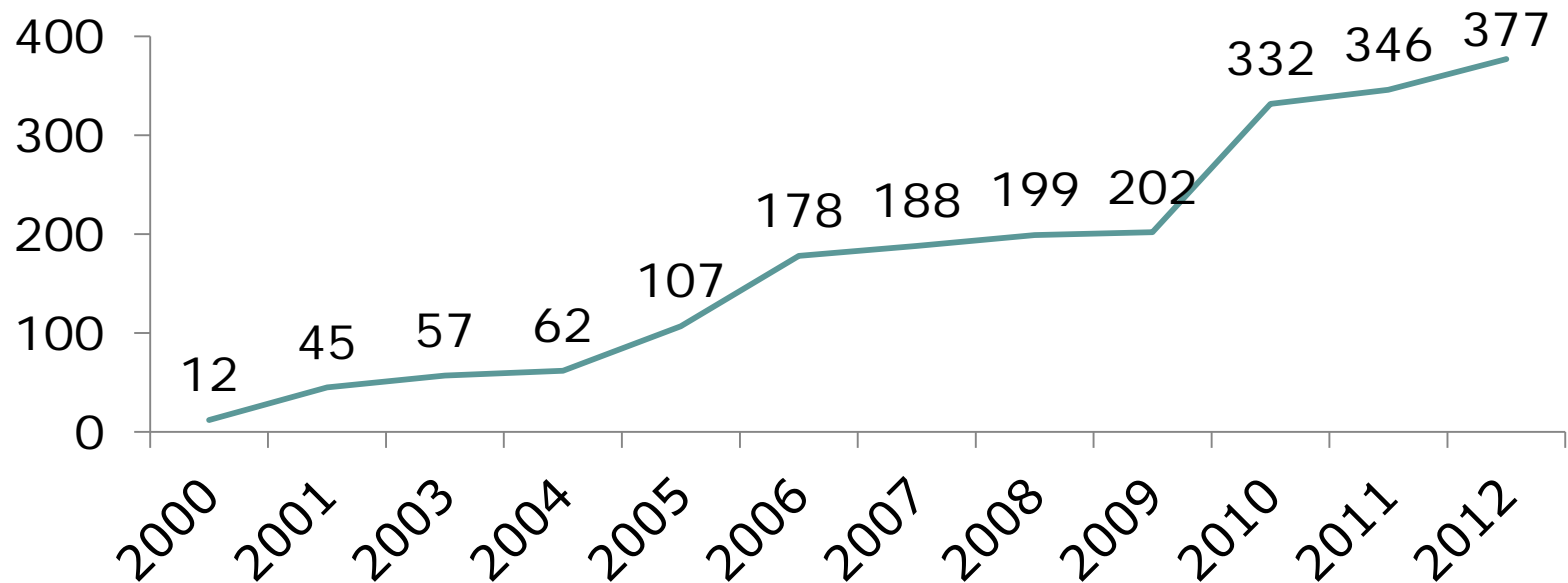
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# MOROCCAN HERBALS DATABASE REPORT

*September 2000 to December 2012*

***“Some data”***

# NUMBER OF HERBALS AEs REPORTED



- ❖ 2105 reports until December 2012
- ❖ A continued increase in reported cases
- ❖ 7 to 10% of all notifications

# GRADING OF THE SEVERENESS OF ADVERSE EVENTS

GRADING OF THE SEVERITY	NO. (%) [n = 1116 ]
Grade 0*	11 (1.0)
Grade 1**	258 (23.1)
Grade 2***	665 ( <b>59.6</b> )
Grade 3****	108 (9.7)
Grade 4*****	74 ( <b>6.6</b> )

\*: no symptoms or symptoms not in relation with AEs of HM

\*\*: symptoms spontaneously regressive

\*\*\*: pronounced symptoms

\*\*\*\*: severe with life-threatening

\*\*\*\*\*: death (which coincide with taking HM)

# ESSENTIAL TOOLS FOR PHARMACOVIGILANCE OF HERBALS

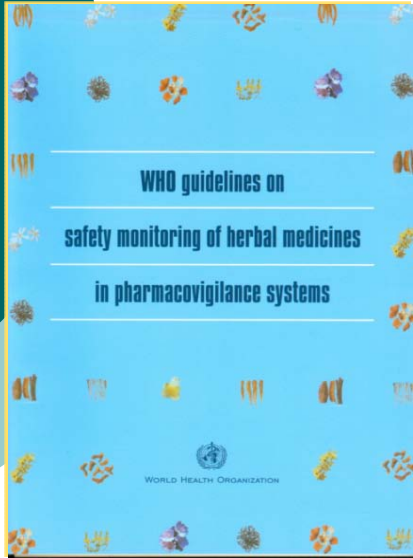
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- ❖ Books (Center Library)
- ❖ Scientific Articles (personal collection)
- ❖ Websites and Databases (PubMed, Toxinz, Micromedex, ...)
- ❖ National pharmacovigilance Centers Bulletins
- ❖ All kind of documents via all types of information sources



