NIMH STUDY DAY

Manchester , Nov 2003

PSYCHOTROPIC PLANTS IN DEPRESSION, ANXIETY & INSOMNIA.

Study Leader : Dr Desmond Corrigan
Senior Lecturer in Pharmacognosy
School of Pharmacy
Trinity College Dublin

SESSION 1

CONDITIONS & DIAGNOSES
PSYCHOTROPIC PHYTOCHEMICALS
ASSESSING THE EVIDENCE BASE

ICD – 10 Chapter V. 1996

Depressive Disorders

Target signs	Associated symptoms
low or sad mood	disturbed sleep
loss of interest or pleasure	feelings of guilt
fatigue or loss of energy	reduced self-esteem
	poor concentration
	disturbed appetite
	decreased libido
	suicidal thoughts or acts
	agitation or slowing of movements or speech
	weight loss

Symptoms of anxiety or nervousness are also frequently present.

Severity of Depression (ICD-10)

Mild depressive episode	mild first manifestation or mild recurrence of 2 target and 2 associated symptoms.
Moderate depressive episode	2-3 target signs plus 3-4 associated symptoms.
Major depressive episode	all target signs plus 4 associated symptoms – some particularly pronounced.

DSM IV. Major Depressive Episode

A. Five or more symptoms within 2 weeks .
   1. Depressed mood.
   2. Loss of interest or pleasure in daily activities.
   3. Significant weight changes – loss or gain.
   4. Insomnia or hypersomnia daily.
   5. Agitation.
   6. Fatigue or loss of energy daily.
   7. Feelings of worthlessness or guilt.
   8. Diminished ability to think or concentrate.
   9. Recurrent thoughts of death, suicidal ideation or attempt.

C. Clinically significant distress or impairment.

D. Symptoms not due to drug use.

E. Symptoms not accounted for by bereavement.

Hamilton Depression Scale

Item	Score	Symptom
1	0-4	depressed mood
2	0-4	guilt
3	0-4	suicide
4	0-2	insomnia initial
5	0-2	insomnia middle
6	0-2	insomnia delayed
7	0-4	work and interests
8	0-4	retardation (apathy)
9	0-2	agitation
10	0-4	anxiety psychic
11	0-4	anxiety somatic
12	0-2	GIT symptoms
13	0-2	general somatic symptoms
14	0-2	genital symptoms
15	0-4	hypochondria
16	0-2	loss of insight
17	0-2	loss of weight

Grading:		
0 absent		0 absent
1 mild		1 slight
2+3 moderate		2 clearly present
4 severe		

Minor Depression

Symptoms

depressed mood
reduced interest or pleasure plus 2-4 of the following
(MDE requires 5 or more)
significant weight change
appetite change
disturbed sleep
noticeable agitation or slowness
fatigue or loss of energy
inappropriate feelings of worthlessness or guilt
reduced concentration
indecisiveness
recurrent thoughts of death or suicide

Anxiety Disorders

1. Panic disorder (and agoraphobia).
2. Specific phobia.
3. Social phobia.
4. Obsessive-compulsive disorder.
5. Post-traumatic stress disorder.
6. Acute stress disorder.
7. Generalised anxiety disorder.
8. Anxiety disorder of medical origin.
9. Substance-induced anxiety disorder.
10. Anxiety disorder (not otherwise specified).

DSM IV. Generalized Anxiety Disorder

A. Excessive anxiety and worry on most days for at least 6 months.

B. Difficult to control worry.

C. Anxiety and worry associated with 3 or more symptoms.
   1. Restlessness or feeling keyed up.
   2. Easily fatigued.
   3. Difficulty concentrating/mind going blank.
   4. Irritability.
   5. Muscle tension.
   6. Difficulty falling or staying asleep.

E. Symptoms cause clinically significant distress or impairment.

F. Not due to drugs or medical condition – hyperthyroidism.

Hamilton Anxiety Rating Scale

Anxious mood	Depressed mood
Tension	Somatic (muscular)
Fears	Cardiovascular system
Insomnia	Respiratory system
Intellect	Gastrointestinal
Behaviour	Genitourinary
	Autonomic system

Grades: 0 - none
1 - mild
2 - moderate
3 - severe
4 - very severe, disabling

DSM IV. Dyssomnias

Primary Insomnia.

