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Bachelor degree now minimum qualification for naturopathy and Western herbal medicine in Australia

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After a period of consultation the Community Services and Health Industry Skills Council recently determined that the Advanced Diplomas of Naturopathy and Western Herbal Medicine are to be aligned at bachelor degree level in Australia. All complementary medicine courses currently available within the Health Training Package (HLT07) are under review to ensure they meet industry needs and comply with the new national Standards for Training Packages. This is an unprecedented move which will no doubt be welcomed by many sectors of the profession, with a bachelor degree qualification more accurately reflecting the level of knowledge and skill needed to practice these disciplines. The changes will come into effect in December 2015. Students who have enrolled in any of these courses before December 2015 will be unaffected.

These changes have been a long time coming in a field that has flourished from its traditional roots. The need for a degree minimum standard for naturopathy and Western herbal medicine was established in 1997 by the Victorian Inquiry into Natural Therapies and since then by the ‘Lin Report’ in 2005. The year 2002 saw a move from a diploma to an advanced diploma as the minimum qualification in Australia with the advent of the health training packages. Many commentators have argued long and hard for these qualifications to align with bachelor standards in the context of a contemporary health care system and greater public interest in these treatment options. These concerns have been underpinned by the notion of safety and the need to safeguard the public by developing a CAM workforce that is able to critically evaluate diverse information, emerging research and the health needs of patients in their care. There is an enormous availability of information relating to complementary medicine approaches to healthcare, now more than ever, and it is critical that trained practitioners are intellectually independent and are able to critically evaluate all information they receive.

Further to this it is crucial that complementary medicine practitioners have a level of education and professional skill to collaborate with other health professionals, especially in an ever-increasing pluralistic healthcare environment. It is abundantly clear that most Australians use complementary medicine, many in conjunction with conventional medicines and practices and a bachelor degree minimum standard will help students develop the necessary skills to work in collaboration with other healthcare professionals.

Bachelor degree programmes have been available in the university and private sectors since 1995 however as of December 2015, a bachelor degree will be the new national minimum standard in Australia.

References

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Introduction

Insomnia is estimated to affect about one-third of all adults of whom 6-10% meet the criteria for insomnia disorder. Common features include: difficulty falling asleep causing reduced sleep latency time (LT); several awakenings during the night and/or early morning awakening; all resulting in non-restorative and poor sleep quality (SQ). Insomnia disorder is defined by these key features occurring at least three nights a week over the course of one month and causing significant impairment to daytime functioning.

Insomnia is a sleep disorder previously diagnosed as independent from 'secondary' influences that are attributed to psychological, physiological, or environmental factors. Recently, the diagnostic criteria for insomnia disorder acknowledge co-morbid conditions and ‘secondary’ influences on disease progression (See Table 2). Chronic insomnia is highly co-morbid with anxiety, depression and heart disease both as a precipitating factor and effect of the condition. Conventional treatment includes sedative/hypnotic drugs that cause drug tolerance, drug dependence, and adverse effects with prolonged use, and are hence often not preferred by patients. Examples of pharmacological treatments include benzodiazepine and non-benzodiazepine agonists, anti-depressants and antihistamines. Herbal medicine has become a popular alternative for the treatment of insomnia, believed by many to be a safe and moderate approach to healing.

Methods

The search strategy sought terms “insomnia” and “herbal medicine” and “clinical trials” across the following databases: Pubmed, Cochrane Collaboration, CINAHL, EBSCO, Medline, Science direct, Scopus and Google Scholar. Additionally, hand searches were conducted from reference lists. The inclusion criteria consists of: insomnia disorder or primary insomnia diagnosis; transient insomnia; ingested herbs; Western herbal medicine; double-blind randomised controlled trials (RCTs); date range from 2003 to May 2014; population group adults.

A meta-analysis by Fernandez-San-Martin et al (2010) and a systematic review by Taibi et al (2007) conducted on valerian for the treatment of insomnia disorder were located. However upon detailed analysis both contained trials with methodological flaws such as poor double-blinding procedures and inadequate randomisation. The trials since 2003 had better methodologies, particularly in these key areas. Furthermore, the majority of more recent trials ranked the highest score of 5 using the Jadad scale that ascertains bias and thus is a reflection of improved
methodological rigour. As such it was proposed that setting a date from 2003 ensured a review of ‘better quality’ RCTs in order to gain a clearer perspective on the efficacy of valerian as a treatment option for insomnia.

Results

Nine research articles were identified that matched the inclusion criteria. Of these five investigated the efficacy of valerian for insomnia in adults; two investigated a combination of valerian and hops; and one each explored the usefulness of German chamomile and passionflower for this condition. The evidence for the efficacy and safety of each herb is detailed below.

Valerian (Valeriana officinalis)

Five RCTs conducted on Valeriana officinalis for the treatment of insomnia disorder in adults met the inclusion criteria (see Table 1) and, of these, no single trial reached statistical significant scoring for either subjective or objective primary outcome measures. Improvements in the valerian group were noted in some trials with the majority of evidence remaining either inconclusive or unsupportive for the efficacy of valerian for sleep disorders.

The largest RCT investigating the efficacy of valerian for insomnia recruited 434 adults with primary insomnia disorder (>5, PSQI diagnosis) that were randomised to receive either placebo or Valeriana Forte ® (Cederroth International AB). The extract corresponded to 1200 mg V. officinalis (dried root) per tablet and the participants took 3 tablets per day for 2 weeks. Primary measures did not reach statistical significance, although modest improvements favouring the valerian group for number of night awakenings and sleep duration were observed. The global self-assessment question for perceived ‘better sleep’ (a secondary measure) reached statistical significance (p=0.04). This RCT was relatively well conducted and included a baseline; adequate blinding procedures that masked the aroma of valerian; stratified randomisation; and stringent exclusion criteria of co-morbidities and some lifestyle factors. The second largest RCT that investigated the efficacy of valerian for insomnia was conducted over 4 weeks and recruited 270 adults that were randomised into three groups: Valerian (6.4mg valerenic acid); Kava (300mg kavalactones) and Placebo. Primary objectives were to assess the efficacy of valerian for insomnia and kava for anxiety. Participants included were diagnosed with anxiety (State-Trait Anxiety Inventory State) and insomnia (Insomnia Severity Index). Primary outcomes measuring changes from baseline compared with placebo showed no major differences between the groups. Three other small RCTs were found with sample sizes of between 16 and 21 participants. No statistical differences between the treatment group and placebo were found.

The RCT by Taibi et al (2008) examined elderly adults (n=16) diagnosed with insomnia disorder (Pittsburgh Sleep Quality Index (PSQI) who were randomised to receive either placebo or valerian (300mg/day Nature’s Resource ® valerian root extract standardised to contain 0.8% valerenic acid per 100mg soft gel capsule) for two treatment phases consisting of sleep laboratory (one night) and home (two weeks) before washout and crossover. The outcome measures included both objective and subjective sleep parameters for the sleep laboratory: Polysomnography (PSG), sleep questionnaire and home recordings (wrist autography and sleep diaries). There were no major differences between the groups, with a decrease in LT reported for both groups indicating a placebo effect. Increased nocturnal wakefulness was noted in the valerian group compared to placebo, indicating a negative outcome.

The small RCT by Diaper & Hindmarch (2004) (n=16) examined two different doses of valerian (300mg or 600mg), from a patented extract Li 156 Sedonium ® (Lichtwer Pharma) against placebo in a three way crossover trial for a treatment duration of one night between six-day washout periods. Objective measures included sleep cycles and psychometric function the following morning. No statistical significance was observed between dosages and placebo, although appreciably more ‘drowsiness’ occurred with the 600mg valerian dosage.

