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# REGULATORY CHALLENGES AND BENEFITS FOR HERBAL AND HEALTH SUPPLEMENTS

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# Definitions

- In this presentation the term '*Complementary Medicines*' will be used
- No universally accepted term but has a similar meaning around the world:-
  - Traditional medicines and health supplements
  - Vitamin and Dietary supplements
  - Nutraceuticals
  - Natural health products
  - Complementary healthcare products

# Long usage of traditional medicine across the globe

- 3300 BC - 'Iceman' had medicinal herbs in intestines

Many ancient compilations of medicinal plants

- 2000 BC - King Assurbanipal of Sumeria ordered compilation of a materia medica - 250 herbal drugs (including garlic)
- In India : The *Rig veda* records medicinal herbs
- In Egypt : *papyri Antiquarium* records medicinal herbs
- In South America : use documented in the *Badianus* manuscript, a text written by the Aztecs

# Long usage of traditional medicine across the globe

- 1500 BC - Egyptian Ebers Papyrus written (includes much earlier information)
  - 876 prescriptions using >500 different substances, including many herbs
- 3<sup>rd</sup> century BC – Chinese ‘Prescriptions for 52 Ailments’ written
  - More than 250 medicinal substances, mainly derived from herbs and wood
- AD 980-1037 - Persia : *The canon of medicine*, written by Avicenna
  - 760 medicines & their use and effectiveness
  - remained a std. medical text in western Europe for 7 centuries



**Yew tree  
known as  
'death tree'  
Taxol derived  
from it**



The name 'hypericum' was first given by the ancient Greeks to a plant placed above religious figures in order to 'ward off evil spirits'

St John's wort used to treat 'nervous unrest'

The spice saffron used in Persian medicine for improving mood



Valerian used in Europe for last 500+ years to treat 'nervousness or hysteria', dyspepsia and flatulence

Kava kava – used in the Pacific islands to welcome people from different tribes, promote co-operation

# Herbal and nutritional supplements are important to the public



# Use of complementary medicines is likely to increase

- Increased patient empowerment and autonomy
  - -> increase in self-care
- Increased access to information
  - eg via internet, social media
- Increase in chronic diseases = diseases with NO cure
  - Increasing aging population
- Increase in news about pharmaceutical medicines not as effective or safe as once thought
  - E.g. 2015 meta-analysis of paracetamol indicating unfavourable risk vs benefit
- Increased interest in optimal health and wellbeing



# Usage in Australia

Australian survey of 1067 adults

- **69% used** at least one form of CM in previous 12 mths
  - 46% used clinical nutrition; 16% herbal meds; 11% naturopathy, 7% Chinese medicine
- 44% visited a CM practitioner (approx 69.2 mill visits in 12 mths)
  - 69.3 mill visits to medical doctors
  - 2 out of 5 CM users visited both CM practitioner and med. doctor
  - 4.9 mill visits to naturopaths, 2.8 mill visits to western herbalists, 2.1 mill visits to Chinese med practitioners

## Western Naturopathic Practice

- ~6000 naturopaths in Australia
- Vitamins, minerals and herbs routinely combined
- Have been used for many years without evidence of harmful interactions
- Used to produce better outcomes

## Western herbalists

- Prescribe & dispense herbal mixtures
- Often recommend dietary changes +/- nutritional supplements

Pizzorno JE, Murray MT. Textbook of Natural Medicine. Edinburgh:Churchill Livingstone, 1999; Jamison J. Clinical Guide to Nutrition & Dietary Supplements in Disease Management. Churchill Livingstone, 2003



# Usage in Australia

Braun et al. *BMC Complementary and Alternative Medicine* 2010, **10**:38  
<http://www.biomedcentral.com/1472-6882/10/38>



**RESEARCH ARTICLE**

**Open Access**

## Perceptions, use and attitudes of pharmacy customers on complementary medicines and pharmacy practice

Lesley A Braun<sup>1,2\*</sup>, Evelin Tiralongo<sup>3</sup>, Jenny M Wilkinson<sup>4</sup>, Ondine Spitzer<sup>2</sup>, Michael Bailey<sup>6</sup>, Susan Poole<sup>5</sup>, Michael Dooley<sup>5</sup>

# Medication & professional services use by Australian pharmacy customers

Survey of **1131** pharmacy customers attending 60 community pharmacies (Vic, NSW, Qld)

In the previous 12 months :

- 61% used prescription medicines
- 93% visited a medical doctor
- **72% used a health supplement**
- 39% saw a CM practitioner
  - ( no.1 naturopaths)

# CM supplement users

- **women > men** reported having taken a CM product in the previous 12 months (76% vs. 58%;  $p < 0.0001$ ).
- Age comparisons of < 50 yrs vs > 50 yrs
  - > 50 yrs significantly more people took glucosamine (33% vs. 10%;  $p < 0.0001$ ) or fish oil supplements (41% vs. 28%;  $p < 0.0001$ ) compared to people under 50 years of age.
- Location and socioeconomic comparisons
  - no significant differences in frequency of CMs use between customers living in metropolitan Melbourne or regional NSW
  - No significant association between use and income or marital status.