A. Primary complaint is difficulty initiating or maintaining sleep for one month.

B. Sleep disturbance/daytime fatigue causes clinically significant distress or impairment.

C. Not related to another mental disorder e.g. MDE/GAD.

D. Not due to a drug/medicine.

Diagnostic and Statistical Manual of Mental Disorders. IV Edition American Psychiatric Assoc. 1994.

Insomnia

Inability to obtain adequate amount of restful sleep due to anxiety.

- Problems in falling asleep. (sleep latency)
- Frequent wakening
- Difficulty going back to sleep.
- Early morning wakening.
- Total sleep time less than 6 hours.

Psychoactive Phytochemicals

- Nitrogenous - Alkaloids: Reserpine
- Monoterpenes - essential oils
- Sesquiterpenes – Valepotriates
- Oxygen-containing
- Alpha – pyrones : Kavapyrones
- Gamma- pyrones : Flavanoids
- Lignans - Valerian

Testing for sedative/anxiolytic activity

Locomotor activity.

Locomotor coordination.

Prolongation of sleeping time.

Receptor binding studies.

Brain glucose measurements.

EEG investigations.

Elevated plus maze test (anxiolytic effects).

Sleep questionnaires.

Activity meters.

Information on the class of evidence should be given in accordance with the Draft Points to Consider on the Evidence of Safety and Efficacy of Well-established Herbal Medicinal Products in Bibliographic Applications (EMEA/HMPWG/23/99) which provides the following details:

Level	*Type of evidence*
Ia	*Evidence obtained from meta-analysis of randomised controlled trials*
Ib	*Evidence obtained from at least one randomised controlled trial*
IIa	*Evidence obtained from at least one well-designed controlled study without randomisation*
IIb	*Evidence obtained from at least one other type of well-designed quasi-experimental study*
III	*Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case control studies*
IV	*Evidence obtained from expert committee reports or opinions and or clinical experience of respected authorities*

Grade	*Recommendations*
A (Evidence levels qualityIa, Ib)	*Requires at least one randomised controlled trial as part of the body of literature of overall good and consistency addressing the specific recommendations.*
B (Evidence levels IIa, IIb, III)	*Requires availability of well-conducted clinical studies but no randomised clinical trials on the topic of recommendation.*
C (Evidence level IV)	*Requires evidence from expert committee reports or opinions and or clinical experience of respected authorities. Indicates absence of directly applicable studies of good quality.*

SESSION II

MAJOR PSYCHOTROPIC HERBS

HYPERICUM
KAVA-KAVA
VALERIAN
PASSIFLORA

HYPERICUM

Phytopharmacology In Vitro

1. Receptor Binding Studies
   - extracts and compounds bind to GABA, BZD, Opioid, NMDA Receptors

   no conclusive mechanism of action

2. Reuptake inhibition
   - serotonin, noradrenaline, dopamine,GABA, and glutamate.
   - diverse mechanisms involved.

HYPERICUM

Phytopharmacology In Vivo

Various extracts show antidepressant effects in different models.

3. Phytochemical groups all + ve.

Hypericum Perforatum
(St John's Wort – SJW)

Clinical evidence

3 meta-analyses

(3) Linde *et al* BMJ 1996; 313: 253-8
(1) Linde *et al* Cochrane Library 2003 issue 3.
(2) Kim *et al* J. Nerv Ment Dis 1999; 187: 532-8.

6 Systematic reviews

Volz HP. Pharmacopsychiatry 1997.
Hippius H. Curr. Med. Res. Opin. 1998.
Wheatley D. CNS Drugs 1998.
Stevinson EUR Neuropsychopharmacol 1999.
Vitiello B. J Pharm Pharmacol 1999.
Gaster B. Arch Intern Med 2000.

Confirmed efficacy of SJW preparations in mild to moderate but not severe depression.

Hypericum perforatum

Negative clinical evidence

- Shelton *et al* JAMA 2001; 285: 1978-86

  Patients with HAM-D > 20
  Average duration 2 years
  Sponsored by Pfizer

- Hypericum Depression Trial Study Group
  JAMA 2002; 287: 1807-14

  Patients with HAM-D > 20
  Sertraline (Lustral) not active!

Conclusion: Study fails to support efficacy of SJW in moderately severe depression!

Hypericum perforatum

Minor Depression

New study by National Centre for Complementary and Alternative Medicine and Office of Dietary Supplements.

Inclusion criteria

2-4 symptoms

HAM-D score 10-17

Symptoms for 6 months but less than 2 years.