The small RCT by Coxeter et al (2003) conducted a series of single patient trials for adult patients diagnosed with chronic insomnia (GP diagnosis), randomised into three treatment pairs of placebo or valerian at a dosage of 2 tablets taken half an hour before bed. Each tablet contained 225mg V. officinalis root/rhizome extract equivalent to 1g of dried root/rhizome standardised to contain 2.94 mg valerenic acids, 0.46 mg valerenal and 1.23 mg valtrates and supplied by Mediherb ® (Warwick, Australia). The dosage was taken for one treatment week before cross-over, taking six weeks to complete. The results did not show appreciable or significant sleep parameter improvements for the patients as individuals or as a group.

Valerian has a statistically significant safety profile when comparing all groups within the trials to date. Oxman et al (2007) found the difference in the proportion of participants experiencing side effects in both the run-in period and treatment period for both groups to be statistically significant suggesting these effects (reduced concentration, drowsiness, tiredness, headache, dizziness, irritability and trembling) were more likely to be symptomatic of insomnia. Taibi et al (2008) did not find any differences in side effects listed between the groups. Coxeter et al (2003) reported a number of predominantly mild side effects, some moderate and a few severe, experienced by both groups such as headache, nervousness, restlessness, and some gastro-intestinal (nausea, diarrhoea) complaints. The authors postulated that some of these effects may be caused by concomitants unable to be screened out in the inclusion process.
Furthermore valerian does not cause dependence and does not have additive effects with alcohol. This is an important factor particularly in light strong evidence associating excessive alcohol consumption with insomnia disorders. According to Bos et al (2002) valepotriates (a minor constituent in Valeriana officinalis) are cytotoxic, mutagenic and carcinogenic in vitro but the relevance of this is questionable since this constituent decomposes before absorption in the human digestive tract.

Evidence of valerian-drug interactions is limited with in-vitro evidence suggesting mild to moderate inhibition of drug metabolizing enzymes, while one in-vivo study showed no significant effect on circulating levels of medications with one valerian preparation. Pharmacodynamic valerian-drug interactions have proven to be beneficial in cases of benzodiazepine withdrawal, with valerian lessening the side effects of drug withdrawal. This is probably due to their similar GABA-mimetic mechanisms of action. Interactions with phenobarbitals, CNS depressants, sedative-hypnotics, anticonvulsants, pre-anaesthetics or adrenergic antagonists theoretically warrant caution due to the uncertainty of these interacting substances. In-vivo studies have demonstrated the ability of valerian to potentiate the effects of barbiturates on sleep.

Valerian – hops combination

Two clinical trials conducted on hops (Humulus lupulus) in combination with V. officinalis met the inclusion criteria for this review (see Table 1). The largest RCT (n=184) compared three groups: valerian-hops (374mg/82mg dried extracts 5-8:1 and 7-10:1 respectively from 45% methanol solvent extraction); Pharmaceutical sedative (diphenhydramine) 50mg; and Placebo. It showed marked improvements in the valerian-hops group in quality of life measures after 14 days of treatment and further improvements in the valerian-hops group in quality of life measures after 14 days of treatment and further improvement after the 28-day treatment duration time. Subsequently a RCT with a four-week duration testing a valerian-hops combination (500mg dried valerian extract /120mg dried hops extract Ze91019) found it was significantly superior to valerian (500mg dried extract) and placebo for sleep latency (primary measure), slow-wave sleep cycles and global impression scores. The valerian group failed to reach statistical significance compared to placebo, though it improved sleep latency times.

Hops can be responsible for allergic skin reactions, bronchial irritations, dry cough and dyspnoea which have been observed in hops processing workers. Furthermore, women processing hops experienced menstrual changes which lead to the discovery of phytoestrogens such as 8-prenylnaringenin (8-PN) and isoxanthohumol. Isoxanthohumul is a pro-oestrogen since it is metabolised into 8-PN by the intestinal microflora. It is difficult to measure the safety profile of hops as an ingested herb, since no RCTs have been conducted on hops singularly. A valerian-hops combination reported no serious adverse effects or cases of rebound insomnia.

German chamomile (Chamomilla recutita syn., Matricaria chamomilla, M. recutita)

One recent RCT pilot study tested adult patients (n=34) diagnosed with chronic primary insomnia (> 6 months - Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria), randomised to receive either placebo or German chamomile dried extract (540mg/day in a split dose of 2 x 3 tablets) for 28 days. Each tablet contained 90mg of dried extract of flowering tops from solvent extraction (6:1) standardised to 2.5mg α-bisabolol and ≥2.5mg apigenin supplied by Mediherb. The outcomes were measured using a combination of subjective sleep parameters. The differences between the groups were not statistically significant but generally favoured the German chamomile group. Limitations to the study include the sample size, and patients on average experiencing milder insomnia compared to other drug studies. Furthermore, no previous studies were available to compare the dosage and formulation, and outcomes were limited to subjective measures.

German chamomile is part of the Asteraceae family which is commonly known to cause allergies in susceptible individuals. Otherwise German chamomile has a good safety profile, with a long-standing history and is generally well tolerated amongst adults. Mild and transient gastrointestinal complaints were experienced by both the active and placebo groups in the recent RCT by Zick et al (2011).

Passiflora incarnata (passionflower)

One recent RCT tested healthy adults (n=41) with transient insomnia, randomised to receive either passionflower herbal tea bags (2g of dried Passiflora incarnata - leaves, stems, seeds and flowers) against a placebo parsley tea bag (2g of dried Petroselinum crispum – parsley) both manufactured by Hilde Hemmes’ Herbal Supplies Pty Ltd, Australia. Treatment was for one week separated by one week washout period before crossing over. Six subjective outcomes were measured using a sleep diary; a Spielberger’s state-trait anxiety inventory (completed day seven of treatment week); and an objective PSG measure for ten of the participants (one night only). The results were statistically significant (p<0.01) for SQ compared to placebo, suggesting a benefit for adults with mild sleep disorders. Double-blinding was confirmed with no statistical difference between the groups correctly identifying the passionflower tea. There were several limitations to the study that may decrease external validity such as: ill-defined sleep disorder inclusion criteria with participants noted to have only transient sleep problems; a strict exclusion criteria applied such as extreme sleep disorders (< 4 hours/night or > 10 hours/night); history/presence of sleep disorder; ≥ three naps per week; and only ten participants were involved in the PSG objective measure thereby limiting statistical power. Overall, the results warrant
further research, particularly due to the external validity limitations although noting that *Passiflora incarnata* tea bags are an easy adjunct to a treatment plan tailored for mild sleep disorders.

Passionflower methanolic extract has a good safety profile classified by the US Food and Drug Administration as safe.27 There have been few incidents of adverse reactions such as: a proposed ‘additive’ effect of *Passiflora incarnata* in combination with *Valeriana officinalis* interacting with the benzodiazepine drug (lorazepam) resulting in hand tremor, dizziness, throbbing and muscular fatigue.27 Other idiosyncratic incidents have linked passionflower with cutaneous vasculitis and IgE-mediated asthma and rhinitis.27 Passionflower contains cyanogenic constituents which thus do not rule out toxicity though humans are regarded as having the physiological functions to detoxify cyanide adequately.28 Furthermore, an understanding of chemical constituent concentrations for passionflower and their exact mechanisms of action remains unclear, thus indicating the need for further research on safety as well as efficacy.27

**Discussion**

Overall the herbs included in this review were found to have a good safety profile but current research has failed to demonstrate the efficacy of these plants for the treatment of insomnia. Valerian is the most studied herb to date but discrepancies are apparent amongst the trials with highly variable research methodologies regarding dosage, sample size, treatment duration, preparation, and possible confounding factors due to various exclusion/inclusion criteria. As such, further research is warranted on valerian for the treatment of insomnia disorder.