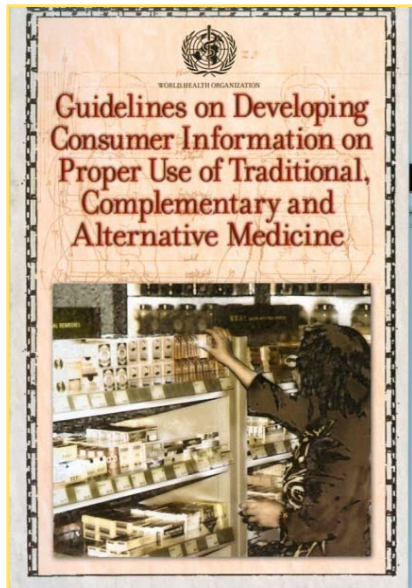
**Essential tools**

# ESSENTIAL TOOLS FOR THE PHARMACOVIGILANCE OF HERBALS



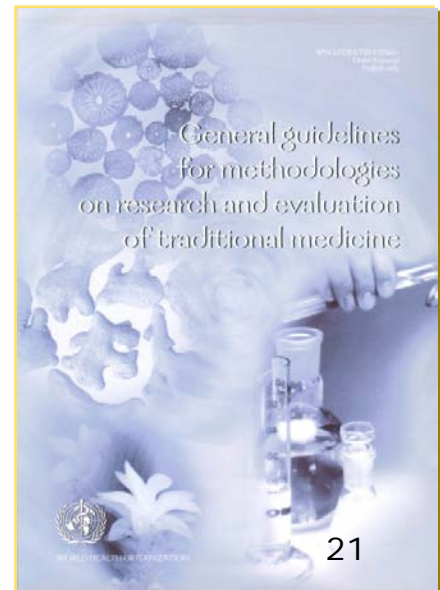
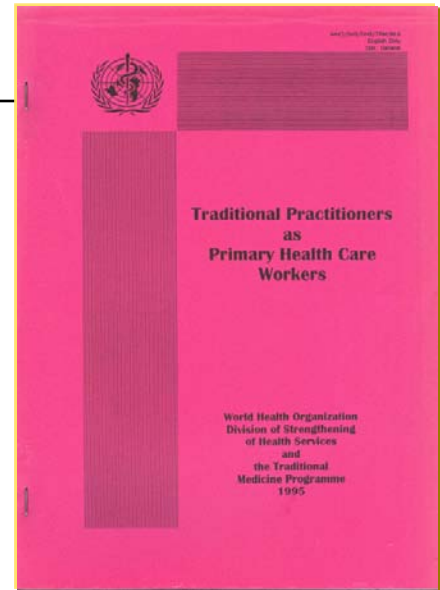
## WHO documents