Kava- Kava
piper methysticum

Phytochemistry

1. **α pyrones, a.k.a. Kava lactones, Kavain, Dihydrokavain, Methysticin**
2. **Chalcones**
   Flavokavains
3. **Stigmasterol**
4. **n-cinnamoylpyrrolidine alkaloids**

Content of α pyrones

Plant	**3.5 – 5.0%**
Alc/H_2O	**30%**
Acetone/ H_2O	**70%**

Kava

Phytopharmacology – In Vitro

- alc.ext enhanced binding to $GABA_A$ sites in brain.
- isolated Kava lactones weak binding to $GABA_A$ and Benzodiazepine receptors.
- effect not based on Benzodiazepine receptor.
- Kavain inhibits uptake of noradrenaline.
- no effect on serotonin.
- anticonvulsive, spasmolytic effects.

Kava

Phytopharmacology – In Vivo

Due to Kava lactones

Synergism important

- Amphetamine hypermotility reduced.
- Spontaneous motor activity reduced.
- Apomorphine - induced hyperactivity suppressed.
- Muscle tone decreased.
- Anticonvulsive effects.
- Neuroprotective effects.

KAVA

Phytopharmacology : Human Studies

Cognitive performance:

- Crossover, Kava, Placebo, Oxazepam. Negative effect on word recognition with Oxazepam but not Kava.
- No effect on alertness in undergraduates.

Vigilance

- no sedative hypnotic effects in EEG.
- mental performance better than placebo diazepam no better than placebo.

Sleep patterns

- improved quality.

Meta analysis of Kava R.C.Ts

3 ex 14 included

Number of patients : 198

Inclusion criterion: Baseline HAM-A score of > 19.

Duration: 24 weeks

Dosage: ≡ 210mg Kava lactones/day

Product: WS 1490

Outcome: significant reduction in the HAM-A of 10 points in favour of Kava.

Adverse events: 1.5 – 2.3%

G.I.T, allergic skin, headache, photosensitivity

Pittler & Ernst - J. Clin. Psychoph.2000

Kava versus Benzodiazepines

n = 176

Kava ext.	210mg. Kava lactones/day
Oxazepam	15mg./day
Bromazepam	9mg./day

HAM-A scores

	Kava	Oxaz.	Bromaz.
t_o	27.3	27.7	27.3
$t_{6\ wks}$	15.6	16.6	13.4

no significant difference between Kava and Benzodiazepines.

Woelk *et al.*
Z. Allgem. Med 1993

Kava Kava
Human Studies

Healthy volunteers 6 studies

R.C.T.'s in general anxiety states
3 studies

R.C.T.'s in anxiety/menopausal states
3 studies

Open studies 5
Other studies 3

Controlled studies with synthetic Kavain n = 6.

Kava and Valerian for stress induced insomnia

Pilot Study n=24

Kava 120mg./day for 6 weeks
2 weeks wash out
Valerian 600mg./day for 6 weeks.

Stress severity	Insomnia severity
t_o 178	t_o 138
$t_{6\ weeks}$ 126*	$t_{6\ weeks}$ 107*
$t_{12\ wks}$ 117	$t_{12\ weeks}$ 83*

*Statistically significant from baseline.

Valerian

Phytochemistry

Valepotriates – Insoluble and unstable

Sesquiterpenes
Valerenal, Valerenic acid

Amino acids
GABA, Glutamine

Lignans
Hydroxypinoresinol – $5HT_{1A}$
Olivil – A_1 Adenosine receptor

Flavonoids
6-Methylapigenin - $GABA_A$

Valerian
Phytopharmacology – in vitro

Aqueous extract.
- influenced GABA transport
- inhibits GABA uptake
- enhances release

linked to GABA and Glutamine in ext.

Various extracts.
- affinity for $GABA_A$ receptor
- affinity for barbiturate receptor
- weak affinity for Benzodiazepine receptor

Aqueous and Hydro alcoholic extracts.
- stimulate release of GABA.
- EtOH ext (no GABA) not active
- displace muscimol bound to $GABA_A$ receptor
- inhibit binding to Adenosine receptor – sedative effect.

Alcohol ext.
- Displaced melatonin from receptor

Lignan
- Binds to opiate and 5HT receptors

Valerian
Phytopharmacology – In vivo

Valepotriates.
Weak Sedative, decreased anxiety, aggression.