Inadequate dosage may be one of the primary problems. According to Coxeter et al (2003)14 the dosage intervention (450mg/day) was taken from the low end of the dosage scale used by clinically experienced Australian naturopathic practitioners, and as such may have hindered the results. Despite this finding a subsequent trial by Taibi et al (2008)10 used an even lower dosage of 300mg/day. Oxman et al (2007)11 used a higher dosage intervention of 600mg/day where results showed a promising trend toward benefiting sleep. This highlights the advantage and possible requirement of a higher dosage of valerian for effective treatment.

A major limitation to several trials was the small sample size (n<21) limiting the statistical power of results and thus impeding internal validity.10,13,14 Furthermore, several trials had a sub-optimal treatment duration phase of two weeks or less. Various authors have suggested that valerian has an accumulative effect after two weeks of treatment.14,29 Further research beyond this time frame is warranted to determine efficacy after a possible accumulative effect.

The inclusion and exclusion criteria amongst the trials ranged from moderate to stringent. Coxeter et al (2003)14 noted that the GP diagnosis of insomnia disorder may have inadequately screened patients with various co-morbidities affecting sleep and as such may account as a confounding factor. Other confounders include stimulants taken throughout the day such as caffeine, sugar containing beverages or nicotine, all known to affect cortisol levels. Several trials failed to account for these stimulants.11,13,14 Only one trial by Taibi et al (2008)10 accounted for these effects, although the exclusion thresholds applied are arguably high such as >6/7 alcoholic drinks per day; >6/7 alcoholic drinks per week and >3/7 caffeinated drinks per day. Caffeine is an adenosine antagonist which may contribute to nullifying the proposed mechanism of action of valerian.10 The trial by Oxman et al (2007)11 accounted only partially for stimulants such as excluding patients with a history of alcohol and drug abuse. Alcohol consumption is known to cause rebound wakening.29 Furthermore, the RCTs by Oxman et al (2007)11 and Coxeter et al (2003)14 advised participants to avoid using other preparations for insomnia and to continue self-help strategies. This highlights the need for a RCT that accounts for all confounders evidenced to contribute to sleep benefit or deficit and by doing so create an even baseline for both groups.

Chemical constituents of valerian vary depending on growing conditions and variety and are very sensitive to manufacturing, processing and storage.31 These variances may have implications for the bioequivalence of manufactured valerian preparations. Furthermore, liquid extracts of valerian to date have not been utilised in an RCT, possibly due to the obvious problem of blinding with its strong odour.10 It would be interesting to elucidate whether a liquid extract preparation may prove more efficacious, particularly in light of the apparent instability of valerian during processing and manufacturing.31

Valerian has a long history of use and was described by Ellingwood (1919)32 as a minor nerve sedative and by Felter & Lloyd (1898)13 as a “cerebral stimulant” to relieve irritability, pain, and “wakefulness”. Primary constituents of valerian include valerenic acid (and derivatives), valerenol and the valepotriates. Valerenic acid is exclusive to *Valeriana officinalis* whilst valepotriates are more dominant in other valerian species. The mechanism of action of valerian is thought to be similar to the drug class benzodiazepines, where it interacts with the delta-amino butyric acid (GABA) neurons in the brain.3 In-vitro evidence suggests valerenic acid targets GABA<sub>α</sub> neuron receptors, and via their stimulation chloride channels open for neural inhibition.34 In-vivo studies on wild mice demonstrated anxiolytic activity of valerenic acid and valerenol on the subunit β3 receptor of GABA<sub>α</sub> neurons.35,36 Recent research by Felgentreff et al (2012)37 suggests that whilst valerenic acid may enhance GABA neuron activity, its derivative acetoxyvalerenic acid inhibits this action on the same binding site – hence causing an opposing response. This may be a plausible reason for the idiosyncratic...
Table 1: Methodological features of trials that meet the inclusion criteria such as (date range from 2003; insomnia disorder; transient insomnia; Western herbal medicine; RCTs: adult population group).

<table>
<thead>
<tr>
<th>Trial</th>
<th>Sample size (n)</th>
<th>Diagnostic</th>
<th>Duration</th>
<th>Dosage</th>
<th>Species</th>
<th>Outcome measures</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Valerian RCTs</strong></td>
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<td></td>
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</tr>
<tr>
<td>Coxeter et al, 2003&lt;sup&gt;14&lt;/sup&gt;</td>
<td>21</td>
<td>GP diagnosis for chronic insomnia</td>
<td>1 week treatment, 6 weeks total (3 treatment pairs of valerian/placebo cross-over)</td>
<td>a) dried extract 450mg/day (each 225mg tablet standardized to 2.94mg valerenic acid, 0.46mg valerenal, 1.23mg valrates and equiv. 1g of dried root/rhizome, (Mediherb ®) b) placebo</td>
<td><em>V. officinalis</em></td>
<td>Subjective: * † ‡§ II ¶</td>
</tr>
<tr>
<td>Diaper &amp; Hindmarch, 2004&lt;sup&gt;13&lt;/sup&gt;</td>
<td>16</td>
<td>Mild sleep complaints diagnosed by sleep researcher</td>
<td>1 night, 6 days washout, cross-over</td>
<td>a) 300mg/day dried extract and b) 600mg/day dried extract c) placebo</td>
<td><em>V. officinalis</em></td>
<td>Objective (11pm–7am): ** Subjective: † ††</td>
</tr>
<tr>
<td>Jacobs et al, 2005&lt;sup&gt;12&lt;/sup&gt;</td>
<td>270</td>
<td>Insomnia Severity Index (ISI) - self reported sleep problems for 2 weeks – LT and sleep maintenance</td>
<td>28 days</td>
<td>a) 6.4mg valerenic acid/day b) placebo</td>
<td>Valerenic acid constituent from <em>V. officinalis</em></td>
<td>Subjective: † † †</td>
</tr>
<tr>
<td>Oxman et al, 2007&lt;sup&gt;11&lt;/sup&gt;</td>
<td>434</td>
<td>Pittsburgh sleep quality index (PSQI) score &gt;5; insomnia &gt; 1 month</td>
<td>14 days baseline and 14 days treatment, 28 days total</td>
<td>a) 600mg/day dried extract equivalent to 3.6g valerian b) placebo</td>
<td><em>V. officinalis</em></td>
<td>Subjective: † † †</td>
</tr>
<tr>
<td>Taibi et al, 2008&lt;sup&gt;10&lt;/sup&gt;</td>
<td>16</td>
<td>&gt; 5 PSQI index</td>
<td>One night treatment (sleep laboratory) + 2 weeks (home), washout and cross-over, 44 days total</td>
<td>a) 300mg (100mg each soft gel tablet equiv. to 0.8% valerenic acid) b) placebo</td>
<td><em>V. officinalis</em></td>
<td>Objective: §§ Subjective: * † † † II II</td>
</tr>
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<td><strong>Valerian-hops combination RCTs</strong></td>
<td></td>
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<tr>
<td>Morin et al, 2005&lt;sup&gt;20&lt;/sup&gt;</td>
<td>184</td>
<td>Self-assessment occasional insomnia</td>
<td>28 days</td>
<td>a) valerian-hops 374mg/84mg dried methanolic extracts b) Diphenhydramine 50mg c) placebo</td>
<td><em>V. officinalis</em> and <em>Humulus lupulus</em></td>
<td>Subjective: * † † Objective: §§ (three separate days)</td>
</tr>
<tr>
<td>Koetter et al, 2007&lt;sup&gt;21&lt;/sup&gt;</td>
<td>30</td>
<td>Standard International criteria for non-organic sleep disorder</td>
<td>28 days</td>
<td>a) valerian 500mg/day dried methanolic extract (Ze 911) b) valerian-hops 500mg/120mg dried methanolic extract (Ze 91019) c) placebo</td>
<td><em>V. officinalis</em> and <em>Humulus lupulus</em></td>
<td>Subjective: * † § Objective: §§ ¶¶</td>
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<td><strong>German chamomile RCT</strong></td>
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<tr>
<td>Zick et al, 2011&lt;sup&gt;+&lt;/sup&gt;</td>
<td>34</td>
<td>DSM-IV criteria</td>
<td>28 days</td>
<td>540mg/day split doses 2x 3 tablets of 90mg dried extract standardised 2.5mg -bisabolol and &gt;/= 2.5mg apigenin (Mediherb ®)</td>
<td><em>Matricaria chamomilla</em></td>
<td>Subjective: * † † § II II (diary)</td>
</tr>
</tbody>
</table>
stimulatory effects that some people experience when taking valerian. Other proposed mechanisms of action involve the serotonergic pathways, namely the 5-HT$_{5a}$ receptor subtype implicated in the sleep-wake cycle. In-vitro studies by Dietz et al (2005)$^{15}$ suggest valerenic acid is a partial agonist of the 5-HT$_{5a}$ receptor. Additional mechanisms of action include the adenosine receptors, where earlier in-vitro research has shown valerenic acid to agonise adenosine receptors.$^{30}$ Adenosine receptors are involved in the inhibitory central nervous system (CNS) pathways, which are typically antagonised by known stimulants such as caffeine and theophylline.$^{30}$