# Pharmacy customer survey

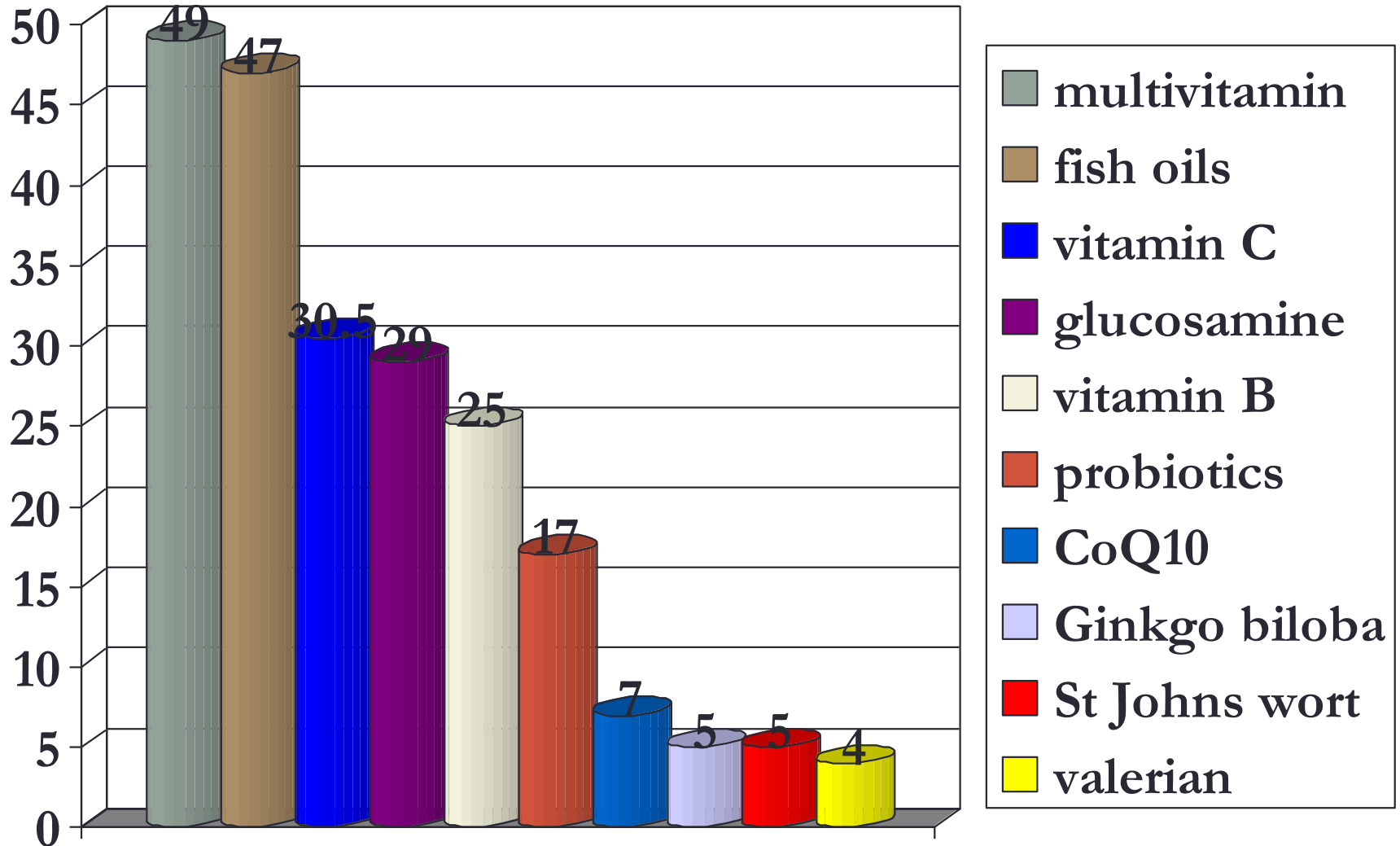
**Overall use of CM supplements doesn't decrease with age**

Over 50 yrs vs under 50: 71% vs 71% NS

Over 60 yrs vs under 60: 69% vs 72% NS

*Braun L et al. BMC CAM July; 2010*

# What CMs were taken ? (n=793)



# Top reasons reported for use

57% 'it keeps me healthy and gives me a sense of wellbeing'

41% 'to treat a specific disease or symptom'

32% 'to prevent disease'

27% 'they were recommended to me'

15% 'because they have few side effects'

15% 'it gives me a sense of control over my health'

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# Who recommends your CM products ?