Valerenic acid and valerenal.
non-specific CNS depressant
decreased motility.
prolongation of sleeping time.

Extracts.
- central depressant
- no sedation or tranquillization
- anticonvulsive activity
- prolongation of anaesthesia
- reduced motility

Clinical Studies with Combination Products

Valerian/Hops (Rodenbeck 1998)
Sleep stage II increased.
Similar effect to Benzodiazepine.

Valerian/Hops (Gerhard *et al*)
Compared to Flunitrazepam
All treatment groups reported improved sleep quality.
Only Flunitrazepam group reported hangover effects next day.

Valerian/Melissa
Dressing *et al* 1996
Effective in insomnia
Useful in ambulatory patients

Cerny and Schmid 1999
N = 98 Higher sleep quality vs placebo (33% vs 9%)
No serious adverse events.

Valerian
Clinical Studies

Leathwood and Chauffard

- Significant improvements in sleep latency and sleep quality.
- Effect more marked in poor sleepers.
- Subjective and objective ratings.
- 400 mg dried aqueous extract.

Valerian
Clinical Studies continued

Double blind studies

- subjective evaluation positive.
- significant improvement of sleep quality in 27 poor sleepers. RCT.
- relevant EEG changes in 12 female poor sleepers given 1.2 g ext. RCT.
- 14 elderly female poor sleepers – 405 mg. t.i.d. for 1 week. Increased slow wave sleep.
- 78 elderly patients – significant improvements in sleep latency and quality.
- 11,168 patients in an open trial.
  72% success in cases of sleep latency.
  76% success in cases of discontinuous sleep.
  72% success in cases of restlessness and tension.

Vorbach Study

121 patients - significant sleep disturbance for at least 4 weeks.

600 mg. dry extract.

No acute effect in first 14 days

Marked placebo effect.

Clinical global impressions

(C1 scale)

Significantly better than placebo after 4 weeks

In 60% of patients both physician and patient assessment for Valerian was good or very good compared to 26% for placebo. Difference was highly significant statistically. ($p \angle 0.001$).

Comparison of Valerian with Oxazepam

N = 75 randomised insomniacs

600 mg Valerian dry extract

Or

10 mg oxazepam

Duration: 28 days

Outcomes.

Sleep quality improved in both groups.

Conclusion: no statistical difference between Valerian and Oxazepan. Adverse effect profile of Valerian more favourable.

Passiflora incarnata

Phytochemistry

Flavonoids – C glycosides of apigenin

Maltol – may be an artefact

Cyanogenic glycoside

Harman type alkaloids

Passiflora

Phytopharmacology – In vitro

Dry extracts and 2 main flavonoids did not interact with Benzodiazepine binding site.

EtOH extract inhibited binding to $GABA_A$ receptor.

Passiflora

Phytopharmacology – In vivo

Passiflora has shown sedative effects in rodents.

- prolonged sleeping time induced by barbiturates (>40%).
- reduced spontaneous motor activity 2 studies.
- reduced amphetamine – induced hyper motility (<17%).
- inhibited aggression and restlessness caused by amphetamine.
- anxiolytic effects demonstrated.

Constituents responsible not yet clear.

Passiflora

Study in humans

RCT
Crossover design
12 Healthy female volunteers.
1.2g Passiflora extract
or 10 mg Diazepam
or Placebo
140 minutes later 100mg caffeine
Alertness – wide awake – almost asleep.
Passiflora reached 1/3 rd Diazepam value.
Quantitative EEG
no difference between Passiflora and placebo.

Schulz.*et al*
Phytomedicine 1998.

Clinical Studies with Passiflora

Generalized Anxiety Disorder.
DSM IV Diagnosis

Randomised Double Blind
Group 1. Passiflora drops and placebo tablet
Group 2. Oxazepam tables and Passiflora drops

Results: Significant reduction in HAM - A
Day 4 Oxazepam
Day 7 Passiflora
Less side effects Passiflora

Akhondzadeh *et al* 2001.

NIMH

James Postlethwaites
Sleep Formula for Drug Dependency Treatment

Equal parts of dried herbs of:

- Skullcap
- Chamomile
- Motherwort
- Damiana
- Passiflora
- Red clover
- Vervain

European J. Herbal Med. 1994.