The WHO offers many guidelines and other documents

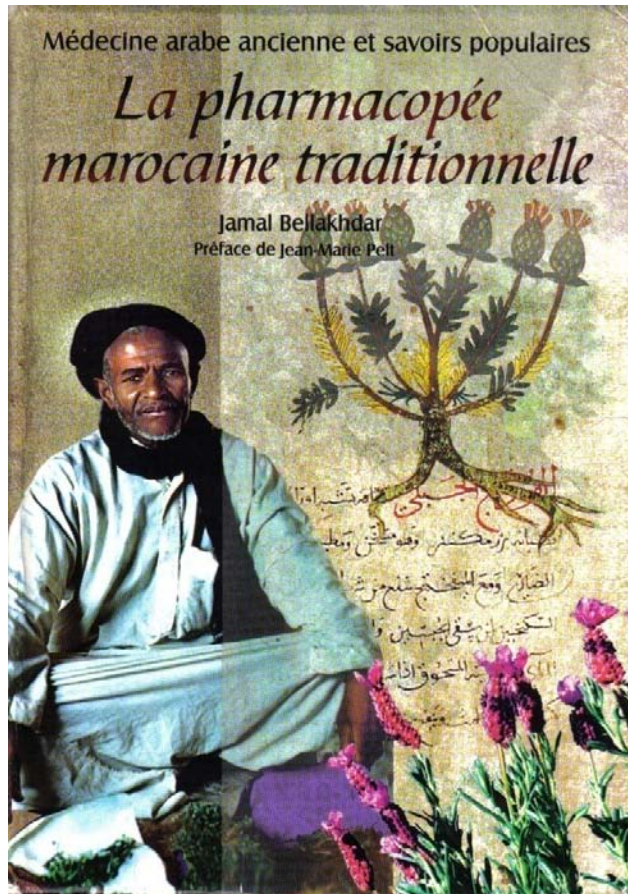


Help to identify the challenges in monitoring the safety of HM

Propose approaches for overcoming them



# MOROCCAN TRADITIONAL PHARMACOPOEIA



# COUNTRIES MAY DEVELOP TOOLS FOR THE MONITORING THE SAFETY OF HERBALS

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**MOROCCAN EXPERIENCE:** S. Skalli, JM. David, G. Palmer et R. Soulaymani. Botanicus & Phytotox: Database of Plant Toxicology. Interest in Emergency Toxicology and in Phytovigilance *Thérapie* 2006; 61(2):133-137

# Botanicus: Nomenclature des plantes toxiques

☒ LATIN

☐ FRANÇAIS

☐ ARABE

☐ AMAZIGH

Cannabis sativa L.

LATIN

FRANÇAIS

ARABE

AMAZIGH

Cannabis sativa L.

chanvre commun  
chanvre indien  
chanvre textile  
chiras  
haschisch  
kif  
marihuana

bâst  
châraneq  
chîra  
h'âchîch  
tîl  
tkroûri  
l-kîf (résine pour fumer)  
l-qanneb (textile)  
qenneb (textile)

el-qenneb  
tifert (textile)

FAMILLE

CANNABINÉES

Mise à jour:

AJOUTER

MODIFIER

SUPPRIMER

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**BOTANICUS**, summarizes more than 279 standard botanical names and their 2294 vernacular ones

**Myristica fragrans Houtt.**

- Partie (s) toxique (s) : graines (la noix) (BELLAKHDAR, 1978 et 1997 ; JOUGLARD, 1977).
- Principe (s) toxique (s) : une huile essentielle (myristicine, acide myristique et terpènes essentiellement) et un hétéroside stérolique : l'ipuranol (BELLAKHDAR, 1978 et 1997 ; JANSSEN et LACKMAN, 1990 ; SPRICIGO et al., 1999).
- Manifestations cliniques : après un temps de latence d'une à quelques heures, vomissements, nausées, douleurs épigastriques, euphorie, céphalées, vertiges, somnolence, stupeur, myosis, hallucinations visuelles, auditives et tactiles (à partir de deux noix) (SANGALLI et CHIANG, 2000 ; STEIN et al., 2001), anxiété (SONAVANE et al., 2002), tachycardie, hypotension artérielle, paresthésie, ...



Mise à jour:

ENREGISTRER

ANNULER

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**PHYTOTOX**, concerns relevant toxic data of 120 plants available in Mediterranean region (Example: **nutmeg**)

# PHYTOTOX

PHYTOTOX : Données toxicologiques des plantes au MAROC.

**Données toxicologiques**

**Myristica fragrans Houtt.**

tachycardie, hypotension artérielle, paresthésie, hypothermie et/ ou hyperthermie et délire (STEIN et al., 2001). Cette intoxication peut conduire au décès en cas d'ingestion d'une quantité importante de graines. Le décès a pu être observé au cours d'un collapsus avec état de choc et acidose (JOUGLARD, 1977).

Les manifestations cliniques sont proches de celles de l'intoxication atropinique à l'exception du myosis (mydriase pour la toxicité atropinique) (BRUNETON, 1999).

- Traitement : décontamination (charbon activé) et traitement symptomatique (traitement sédatif et antihallucinatoire pour les désordres psychiatriques en plus de l'équilibre hydroélectrolytique et de l'hématose essentiellement) (JOUGLARD, 1977 ; SANGALLI et CHIANG, 2000).

Mise à jour:

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PHYTOTOX : Données toxicologiques des plantes au MAROC.

**Données toxicologiques**

**Myristica fragrans Houtt.**

essentiellement) (JOUGLARD, 1977 ; SANGALLI et CHIANG, 2000).