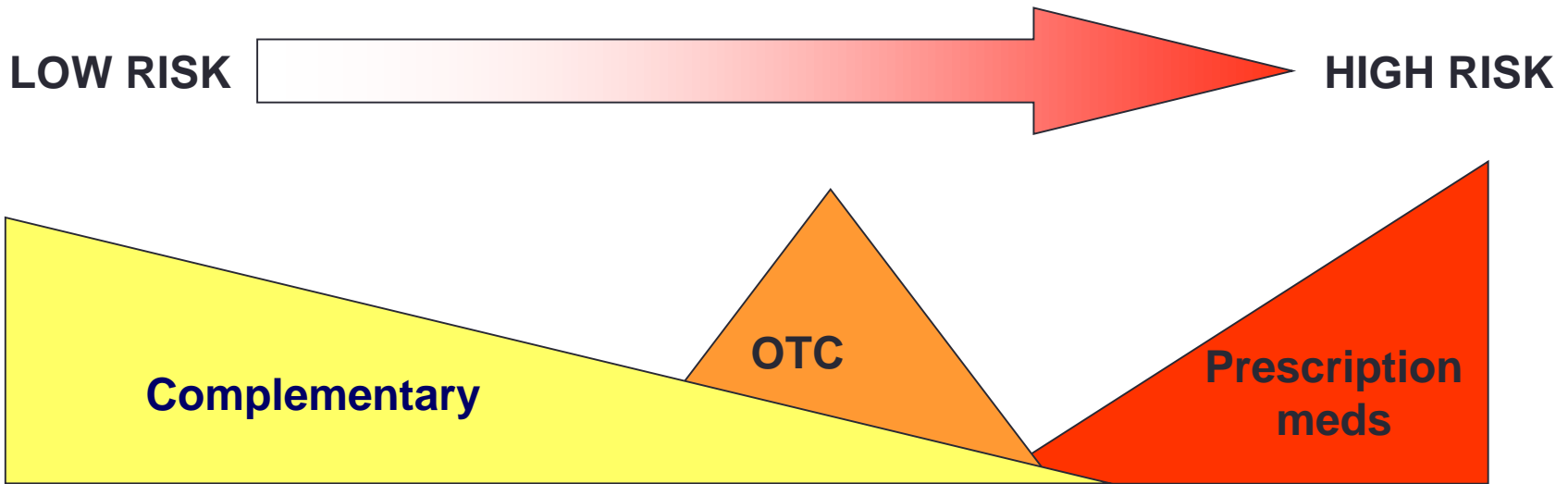
- **Myself** 42%
- Medical doctor 32%
- Friends/family 20%
- Naturopath/herbalist 20%
- Pharmacy assistant 12.5%

Significantly more customers over 50 yrs were recommended CM supplements by a medical doctor than younger people (27% vs. 20%;  $p=0.007$ ).

# Customer attitudes to meds

- **‘I have confidence in CMs’**
  - **74% SA or A**
  - 22% neutral
  - 3% disagree
- **‘I have confidence in OTC pharma meds’**
  - **66% SA or A**
  - 22% neutral
  - 12% D or SD
- **‘I have confidence in prescription meds’**
  - **82% SA or A**
  - 11% neutral
  - 7% D or SD

# Medicines risk continuum



# Safety of OTC CM products

**IJPP**  
International Journal of  
**Pharmacy Practice**

IJPP 2010, 18: 242–244  
© 2010 The Authors  
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Short Communication

## Adverse reactions to complementary medicines: the Australian pharmacy experience

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## Abstract

**Objectives** The primary aim was to determine the prevalence of adverse reactions to over-the-counter complementary medicines and their severity, as described by consumers. Secondary aims were to identify consumers' reporting behaviours and understanding of the AUST L designation on product labels.