SESSION III

MINOR PSYCHOTROPIC HERBS

HUMULUS
CHAMOMILE
MELISSA
CALIFORNIAN POPPY
LAVENDER, LETTUCE
TROPHORESTORATIVES

Hops

Humulus lupulus

Phytochemistry

1. Bitters:
   (a) Lipophilic soft resin
   - humulones
   - lupulones

   (b) Hard resin
   - hydrophilic α resin
   - lipophilic γ resin

2. Essential oil:
   traces of 2-methylbutenol
   (approx. 0.15% after 2 years).

3. Chalcones, flavonoids
   - prenylated flavonoids
     (potential phytooestrogens).

Hops

Phytopharmacology – In Vivo

- spontaneous motor activity depressed. (500mg extract per kg body weight)
- prolongation of sleep time.
- 2 Methylbutenol (800mg/kg) CNS depressant activity.

  comparable to chemically similar

  commercial sedative Methylpentynol.
- no phytooestrogen effects from bitters or essential oil.
- phytoestrogen effect from prenylated flavonoids.
- colupulone
  induces cytochrome P450.

Chamomile
Matricaria recutita

Phytochemistry

1. Essential oil
   sesquiterpenes eg. bisabolol
   spiroethers.

2. Flavonoids
   - Apigenin – 7 – glucoside

3. GABA

4. Coumarins, phenolic acids, polysaccharides.

Chamomile

Phytopharmacology – In vitro

- Apigenin inhibits flunitrazepam binding to Benzodiazepine receptor.
- No effect on GABA receptor.
- Fractions from MeOH EXT.
  - block binding to Benzodiazepine receptors (central & peripheral).

Chamomile

Phytopharmacology – In vivo

Extract

- reduced spontaneous motor activity.
- reduced explorative activity.
- prolonged sleeping time.

Essential oil

- inhalation < stress markers
- effect blocked by flumazenil (Benzodiazepine antagonist).

Chamomile

Clinical studies

Chamomile Tea

12 patients undergoing cardiac catheterisation.

Deep sleep in 10 patients.

No cardiac effects.

Gould *et al.* 1973

Lemon Balm
Melissa officinalis

Phytochemistry

1. Essential oil
   - Citrol
2. Flavonoids
   - Apigenin and relatives
3. Rosmarinic acid
4. Triterpenes

Lemon Balm

Phytopharmacology – In vivo

Essential oil

- contradictory evidence of sedative effects.

Lyophilised hydroethanolic extract.

- prolonged sleeping time after barbiturate.
- sleep induced after low doses.
- sedative effect in activity models.

Lemon Balm
Clinical Studies

- Ballard *et al* J Clin Psychiat. 2002;63:553-8 RCT of Melissa Oil in patients with severe dementia
- 60% (Placebo 14%) showed 30% reduction in agitation
- Kennedy *et al* Pharmacol Biochem. Behav.2002;72:953-964
- RCT of Extract in healthy young people : self-rated "Calmness" increased & "Alertness" reduced

Californian Poppy

No. RCT

French Case Studies

1. 32 year old female insomniac.
   3 weeks tinct. of Californian Poppy.
   Sleep pattern normal.

2. 44 year old male.
   1 month similar results.

3. 150 patients with insomnia.
   60% improved.

Safety: Low acute toxicity.
Concern over cytotoxicity in pregnancy.

Californian Poppy
Eschscholtzia californica

Phytochemistry

Benzophenanthridine alkaloids
- chelerythrine
- sanguinarine
- cytotoxic compounds!

No Morphinan alkaloids

Californian Poppy

Phytopharmacology – In Vitro

- binding to opiate receptors
- inhibition of enzymatic degradation of catecholamines (adrenaline, dopamine)

Phytopharmacology - In Vivo

- aqueous extract
  anxiolytic and sedative in mice.

Mills and Bone

Nervine tonics and Trophorestoratives

Herbal sedatives and Hypnotics

Corydalis, Humulus, Lactuca
Passiflora, Kava
Piscidia, Scutellaria

Trophorestoratives

Avena, Hypericum, Scutellaria
Damiana, Verbena, Withania.