Further research on the efficacy of valerian is warranted utilising a large sample sizes, higher dosage, longer duration (> three weeks) and inclusion/exclusion criteria that eliminate confounding factors such as caffeine and alcohol consumption for all participants. Due to the variable influences of sleep deficit the trial, as investigated by Ngan & Conduit (2011)$^{26}$ over with placebo washout, cross-over with placebo 1 week treatment, a particular ‘synergy’ or via a more broad and unknown mechanism of action of hops. Historically, hops is described as having a hypnotic action to produce sleep and remove “restlessness”.$^{42}$ The primary constituents are the volatile oils (terpenes) and bitter acids shown in animal
studies to produce sedative effects via their involvement in GABAergic pathways and adenosine receptors. Herbal medicine combinations may be more efficacious when combined with ‘sleep hygiene’ techniques and with consideration to all factors contributing to insomnia.

The aetiology and pathophysiology of insomnia disorder may differ from one individual to another due to multi-factorial causes such as genetic, environmental, behavioural and physiological factors. As such, a ‘holistic’ approach that utilises herbal medicine whilst considering other contributing factors may be advantageous and more realistic in a naturopathic setting.

Whole systems research (WSR) is a relatively new phenomenon, which may be a useful tool for researching the treatment of complex health conditions by a system of medicine such as naturopathy as opposed to a single agent. The current evidence in this field is limited although promising, particularly with disorders with multi-factorial causes. The current typical ‘gold standard’ RCT that attempts to align all independent variables may realistically not be the best vehicle for such research and may limit internal and external validity. A WSR approach or insomnia disorder that examines holistic treatment and outcomes includes herbal medicines may be more relevant.

An example of a modified WSR approach was conducted by Cooley et al (2009) in a RCT that examined the efficacy of Withania officinalis for the treatment of anxiety by including a ‘naturopathic’ baseline for placebo and intervention groups. Clearly the benefits of this clinical trial methodology would extend to disorders with multifactorial causes such as insomnia.

**Conclusion**

Based on the evidence to date, *V. officinalis* is the most researched herb for the treatment of insomnia disorder in adults but the results do not support its use as a sole treatment. There may, however, be questions about the adequacy of the dosage and quality of valerian used in the trials reviewed. RCTs investigating the efficacy of a valerian-hops combination have shown improvement on subjective sleep measures with statistical significance proving efficacy for the fixed standardised extract Ze91019. Recent RCTs show promise for both German chamomile and passionflower in improving insomnia disorder in adults, although further research is warranted to elucidate the dosage for German chamomile, and to explore safety and efficacy of methanol extraction processes for passionflower.

Current evidence of clinical trials is lacking in the field of WSR that utilises herbal medicine in synergy with a ‘naturopathic’ treatment approach for insomnia disorder. Due to the myriad of factors that cause insomnia, future research in this area is necessary. A ‘holistic’ approach to treatment that considers a wide range of factors and advises on dietary, lifestyle, and stress management techniques as well as utilising herbal medicine may be more efficacious. Future research that addresses this gap by utilising WSR or a modified version that incorporates a standardised ‘naturopathic’ treatment group and placebo baseline would be advantageous. Furthermore, evidence has demonstrated the safety of valerian, hops, German chamomile and passionflower which is reassuring, particularly in light of high utilisation.

**References**

1. American psychiatric Association 2013, Diagnostic and Statistical Manual of Mental Disorders, 5th edn, American Psychiatric Association, Arlington, VA.

**Table 2: Examples of co-morbidities and/ or secondary influences for insomnia disorder**

<table>
<thead>
<tr>
<th>Influencing factors</th>
<th>Examples</th>
</tr>
</thead>
</table>
| Psychological       | Major depressive disorder 1  
|                     | Anxiety 1  
|                     | Cognitive arousal 1  |
| Physiological       | Pain 1  
|                     | Breathing-related sleep disorder 1  
|                     | Neurological or somatic diseases 2  |
| Environmental       | Maladaptive sleep habits and conditioning associated with the ‘sleep’ environment 1  
|                     | Noise, light, temperature 1  |


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Holy Basil is one of the holiest and most revered medicinal plants of the Orient. It is renowned for its religious and spiritual sanctity and holds immense importance in Ayurvedic Medicine. Traditionally, it was known as an adaptogen and general panacea; it was regarded as an “elixir of life” and therefore used to promote longevity. Current research has investigated its therapeutic effects on the endocrine system, in particular its hypoglycaemic properties, immune system, nervous system (anti-stress) and cardiovascular system. Much of this plant’s therapeutic value stems from its reported systemic antioxidant action. Holy Basil will make a valuable addition to any well stocked herbal medicine dispensary.

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<th>Optimal Rx</th>
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<th>Natural Remedies Group</th>
<th>BettaLife Distributors</th>
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<td>P 1300 887 188</td>
<td>P 1300 138 815</td>
<td>P 1300 553 223</td>
<td>P 1300 883 716</td>
</tr>
</tbody>
</table>
Inhibition of the poliomyelitis viral–induced cytopathic effect by extracts of *Moringa oleifera* Lam.