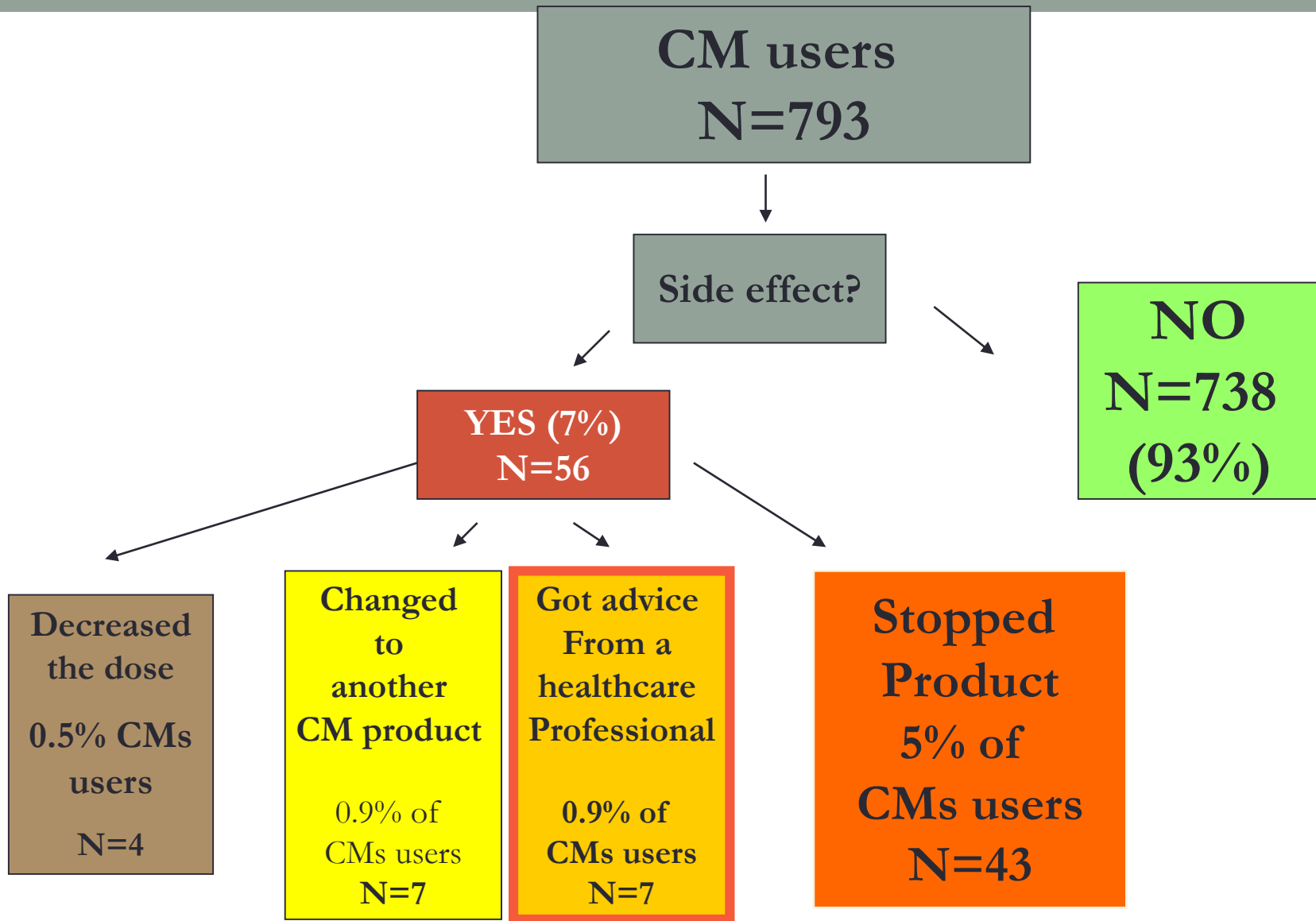
**Methods** An anonymous, self-administered survey was completed by randomly selected pharmacy customers at 60 community pharmacy locations between August 2008 and February 2009.

**Key findings** Of the 1121 survey participants (response rate 62%), 72% had used a complementary medicine product in the previous 12 months, and 7% of this group ( $n = 55$ ) reported having experienced an adverse reaction at some time. Of these, 71% described the reaction as mild and not requiring treatment, 22% as moderate and/or requiring advice from a healthcare professional and 7% ( $n = 4$ ) described it as severe and requiring hospitalisation. If they were to report the reaction, it was most commonly to a medical practitioner. Most (88%) of complementary medicine consumers had never noticed the term 'AUST L'.

**Conclusions** Complementary medicines are widely used by pharmacy customers. Adverse reactions to these products are under-reported to healthcare authorities. Most adverse reactions are mild and serious reactions are rare. Customers have little awareness of the designation AUST L.

# Safety of OTC CM products

- Have you ever experienced a side effect to a CM product?
  - **7%** of CM users YES (n=56)
- Who did you tell ?
  - 36% told their doctor
  - 24% told family and/or friends
  - 22% told a pharmacist about the reaction



# Adverse reactions

- People experiencing an adverse effect were significantly more likely to :
  - Have self reported 'poor health' ( $p=0.0002$ )
  - Be unemployed ( $p<0.0001$ )
  - Not have private health insurance ( $P=0.018$ )
  - Think its important for a naturopath to be located in pharmacies ( $p=0.001$ )
- No association with
  - Gender, age, education, earnings
  - Medicines - warfarin, digoxin, OCP