Indications for Trophorestoratives

Nervous exhaustion

Neuralgia, herpes infection

Depressive states

Insomnia

Convalescence

Neurasthenia

Mills and Bone

SESSION IV

ADVERSE REACTIONS & INTERACTIONS

GENERAL PHYTOTOXICOLOGY
HEPATOTOXICITY & KAVA
INTERACTIONS

Kava & Valerian
Hypericum

REGULATORY ISSUES
BIBLIOGRAPHY

FINAL DISCUSSION & CLOSE

Valerian
Phytotoxicology

1. Acute toxicity: low
   Repeated dose toxicity: low -
2. Mutagenicity/carcinogenicity.
   valepotriates mutagenic and cytotoxic
3. Interactions.
   no evidence of synergism with Ethanol.
   - EMEA – "none reported".
4. Ability to drive and use machines
   Valerian syrup: vigilance impaired 1-2 hrs.
   EMEA – "may cause drowsiness....This effect may be enhanced by consumption of alcohol"!!
5. Pregnancy and lactation.
   no experimental evidence – not recommended.
   no effects reported from common usage.
6. Dependence potential.
   none known – unlikely.

KAVA
Phytotoxicology

Acute toxicity: low
Repeated dose toxicity: low
Reproductive toxicity:
DHM – no teratogenic effect

Mutagenicity: none

Preclinical Safety
n= 3029 patients: 2.3% adverse effects (minor)
n= 1673: 1.73%

St. John's Wort

Side effects

1. Photosensitivity due to hypericin.
2. Neuropathy.
3. Mild GIT disturbances.
4. Restlessness, fatigue, headache, allergic reactions.

KAVA

Hepatotoxicity

- 1988 Study: GGT Levels elevated in Aboriginal heavy users.
- No reports prior to late 1990's.
- 68 cases to July 2002
  - 6 liver transplants
  - 3 deaths
- Probable link in 15 cases
  definite link in 2 cases
- Key factors – 210mg Kavalactones/day
  –> 8 weeks use
- Relative risk

Diazepam	2.12 cases/million daily doses
Kava	0.89 cases/million daily doses

Lower than for Voltarol, Losec!

Responses to Kava-Kava Ban

1. **Kommission E - Germany**

- Prescription control.
- Use only for GAD.
- Max. dose of 120 mg. Kavapyrones/day.
- Use for max. of 2 months.
- Monitor liver enzymes.
- Contraindicated in liver disease.
- Contraindicated with hepatotoxic drugs e.g.
  β – blockers, antidepressants, migraine analgesics, paracetamol
- Caution with alcohol.

Responses to Kava-Kava Ban

2. **American Botanical Council**

- Not to be used by patients with liver problems.
- Not to be used with other potentially hepatotoxic drugs.
- Not to be used by regular consumers of alcohol.
- Restrict to max. of 4 weeks use.
- Discontinue use if jaundice appears.

St John's Wort Interactions I

- Induction of cytochrome P450 Isoforms

Medication affected

- < theophylline
- < cyclosporin*
- < warfarin*
- < ethinyloestradiol
- < phenprocouman
- < irinotecan + other anticancer drugs

* Life threatening

St John's Wort Interactions II

- Induction of transporter P-Glycoprotein – a drug pump.

Medication affected

- < cyclosporin*
- < digoxin
- < indinavir*
- < ritonavir

*Life threatening.

St John's Wort Interactions III

- Pharmacodynamic

Medication affected

SSRI – type antidepressants
Anti-migraine Triptans

Results: Serotonin Syndrome

Kava interactions

1. **Alcohol**

Kava extract & alcohol (BAC 50mg %) in 40 volunteers.

No negative safety relevant effects.

Some evidence of counteracting effect.

2. **Benzodiazepines.**

Interaction with alprazolam (Xanax)® reported.

Cimetidine & terazosin also involved.

Cimetidine/alprazolam interaction?

No interaction with Bromazepam reported.

Selected Bibliography

1. **ESCOP monographs on the medicinal use of:**

   Valerian
   Melissa
   Passiflora
   Hops

2. **Mills S. and Bone K.**
   Principles and Practice of Phytotherapy
   Churchill Livingstone 2000.

3. **Weiss R.F.**
   Herbal Medicine
   AB. Arcanum 1988.

Selected Bibliography
(continued)

4. **Blumenthal, Goldberg, Brinckmann**
   Herbal Medicine – Expanded Commission E Monographs.

5. **Robbers J.E. and Tyler V.E.**
   Herbs of Choice – the therapeutic use of phytomedicinals.
   Haworth Press 1999.

6. **Schulz, Hansel, Tyler**
   Rational Phytotherapy – a physicians guide to herbal medicine.
   Springer 3rd Edition 1998.

7. **Herb contraindications and drug interactions.** 3rd Edition.
   F. Brinker - Eclectic Medical Publications
   Sandy Oregon 2002.