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Abstract
Extracts of *Moringa oleifera* Lam. (Moringaceae), a medicinal plant used in complementary and alternative medicine for the treatment of diverse ailments, were studied for antiviral activity on poliomyelitis virus. The dried and powdered leaves of the plant, *Moringa oleifera*, were extracted with methanol, water and petroleum ether using standard methods. Cytotoxicity of the extracts was evaluated using the end-point cytopathic effect assay on L20B cell lines. Phytochemical evaluations of the extracts were also carried out. The poliovirus was titrated and determination of the 50% tissue culture infective dose (TCID\textsubscript{50}) done on L20B cells. Antiviral properties were determined against the three sero-types of poliovirus (SL1, SL2 and SL3) using the end-point cytopathic effect assay on L20B cell lines. Phytochemical analysis of the extracts revealed the presence of saponins, alkaloids, glycosides, tannins, flavonoids, carbohydrates, reducing sugar, resins, fats and oil, acidic compounds and proteins. Poliomyelitis viral infectivity was inhibited by the extracts giving a range of specificity indices of 2.47 - >125. This shows that the extracts selectively inhibited the virus and that their activity against the virus was not just a consequence of toxicity to the cells. The research has shown that the plant possesses potent antiviral potentials and could serve as a possible source of lead antiviral drug against poliomyelitis since the disease has no known drug for treatment.

**Key Words:** *Moringa oleifera* Lam., poliomyelitis virus, cytotoxic activity, antiviral activity, phytochemical analysis.

Introduction
Herbal medicine is one of the main streams of complementary and alternative medicine (CAM), and its use is a practice common to all societies, especially the African society. The plant *Moringa oleifera* Lam. is one of the many medicinal plants claimed to possess antiviral activities in complementary medicine. It is the most widely cultivated species of a monogeneric family; the *Moringaceae* is native to the sub-Himalayan tracts of India, Pakistan, Bangladesh and Afghanistan. It is a rapidly growing tree that is also known as the horseradish tree, drumstick tree, benzoil tree, kelor, marango, mlonge, moonga, mulangay, sajhan, sajna or benoil tree. In Nigeria, it is called “zogale” in Hausa language, “ewe ile” in Yoruba language and “okwe oyibo” in Igbo language. *Moringa oleifera* is a very versatile plant with many valuable medicinal and nutritional uses and is found widely in tropical and subtropical regions of the world. Many bioactive phytoconstituents have been reported in different parts of the plant, such as beta-carotene, proteins, vitamins and a variety of phenolics.

*M. oleifera* is rich in zeatin, quercetin, beta-sitosterol, caffeoylquinic acid and kaempferol, a rare combination of important bioactive compounds. Various parts of this plant such as the leaves, roots, seed, bark, fruit, flowers and immature pods have been reported to act as cardiac and circulatory stimulants, have antitumor, anti-inflammatory, antiulcer, antisplasmodic, diuretic, antihypertensive, cholesterol lowering, antioxidant, antidiabetic, hepatoprotective lowering and antibacterial and antifungal activities and for these reasons have been employed in folk and Ayurvedic traditional medicine of Africa and South Asia for a variety of medicinal purposes. In African traditional medicine (ATM), *M. oleifera* is one of the many medicinal plants employed by herbalists to treat diverse diseases. These claims led to the screening of this medicinal plant for its antiviral activity against polio virus which is the causative agent of poliomyelitis (an acute viral infectious disease spread from person to person, primarily via the faecal-oral route). Poliomyelitis is highly contagious and spreads easily by human-to-human contact. In endemic areas, wild polioviruses can infect virtually the entire human population. In fact, poliomyelitis has been a public health concern and there is no drug for its treatment but prevention has been by the use of vaccines. There is therefore a need for an antiviral agent that will be used for the treatment of this disease and this need led to the present study.

Materials and methods

Collection and extraction of plant materials
The leaves of *Moringa oleifera* plant were collected from Nibo in Awka south L.G.A, Anambra State, Nigeria.
The leaves were identified by Prof. C.C.Okeke of the Department of Botany, Nnamdi Azikiwe University, Awka. They were oven-dried at 50°C for 24 hrs and ground to powder using a mechanical grinder.

A forty gram (40 g) portion of the plant powder was macerated in 400 ml of distilled water in a conical flask and left at room temperature for 24 hours. For the methanolic and petroleum ether extract, the forty gram (40 g) portion of plant powder was macerated in 200 ml of either methanol or petroleum ether and left at room temperature for 48 hours. These were filtered using Whatman No 1 filter paper. The filtrates were concentrated to dryness in the oven at 50°C

**Cell line and virus**

The continuous cell line used - L20B cells (a genetically engineered mouse cell line expressing the human poliovirus receptor) was propagated using Eagles Minimum Essential Medium (EMEM) (Gibco, Germany) supplemented with 10% (maintained with 2%) heat-activated fetal calf serum (FCS), 100 U/ml penicillin and 100µg/ml streptomycin. The L20B cells were obtained from the WHO polio laboratory, Department of Virology, University College Hospital (UCH), Ibadan, Nigeria.

Stock suspensions of the three sero types of polioviruses, namely P1 (SL-3978 (LR)), P2 (SL-4493 (LR)) and P3 (SL-4785 (RLR)), were obtained from the World Health Organization (WHO) polio laboratory in the University College Hospital (UCH), Ibadan, Nigeria.

**Phytochemical analysis of plant extracts**

The extracts were first reconstituted in the respective solvents used for their extraction and then tested by standard phytochemical methods for presence of alkaloids, flavonoids, tannins, saponins, glycosides, protein, carbohydrate, terpenoids, resins, fats and oil, acidity, steroids and reducing sugar.

**Preparation of virus stock**

A 0.2ml aliquot of each type of stock polio suspension was measured out using a micro pipette and used to infect a confluent monolayer of L20 B cells in 25ml tissue culture flask (T25). The three flasks were incubated at 37°C and observed daily for 7 days until full cytopathic effect was seen on the cells. The virus was harvested and further passaged twice and the harvested virus stored in well labeled cryo vials at -86°C (Ultralow) until used.

**Cytotoxicity assay of the extracts**

The cytotoxicity assay was performed before the antiviral screening using the end point cytopathic effect assay method on L20B cells. In this assay, L20B cells were seeded onto a 96-well plate at a concentration of 10⁵ cells/well and a volume of 100 µl per well. A volume of 100µl of the different concentrations of test extracts (5mg/0.01ml, 2.5mg/0.01ml and 1.25mg/0.01ml) were added to culture wells in quadruplicate. Culture medium without any drug was used as the “no-drug” control. The plates were incubated at 37°C under 5% CO₂ and observed daily under the inverted microscope for cytopathic effect for 7 to 10 days before termination.

**Titration of the virus and determination of the 50% tissue culture infective dose (TCID₅₀)**

Stepwise 10-fold (1/10) dilutions of the virus suspensions were made up to 10⁻⁸ in tissue culture tubes using 2% Eagle’s Minimum Essential Medium (maintenance medium). Then, 100µl aliquots of each dilution step was inoculated into the wells of a 96 well tissue culture plate containing confluent L20 B cells and 100µl of 2% Eagle’s Minimum Essential Medium (EMEM) bringing the overall volume to 200µl. Each dilution step was seeded into four separate (quadruplicate) wells. The plates were incubated at 37°C and scored for cytopathic effect daily for 7 to 14 days before terminating the readings. The end point titres were calculated using the method of Kinchinton et al.

**Assay of antiviral activity**

Various concentrations of the extracts (0.02mg/ml, 0.01mg/ml and 0.005mg/ml) were mixed in equal volumes (100 µl) with 100 TCID 5₀ of the virus, all in 2% EMEM. These were incubated for 1 hour before aliquots of 200 µl of each mixture were used to infect a confluent monolayer cells in a 96 well tissue culture plate. The virus and cell controls were also set alongside these. They were later incubated at 37°C and scored daily using an inverted microscope for cytopathic effect for 10 days.