# Severity as described by patients reporting suspected ADR

- N= 39 (71%) of the 55 reporting an adverse reaction described the reaction as **mild and not requiring treatment**
- N= 12 (22%) described the reaction as **moderate, requiring professional advice**
- n= 4 (7%) required **hospitalisation**

***Limitation of the study : causality not established***

# Importance of regulation of CM supplements

Most people self-select supplements

Fewer are recommended professionally

They are used by people of all ages and background for numerous reasons

Use of combination products common



# Benefits of good regulation

Ensuring all people have ready access to over-the-counter supplements which meet their needs and are safe, of good quality, have a desirable 'benefit vs risk' ratio

Whilst also maintaining respect for patient autonomy, philosophical and cultural diversity

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# Ready access to products that meet consumer needs

- Established list of “safe/acceptable ingredients” which grows and adapts to new evidence on a regular basis
- Listing process for new ingredients is straight forward for industry
  - Appropriate guidelines available and assistance when necessary
- Rapid market access – listing process is efficient

# Benefits of good regulation - safety

- Harm minimisation achieved using multiple strategies
  - Appropriate labelling e.g. storage conditions, batch numbers, usage and safety information
  - Maximal levels of particular ingredients in products where relevant e.g. kavalactones, iodine
  - Appropriate administration forms for OTC e.g. ingestible, not injectable
  - Claims in consumer-friendly language

# Benefits – considers relevant evidence

- Appropriate evidence requirements for low risk OTC substances
  - High risk treatments need high benefit ?
- Takes into account traditional evidence for traditional medicines
- Considers what is known and makes allowances for what is not known (where relevant)

# Benefits of regulation – Quality assurance

- Increasing consumer safety
- Increasing consumer confidence
- Optimising therapeutic benefits

# Challenges – Herbal medicine evidence

***Many types of evidence and different challenges  
compared to pharma drugs***

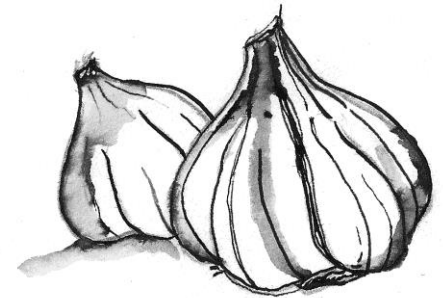
***Overall, more complex picture than for pharma drugs***

- Herbal medicines are chemically complex
- Some have known mechanisms of action from a biomedical perspective, others from different paradigms (eg Chinese med)
- Many have traditions of use and/or been part of the food-chain
- Many contain phytochemicals with pharmacological actions + nutrients e.g. garlic, valerian



# Challenges – Herbal medicine evidence

- Evidence comes from epidemiological studies, traditional resources and scientific investigation
- Some scientific evidence is poorly reported making interpretation difficult
  - e.g. description of herbal extract tested, extraction solvent
- Some scientific studies are poorly conducted
  - E.g. was presence of key actives confirmed?



# Traditional evidence challenges

- Quick, positive responses most likely to be detected
- Acute, adverse reactions most likely to be detected
- Benefits or adverse reactions due to long-term use harder to identify
- Harder to identify rare adverse reactions
- Traditional evidence may consist of an 'oral history' with little written words
- Herb may be described in non-biomedical terms – how do we understand this ?



# Challenges for CM supplement regulation

- Evidence
  - Poor funding means less opportunity to undertake quality research
  - Little industry incentive to fund research – no patent protection
  - Scientific evidence not always available (e.g. safety in pregnancy)
  - Generic evidence generally relates to single ingredients
  - Herbal meds often used in combinations
- Evidence requirements that is relevant to low risk ingredients & take into account **what is possible & important to produce**

# Challenges for CM supplement regulation

## Registration and listing – industry perspectives

- Relatively easy to ‘list’ new ingredients with high hurdle to registration
  - Disincentive to industry to apply for registration, even if holding sufficient evidence as no ‘data protection’, costly, high risk & time consuming
  - Do consumers ‘care’ anyway ?
- Little incentive for innovation and listing new ingredients as competitors can copy products in as little as **6 weeks**

# CMs available in Australia

- Blackmores has biggest market share in Australia & Malaysia
- Consistently wins 'Most trusted brand' in Readers Digest surveys
  - Over 200 different products sold in Australia
  - **Over 20 million bottles** sold per year
  - TGA has no restrictions on herbs + nutrients in one product



# Popular Blackmores products :

- Multivitamins – typically nutritionals + herbals or fruit + vegetable powder concentrates
- Fish oils – various EPA/DHA ratios
- Single nutritionals e.g. Coenzyme Q10
- Pregnancy and Breastfeeding Gold - nutritional combination
- Cold and flu combinations – Echinacea + nutritionals (vitamins A,C,E zinc)
- OA support - glucosamine and chondroitin, lyprinol
- Bone support - calcium + vit D
- Sleep products – herbals + nutritionals (eg valerian, lemon balm, magnesium)
- Stress products – Executive B stress formula (B complex + herbs passionflower + oats)
- Single herbals – e.g. Evening primrose oil, andrographis, echinacea