**Bibliographie**

- BELLAKHDAR J (1978). Médecine traditionnelle et toxicologie ouest-sahariennes. Rabat, Editions Techniques Nord-africaines, 365p.
- BELLAKHDAR J (1997). La pharmacopée marocaine traditionnelle. Médecine arabe ancienne et savoirs populaires. Ibis Press, 764p.
- BRUNETON J (1999). Pharmacognosie Phytochimie Plantes médicinales. Editions Technique & Documentation, 3ème édition, Paris, 1120p.
- JANSSEN J et LACKMAN G M (1990). Nutmeg oil: identification and quantification of its most

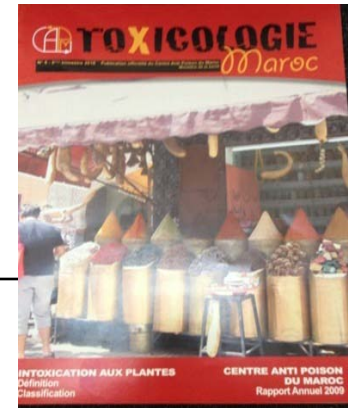
Mise à jour:

Contact: skalli\_s@hotmail.com



# TO MAKE US KNOWN

## More HM ARs Reporting



- ❖ BIP & Revue Toxicologie Maroc
- ❖ Dedicated page with general information on safety of HM on the web site ([www.capm.ma](http://www.capm.ma))
- ❖ Reporting form can be downloaded
- ❖ Meetings dedicated to HM
- ❖ TV & radio programmes (local language mainly)

# OPPORTUNITIES

- ❖ A PhD Scientist specialized in Aromatic and Medicinal Plants was recruited to the center, who initiated the pharmacovigilance of HM activity
- ❖ The same two persons: acquisition of specific technical expertise over the years



# OPPORTUNITIES

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- ❖ Work in tandem with the Poison Control Center, with whom we share the same building

*The proximity is important for better quality and quantity of reporting*

- ❖ We use the Poison Control Center database as an important source for HM adverse effects



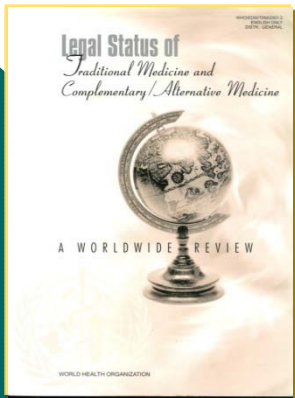
*Indeed*

# POISON CONTROL CENTER DATABASE

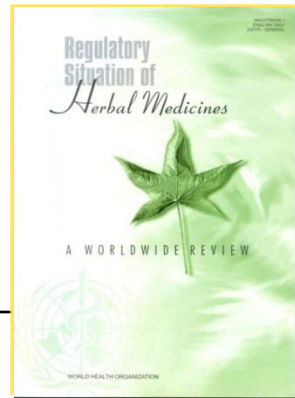
REPORTING SYSTEM	No. (%) [n = 1157]
<b>SPONTANEOUS</b>	
Phone	20 (1.73)
Internet	18 (1.56)
On-site consultation to the center	78 (6.74)
Post	29 (2.51)
Toxicovigilance (Poison Control Center)	80 (6.91)
Toxicological Information (Poison Control Center)	635 (54.88)
Total	860 (74.33)
<b>INTENSIVE MONITORING PROGRAMMES</b> (Surveys and prevalence studies)	
	252 (21.78)
<b>LITERATURE</b> (Published national case reports)	
	45 (3.89)

**61,79 %**





# CHALLENGES



## Regulation & Quality Assurance and Control

### *Main challenge !!!*

- ❖ National regulation for HM doesn't exist
- ❖ Registration of some HM products (about 10%)
- ❖ No quality assurance and control
- ❖ Other sources of poor quality of HM: counterfeiting, open borders and uncontrolled distribution channels

# CHALLENGES



**Many others ....**

- ❖ *Underreporting*
  - ❖ Causality assessment *special HM*
  - ❖ Herbal practitioners
    - ❖ A useful source of information (prescribers and dispensers)
    - ❖ *Excluded from reporting system*
    - ❖ *No effective regulation of HM practitioners*
- identifiable in law, governed by professional codes of practice and have agreed standards of training and competency ??

# CONCLUSIONS

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**There is way to go ...**

- ❖ Moroccan pharmacovigilance of HM database is an important source of information that can be used as *part of* the surveillance system of HM
- ❖ The regulatory issues constitutes the *main challenge* for HM safety monitoring
- ❖ Pharmacovigilance of HM situation is different from that of conventional drugs



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# THANK YOU FOR YOUR ATTENTION