**Results**

The phytochemical analysis of the crude extracts of the plant *Moringa oleifera* (Table 1) showed the presence of saponins, alkaloids, glycosides, tannins, carbohydrates, flavonoids, resins, acidic compounds and proteins.

The antiviral assay against the three sero-types of poliovirus (P₁, P₂, P₃) were evaluated on the L20B cells. The cytotoxicity effect of the extract on the L20B cells was also evaluated. The result shows the concentration of extracts that was toxic to 50% of the cells (TC₅₀) and also the concentration of extracts that inhibited viral infectivity (cytopathic effect) by 50% (IC₅₀). The selectivity indices of the extracts were calculated by dividing the TC₅₀ by the IC₅₀. The selectivity indices ranged between 2.47 and >125. This shows that the extracts selectively inhibited the virus without having much effect on the cells.

Table 2 shows the result of the antiviral activity against polio 1 virus by the three extracts. The methanolic extract of *Moringa oleifera* gave the lowest concentration for IC₅₀ and the highest concentration for the TC₅₀, thus giving the highest selectivity index. This showed that at
such a low concentration (<0.03mg/ml) the extract was able to inhibit viral infectivity by 50% and the selectivity index of >125 shows that before the extract will be toxic to 50% of the cells, it will be at a concentration <0.03mg/ml multiplied by >125. This suggests that the extract can serve as a potential antiviral drug with minimal toxicity to the cells. The same thing applies to the aqueous extract that gave a selectivity index of 75.00. The ether extract gave the least selectivity index of 10.44.

Table 3 is the result of the antiviral activity against polio 2 virus by the three extracts. The methanolic extract showed inhibition of 50% of viral infectivity (IC₅₀) at a concentration of 0.09µg/ml while cytotoxicity of 50% of the cells (TC₅₀) was at 3.75 µg/ml, giving the highest selectivity index of 41.67 for the polio 2 virus. This was followed by the aqueous extract with IC₅₀ of 0.75 µg/ml, TC₅₀ of 3.75 µg/ml and SI of 5.00, while the ether extract gave the least selectivity index of 2.47 with IC₅₀ and TC₅₀ of 0.38 µg/ml and 0.94 µg/ml respectively.

In Table 4, the methanolic extract also gave the highest selectivity index of 19.70 for polio 3 virus followed by the aqueous (9.87) and the ether which gave the least (2.47). Thus, for the three polio viruses, the methanolic extract showed the highest antiviral potency while the ether extract showed the least.

Table 1: Phytochemical constituents of Moringa oleifera extracts

<table>
<thead>
<tr>
<th>Constituents</th>
<th>Ether</th>
<th>Aqueous</th>
<th>Methanol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saponins</td>
<td>-</td>
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<td>++</td>
</tr>
<tr>
<td>Alkaloids</td>
<td>++++</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Glycosides</td>
<td>-</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Tannins</td>
<td>-</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Carbohydrates</td>
<td>-</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Reducing sugar</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Flavonoids</td>
<td>++++</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td>Resins</td>
<td>+</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td>Steroids</td>
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<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Terpenoids</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Fats and oil</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Acidic compounds</td>
<td>-</td>
<td>+++</td>
<td>-</td>
</tr>
<tr>
<td>Proteins</td>
<td>-</td>
<td>+</td>
<td>++</td>
</tr>
</tbody>
</table>

Key: (-) not present
(+): present in small concentration
(++) present in moderately high concentration
(+++): present in very high concentration
(++++) abundantly present

Table 2: Antiviral activity against polio 1 (sl 1) virus

<table>
<thead>
<tr>
<th></th>
<th>AM</th>
<th>EM</th>
<th>MM</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC₅₀ (µg/ml)</td>
<td>3.75</td>
<td>0.94</td>
<td>3.75</td>
</tr>
<tr>
<td>IC₅₀ (µg/ml)</td>
<td>0.05</td>
<td>0.09</td>
<td>&lt;0.03</td>
</tr>
<tr>
<td>Selectivity index (TC₅₀/IC₅₀)</td>
<td>75.00</td>
<td>10.44</td>
<td>&gt;125</td>
</tr>
</tbody>
</table>

Key: AM = Aqueous extract of Moringa.
EM = Ether extract of Moringa.
MM = Methanolic extract of Moringa.
IC₅₀ = Concentration of extract that inhibited viral infectivity (cytopathic effect) by 50%
TC₅₀ = Concentration of extract that is cytotoxic to 50% of cells
The result represents mean values of quadruplicate experiment.

Table 3: Antiviral activity against polio 2 (sl 2) virus

<table>
<thead>
<tr>
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<th>EM</th>
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<tbody>
<tr>
<td>TC₅₀ (µg/ml)</td>
<td>3.75</td>
<td>0.94</td>
<td>3.75</td>
</tr>
<tr>
<td>IC₅₀ (µg/ml)</td>
<td>0.75</td>
<td>0.38</td>
<td>0.09</td>
</tr>
<tr>
<td>Selectivity index (TC₅₀/IC₅₀)</td>
<td>5.00</td>
<td>2.47</td>
<td>41.67</td>
</tr>
</tbody>
</table>

Key: AM = Aqueous extract of Moringa.
EM = Ether extract of Moringa.
MM = Methanolic extract of Moringa.
IC₅₀ = Concentration of extract that inhibited viral infectivity (cytopathic effect) by 50%
TC₅₀ = Concentration of extract that is cytotoxic to 50% of cells
The result represents mean values of quadruplicate experiment.

Table 4: Antiviral activity against polio 3 (sl 3) virus

<table>
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<tr>
<td>TC₅₀ (µg/ml)</td>
<td>3.75</td>
<td>0.94</td>
<td>3.75</td>
</tr>
<tr>
<td>IC₅₀ (µg/ml)</td>
<td>0.38</td>
<td>0.38</td>
<td>0.19</td>
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<tr>
<td>Selectivity index (TC₅₀/IC₅₀)</td>
<td>9.87</td>
<td>2.47</td>
<td>19.70</td>
</tr>
</tbody>
</table>

Key: AM = Aqueous extract of Moringa.
EM = Ether extract of Moringa.
MM = Methanolic extract of Moringa.
IC₅₀ = Concentration of extract that inhibited viral infectivity (cytopathic effect) by 50%
TC₅₀ = Concentration of extract that is cytotoxic to 50% of cells
The result represents mean values of quadruplicate experiment.
Poliomyelitis, often called polio or infantile paralysis, is an acute viral infectious disease of tremendous public health concern. Over the years, oral polio vaccine (OPV) has been a vaccine of choice for controlling poliomyelitis in many countries, but on very rare occasions, the attenuated virus in OPV reverts into a form that can paralyze. Therefore, there is an urgent need of developing safe and effective drug for poliomyelitis and medicinal plants seems to present suitable alternative sources of antiviral drugs.

In the present study, virus-induced cytopathic effect assay technique was used to screen the extracts of *Moringa oleifera* for inhibitory activities against poliomyelitis viral infectivity. The phytochemical screening of the extracts of *M. oleifera* showed the presence of saponins, alkaloids, glycosides, tannins, carbohydrates, flavonoids, resins, acidic compounds and proteins.