# Popular Blackmores products :

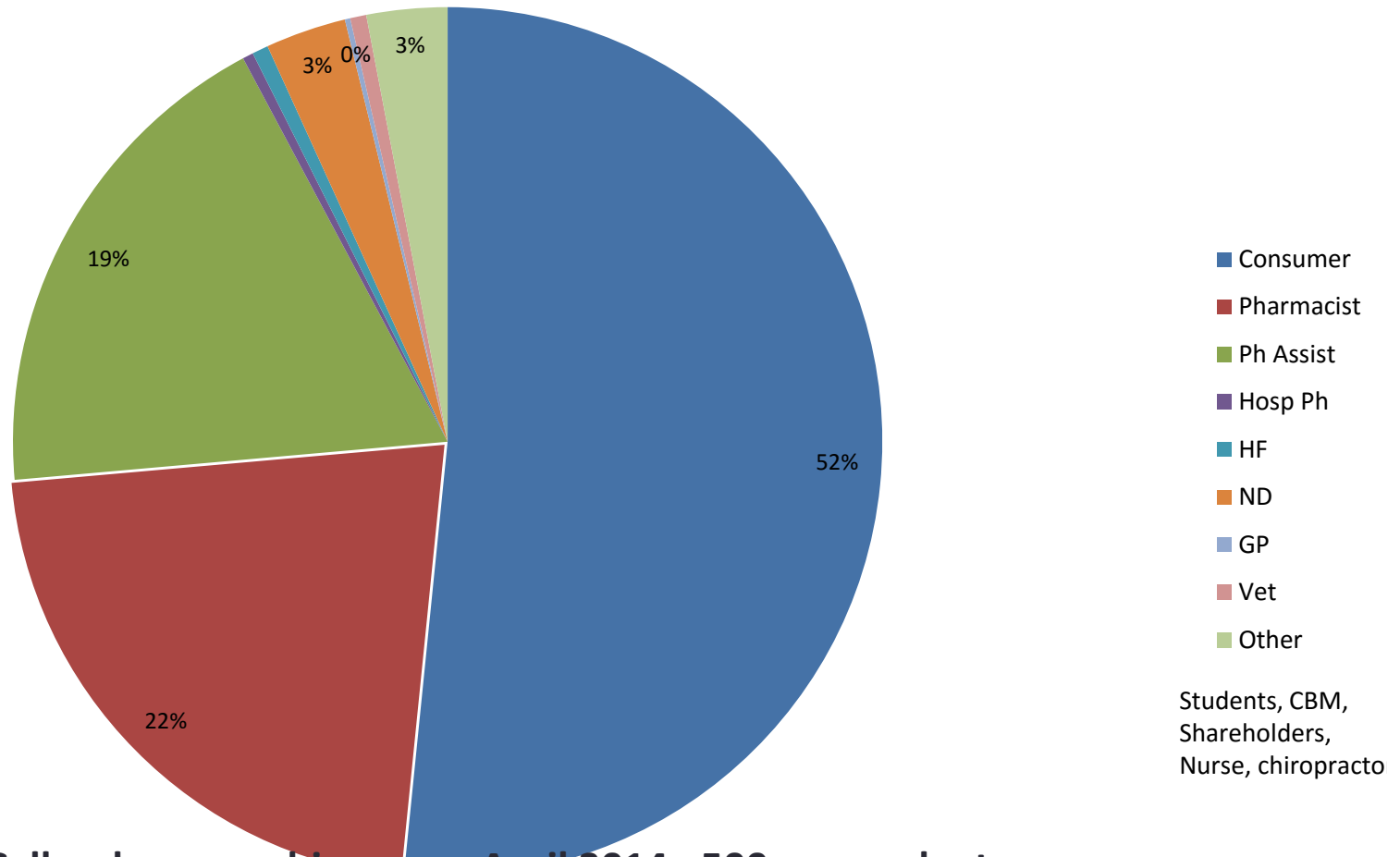
- **Multivitamins – typically nutritionals + herbals** or fruit + vegetable powder concentrates
- Fish oils – various EPA/DHA ratios
- Single nutritionals e.g. Coenzyme Q10
- Pregnancy and Breastfeeding Gold - nutritional combination
- **Cold and flu combinations – Echinacea + nutritionals (vitamins A,C,E zinc)**
- OA support - glucosamine and chondroitin, lyprinol
- Bone support - calcium + vit D
- **Sleep products – herbals + nutritionals (eg valerian, lemon balm, magnesium)**
- **Stress products – Executive B stress formula (B complex + herbs passionflower + oats)**
- Single herbals – e.g. Evening primrose oil, andrographis, echinacea

# Blackmores Institute Advisory team

- 30,000 + contacts per year
- Provides ready access for the public and health care professionals to free advice & adverse reaction reporting
- Most common queries relate to safety
  - Drug interactions and safety in pregnancy
- Also, information about excipients eg lactose, gluten
- Survey showed 99% of users would use the service again



# Who are our callers ? N=500



Source: Caller demographic survey April 2014 : 500 respondents

**10% of calls involved drug/nutrient interaction information**

# Most commonly reported side effects

Gastrointestinal - Reflux, nausea, loose bowels

Dermatological/ immunological, headache

From Oct 2013 to Oct 2014 → 4 suspected serious  
ADRs reported to BKL

**Over 20 million bottles** sold in Australia during  
this period

1 in 10 patients visiting a GP experienced a significant  
ADR ~ 50% diagnosed by GP as moderate – severe\*

\*Miller GC et al. Adverse drug events in general practice patients in Australia. Med J Aust 184 (2006): 321–324.

# Factors which increase risk



# Key determinants of risk – not just the medicine

## Medicine

Inherent toxicity

- Side effect profile
- Quality
- Administration form
- Therapeutic margin
- Pharmacodynamics

## The Individual

General health

Comorbidities

Ability to self administer, self monitor, communicate clearly

Predisposition

Pharmacokinetics

## Persons Situation

- Community living
- Hospital setting
- Access to HCPs
- Access to quality products & services
- Access to information
- Polypharmacy & other drugs used

# Interactions



# Main types of interactions

- Physicochemical and chemical
- Pharmacodynamic
- Pharmacokinetic

## Main clinical outcomes

- Increased therapeutic or adverse effects
  - Decreased therapeutic or adverse effects
  - Unique effect
- **Often, exact outcome unknown but theoretically predictable**

# Evidence about interactions

	Strength	Limitation
Test tube studies	Fast, low cost	Dose may be clinically irrelevant Agent may have poor bioavailability
In vivo	Faster than RCTs Some bioavailability issues resolved	Dose clinically relevant ? Species differences
Clinical trial	More accurate	Costly and takes time Wont have RCTs for everything
Case report	Suggestive	Uncontrolled Often poor reporting Confounders often missed

# Problems extrapolating evidence

- e.g. In vitro & tests w animal models show both CYP induction and inhibition for ***ginkgo biloba***

In contrast, **4 clinical studies** did NOT identify a clinical significant effect on a variety of cytochromes

e.g. in vitro tests show ***saw palmetto*** inhibits CYP3A4 & CYP2D6

In contrast, **2 clinical studies** did NOT identify a significant effect on CYP3A4 or CYP2D6



# Pharmacokinetic Herb-Drug Interactions (Part 2): Drug Interactions Involving Popular Botanical Dietary Supplements and Their Clinical Relevance

Bill J. Gurley<sup>1</sup>, Espero Kim Fifer<sup>2</sup>, Zoë Gardner<sup>2</sup>

<sup>1</sup> Department of Pharmaceutical Sciences, University of Arkansas for Medical Sciences, College of Pharmacy, Little Rock, AR, USA

<sup>2</sup> Department of Plant, Soil & Insect Sciences, University of Massachusetts, Amherst, MA, USA

Gurley BJ et al. Pharmacokinetic Herb-Drug Interactions (Part 2)... *Planta Med* 2012; 78: 1490–1514

Review of in vitro, in vivo and clinical studies

# Herbs with clinically relevant pharmacokinetic interaction potential

- Black pepper
  - >10mg piperine, piperamides
  - Bioavailability enhancer via CYP3A & P-gp
- Goldenseal
  - Inhibits CYP 2D6, 3A4
- Schisandra
  - Inhibits CYP 3A4, Pgp
- St Johns wort
  - Induces CYP 3A4, P-gp