This finding correlates with the work done by Benett et al (2003), Sabale et al (2008) and Anwar and Bhangar (2003) which found that the leaves of *Moringa oleifera* contain flavonoids, glycosides, proteins, alkaloids and saponins. In other previous studies, *M. oleifera* was shown to be rich in compounds containing the simple sugar, rhamnose, and a fairly unique group of compounds called glucosinolates and isothiocyanates.

The extracts have shown varying degrees of antiviral activities against the poliomyelitis virus assayed. The different solvent extracts of *M. oleifera* inhibited poliomyelitis viral infectivity giving the selectivity indices ranging from 2.47 - >125. The selectivity indices are sufficiently high and specific demonstrating that the antiviral activities observed are not due to the cytotoxicity of the plants L20B cells used in the study. The methanolic extract showed the highest antiviral potency against the three polio viruses assayed, thus suggesting that methanol may be the best solvent for extraction of the active components of the plant. The antiviral activities may be attributed to the rich phytochemicals contained in the extracts since various studies have shown that phytochemicals like tannins found in almost all plant parts cure or prevent a variety of viral infections. Similarly, flavonoids have been shown to exhibit inhibitory effects against viruses. *M. oleifera* is also rich in saponins which have been reported to inhibit HIV infectivity in vitro. In an earlier study, the structure of a bioactive thiocarbamate, niaziminin, extracted from the leaf of *M. oleifera*, was shown to be enough in inhibiting the activation of a tumour promoting virus, Epstein Barr virus (EBV) and a previous report has shown that *M. oleifera* leaf may be applicable as a prophylactic or therapeutic anti-HSV (Herpes simplex virus type 1) medicine and may be effective against the acyclovir-resistant variant of the virus. In another recent study, hydroalcoholic extract of *M. oleifera* fruits showed anti-hepatitis B virus (HBV) activity.

Cytotoxicity studies conducted in parallel showed that the inhibition of viral infectivity by these extracts was not due to diminished viability of the cells induced by the extracts. The extracts selectively inhibited viral infectivity of the cells. This suggests that the antiviral activity against the polio viruses is really specific and not just a consequence of its influence on cell metabolism and/or toxicity.

One emerging fact from the titration of the viruses/determination of the TCID₅₀ is that the polio 3 virus (SL₃) had the highest titre (7.5) followed by polio 1 (SL₁) (7.0) and polio 2 (SL₂) that had 6.5 titre. These findings show the relative infectivity and the amount of virus particles per specimen.

**Discussion**

The extracts’ inhibition of the polio virus-induced cytopathic effect on L20B cells is highly plausible. The selectivity indices showed that the extracts were very potent against the different Polio viruses (SL₁, SL₂ and SL₃). Based on this, one can recommend the plant (*Moringa oleifera*) as

<table>
<thead>
<tr>
<th>Virus dilution</th>
<th>Polio 1 (SL)</th>
<th>Polio 2 (SL₂)</th>
<th>Polio 3 (SL₃)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Well 1</td>
<td>Well 1</td>
<td>Well 1</td>
</tr>
<tr>
<td></td>
<td>2</td>
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<td>10⁻¹</td>
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<td>10⁻⁶</td>
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<td>+</td>
<td>+</td>
</tr>
<tr>
<td>10⁻⁷</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>10⁻⁸</td>
<td>-</td>
<td>-</td>
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</tr>
<tr>
<td>10⁻⁹</td>
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<td>-</td>
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</table>

**TCID₅₀**

<table>
<thead>
<tr>
<th>Polio 1 (SL)</th>
<th>Polio 2 (SL₂)</th>
<th>Polio 3 (SL₃)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P₁ = 10⁻⁷</td>
<td>P₂ = 10⁻⁶.⁵</td>
<td>P₃ = 10⁻⁷.⁵</td>
</tr>
</tbody>
</table>

Key: + = Cytopathic effect, - = No cytopathic effect

**Table 5: Result of titration of the TCID₅₀ of poliovirus**

**Conclusion**

The extracts’ inhibition of the polio virus-induced cytopathic effect on L20B cells is highly plausible.
a possible source of lead antiviral drug against poliomyelitis since it can selectively inhibit the virus without having much toxic effect on the host cells.

References


The efficacy and safety of herbal medicine for insomnia in adults: an overview of recent research continued from page 93

Herbal medicine in the management and treatment of HIV-AIDS - A review of clinical trials

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Abstract
HIV is a retroviral disease of the immune system that leads to decreased immunity via reduced CD4+ T-helper cells (CD4 cells) and increased susceptibility to infections, and ultimately AIDS. Currently it is an epidemic in parts of Asia such as southern Yunnan, China and regions of southern Africa. Herbal medicines are widely used by patients with HIV especially in developing countries due to the high cost of pharmaceuticals and also cultural factors. In these countries herbal medicines are often used for primary care and treatment of opportunistic infections, whereas in developed countries they are used along with conventional modern medicine as ‘complementary medicines’. Herbal medicines are also commonly used in HIV-AIDS treatment, in line with growing evidence suggesting the utility of herbal medicines to be beneficial for immune support, anti-oxidant status and anti-retroviral activity. There are concerns about the safety of some herbs and about false claims of efficacy. We reviewed clinical trials of herbal medicines employed in the treatment of HIV-AIDS using clinical trials from PubMed data and Google Scholar from 1995-2013. Our review clearly suggests that herbal medicines are being used in the management of HIV-AIDS primarily for immune support to maintain immunological parameters. However, further extensive clinical studies are required to establish the safety and efficacy of herbal remedies in the treatment of HIV-AIDS.

Keywords: AIDS, HIV, herbal medicine, traditional Chinese medicine.

Introduction
Human immunodeficiency virus infection / acquired immunodeficiency syndrome (HIV-AIDS) is a viral infection that affects the human immune system. The HIV virus comprises of two types, HIV-1 and HIV-2, and is a retrovirus that infects and destroys T-cells, macrophages and dendritic cells. HIV-2 is predominant in West Africa, whereas the more virulent HIV-1 is the cause of the majority of infections globally.

Symptomatically, within two weeks of initial infection, infected individuals may experience an influenza-like illness, with associated swelling of lymph nodes and skin rash, which then subsides with no further symptoms.1 As the disease progresses the individual’s immune system becomes suppressed via the reduction of cluster differentiation 4 protein (CD4), which is a glycoprotein found on the surface of immune cells, such as T-helper cells (herein abbreviated CD4 cells), which has an important role in the adaptive immune system. Clinically, HIV infected patients display CD4 cell counts <200/mL blood.1

The patient’s prognosis includes a higher relative risk of infections, including opportunistic infections and tumour development. HIV transmission is spread primarily via unprotected sexual intercourse, blood transfusions, hypodermic needles, pregnancy, breastfeeding and body fluid exposure to sensitive tissues such as the eyes and tear ducts. At present there is no HIV vaccine available, with anti-retroviral treatment only slowing the progression of the disease. Immune system support appears to be another therapeutic opportunity, with certain herbal medicines appearing useful in the management of the immune system and thus HIV management.

According to the World Health Organization (WHO), traditional medicines, which include herbal medicines, acupuncture, manual therapies, spiritual therapies, exercise, etc., are the most commonly used form of medicines/treatments in many parts of the world.2 The use of traditional medicine is especially common in developing countries (i.e. Africa, Asia and Latin/South America). In developing countries, an estimated 60 to 90% of the population use traditional medicines which mainly serve their primary healthcare needs. On the other hand, in developed countries (i.e. Australia, Europe and North America) traditional medicine is commonly used in parallel with allopathic medicine (i.e. highly active antiretroviral therapy (HAART)).2 The use of complementary and ‘alternative medicines’ is widespread in chronic conditions, including HIV-AIDS infection. Even though herbal medicine is one of the most commonly used traditional medicines, statistics on the utilisation of herbal medicine in the treatment and management of HIV among the Australian population are largely unavailable. According to a US study, 26%
of HIV-infected people use herbal medicine as part of their treatment. A European study showed that herbal medicines are used by approximately 25% of HIV-infected people.