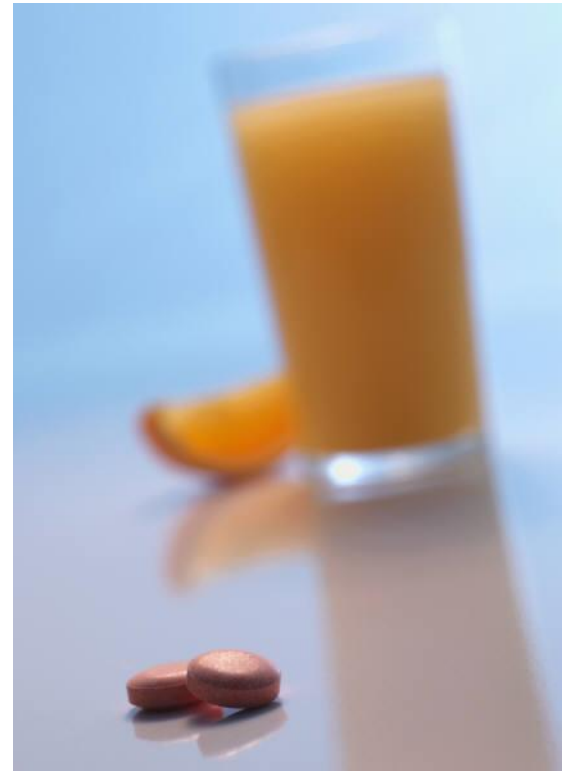


Gurley B, Fifer E, Gardner Z; *Planta Med* 2012; 78(13): 1490-1514

# Low risk of clinically significant pharmacokinetic interaction

- ✓ Black cohosh - *Actaea racemosa* L, (syn. *Cimicifuga racemosa*)
- ✓ *Echinacea* spp.
- ✓ Garlic - *Allium sativum*
- ✓ Ginseng spp. – Asian ginseng (*Panax ginseng* C.A. Meyer) & American ginseng (*Panax quinquefolius* L.)
- ✓ *Ginkgo biloba* – at doses <240mg/d
- ✓ Kava kava - *Piper methysticum*
- ✓ St Mary's thistle - *Silybum marianum*

# Nutrient interactions



# 4 mechanisms well established

## 1. **Ex vivo inactivation**

- E.g. Complexation upon physical contact
- Calcium and tetracyclines

## 2. **Reduced absorption resulting in decreased bioavailability**

- E.g PPI drugs and magnesium

## 3. **Altered systemic disposition**

- E.g. Changing tissue distribution or concentration at target site
  - Vitamin K and warfarin

## 4. **Altered elimination**

- E.g. Impaired renal or enterohepatic elimination
  - ACE inhibitors and ARBs affecting zinc nutrition

# Zinc and BP meds

SYSTEMATIC REVIEW

THE INTERNATIONAL JOURNAL OF  
CLINICAL PRACTICE

## Pharmaco-nutrient interactions – a systematic review of zinc and antihypertensive therapy

L. A. Braun,<sup>1,2</sup> F. Rosenfeldt<sup>3</sup>

People taking ACE-inhibitors, ARBs or thiazides long term are at risk of Zn deficiency

Due to increased renal excretion  
Possible alteration to Zn absorption

### Review criteria

We undertook a systematic review of electronic databases and collected all English language articles, which reported on results from clinical studies, which were relevant to meeting the aims of the review. We only included studies when the full-length article was available so that important details, such as number of study participants, medicines used, time frames for use and zinc measures were clearly reported.

### Message for the clinic

The take home message for clinicians is that current evidence suggests that patients using ACE inhibitors, ARBs and thiazides long-term could be at risk of low zinc. Clinicians should consider the possibility of low zinc nutrition in patients with poor dietary intakes, the elderly people and diabetic patient who has taken these medications long-term. A trial of zinc supplements in suspected cases of low zinc is a safe option.

# Vitamin/mineral interactions

- Vitamin C increases iron, aluminium and chromium absorption and decreases copper absorption
- Vitamin D increases calcium and phosphate absorption
- Vitamin E decreases vitamin A and vitamin K activity
- Folate decreases zinc absorption
- Calcium decreases iron, magnesium and zinc absorption

# Vitamin/mineral interactions

- Iron decreases zinc absorption and vice versa
- Magnesium decreases zinc absorption
- Phosphate decreases iron and magnesium absorption
- Zinc and iron decrease copper absorption
- Zinc increases vitamin A activity and decreases calcium absorption



# Herb and vitamin/mineral interactions

- Laxative herbs (cascara, psyllium, senna) may decrease absorption of vitamins/minerals by decreasing intestinal transit time
- Green tea may decrease non-haem iron absorption
- There are few other confirmed interactions between herbs and vitamins or herbs and minerals reported in the literature



# Regulation of OTC CM products is important but challenging

- For the public :
  - Safeguarding the public whilst respecting their right to choose different healthcare products & respecting their culture and traditions
  - Having access to low risk OTC products
  - Having confidence in CM products
- For industry :
  - Appropriate evidence requirements
  - Appropriate quality requirements
  - Timely and straight-forward listing and registration processes
  - Ideally – making provisions for innovation, incentives to conduct more research

# Summary and Conclusion

- Traditional medicine has used combined herbs + vitamins/minerals for centuries
- Today, the public frequently use both herbs and nutrients together
- Naturopathic and Chinese medicine practice combine herbs and nutritional supplementation
- Products containing herbs/vitamins/minerals have been used worldwide for many years without significant incidence of adverse events



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