The primary reason for the use of traditional medicines in the treatment of HIV, especially in developing countries, is the high cost and/or the unavailability of HAART. Herbal medicines are more likely to be used in HIV-AIDS treatment in western countries as an adjunct therapy to support the immune system, reduce the side-effects of medication (for example nausea and depression), reduce viral replication and improve general wellbeing (i.e. act as an adaptogen). Herbal medicines may function in different ways in HIV infection and associated conditions. In many cases the mechanisms of action are not clear and the whole herbs or specific phytochemicals require further research. Emerging evidence suggests the possibility of immune-modulatory and anti-viral properties conferred by various herbal species and their extracts. There are however concerns related to unsafe or erroneous practices as well as the increasing frequency of claims of a cure when there is insufficient evidence to support such claims. In addition, herbs or their phytochemicals may display adverse effects in conjunction with anti-retroviral drugs and may be contraindicated for use with these medications. A list of commonly used herbs in HIV-AIDS adjunct therapy is shown in Table 1.

Methodology

A review of clinical trials available on the use of herbal medicine in the treatment of HIV-AIDS or in conjunction with conventional anti-retroviral drugs was conducted using PubMed and Google Scholar databases. The journal articles were obtained using respective online journal databases. The selection criteria were restricted primarily to clinical trials examining herbal medicine in HIV-AIDS treatment, and human health surveys of CAM use from 1st January 1980 – 30th September 2013. In vitro studies were included if they supported the explanations of observations made in the clinical trials to elaborate on the molecular mechanisms and explain the observed efficacy of the particular herbal medicine.

The search terms included the following string of terms in combination:


Publications were selected if the term(s) appeared in the publication title. Also a number of publications were observed in multiple or all of the search terms and their respective combinations. Duplicates were removed. Results of these search terms can be seen in Table 2.

Herbal medicines reviewed included Western herbal medicine species, Thai, Chinese and also African species. Although there was some language restriction the review attempted to include herbal medicines from publication in languages other than English where the herbal species is found to be clearly identified. Two of the authors read Mandarin (Han character script) and were able to determine the genus and species of some of the herbal medicines used in Chinese medicine treatments. The review also focused on the safety and efficacy of herbal medicine. After research publications and reviews were compiled with respective search terms, only human clinical trials and epidemiological studies were used for the review (PubMed database). With respect to Google Scholar, the search term(s) were required to be included in the title of the article. Articles repeated with different search terms, databases, as well as some studies with no major relevance to HIV-AIDS were deleted from the review. Publications were accessed directly from the publisher websites. Results from studies were examined such as number of observations, type of research design, and major outcomes of the study. A discussion of these results and conclusions was conducted, sometimes using in vitro studies as references to interpret the results shown in the research articles.

Results

As Table 2 depicts, there was a high number of clinical trials repeated for different search terms (42%) that were deleted. Further, there were another 19.7% of publications which had no direct relevance to HIV-AIDS (Table 2) and subsequently deleted from this review. There were 33 clinical studies and epidemiological studies finally selected and tabulated for the review with major outcomes of the research listed (Table 3).

Discussion

Role of herbal medicine in HIV-AIDS treatment

Only a few clinical trials are available on the use of herbal medicine in HIV-AIDS. They are often administered due to their low cost wide availability in third world and developing nations where anti-retroviral drugs are not easily accessed. One issue is the misguided healthcare provided by uneducated and unqualified herbalists’ misuse of herbal therapy in the treatment of HIV-AIDS in the third world and developing nations, although this may represent traditional use of the herbal medicines for infection and inflammatory conditions.

In the developed world CAM treatment appears to be widely used in conjunction with HIV conventional treatment such as anti-retroviral drugs. Herbal medicines are used in combination with anti-retroviral drugs to reduce adverse effects of nausea and depression and for immune support/modulation. In the Third World and developing nations, due mainly to the cost of anti-retroviral drugs, herbal medicines appear to be more widely used, especially in management of associated conditions such as immune suppression and opportunistic
infections. A study in Mexico revealed that of 293 HIV patients, 73.4% used CAM of which 29.7% were herbal products. The correlation of the use of CAM was highest in lower income earners due to the price of anti-retroviral treatment.9 In Tanzania, due to cost restrictions, HIV sufferers resorted to the use of an array of 75 herbal medicine species, mostly leaf extracts and consumed as decoctions for the treatment of associated infections such as tuberculosis and oral candidiasis.10 In Uganda, herbal medicine treatment has been observed as a beneficial treatment option for herpes zoster virus (i.e. reduced pain severity) in HIV patients.11

**Survey of herbal medicine used in treatment of HIV-AIDS in Thailand**

A study from Thailand indicated that 31% of the population reported using herbal medicine. With regard to government support for modern treatment, the study showed that people living with HIV tended to seek assistance from health care services for obtaining treatment. However, females living in up-country areas received less modern treatment but found herbal remedies more accessible for treatment. Respondents from provincial towns were found to use herbal remedies more often than those from Bangkok or highly urbanized areas, and the most commonly used herbal remedy (by 21% of respondents) was bitter cucumber (*Momordica charantia*).12

**Evaluation of herbal medicines used for treating HIV-AIDS in South Africa**

In a descriptive, prospective, follow-up study in South Africa, 33 HIV-positive volunteers (7 men and 26 women between 22 and 43 years of age) were evaluated regarding the effectiveness of commonly used traditional herbal medicines in the management of HIV-AIDS. The study evaluated the treatment efficacy of using herbal medicines by a number of qualitative parameters. The study was conducted over a period of one year. Participants showed significant health improvement: 80% of the patients displayed a better physical appearance, 65% had increased appetite, 70% had disappearance of skin marks/lesions, 100% had disappearance of urogenital lesions, and 80% of participants had gained body weight, although body composition was not specified. There was a significant decrease in viral loads with a corresponding significant increase by 2.5 fold in CD4 T-cell counts. Over 60% of patients resumed workplace duties. The study strongly suggested the effectiveness of these traditional South African herbal medicines as supplementary or alternative medicine in HIV-AIDS treatment, and the improvement in viral load suggested they had an anti-viral action. The authors suggested the anti-viral activity may be due to the phytochemical composition of Calendula officinalis or Agastache rugosa,13 which are used traditionally for their anti-spasmyotic and anti-bacterial actions.

**Modulation of the immune system with astragalus**

Astragaloside II, a key phytochemical present in *Astragalus spp.*, at a concentration of 100nmol/L, has been shown to initiate T-cell activation in primary murine cell culture (*in vitro* study). The specific mechanism is through the regulation of CD4 cells via 5 protein tyrosine phosphatase activity (regulates phosphorylation state of various signalling molecules), and may be the specific mechanism by which astragalus modulates the immune system during disease.14 including HIV-AIDS. Astragalus (*Astragalus spp.*) was traditionally used as a tonic for diabetes and as an adaptogen for ‘healing’ in Chinese medicine.

**Assessment of Immunoxel in treatment of TB among HIV-AIDS patients**

The herbal medicine (Immunoxel) was administered with anti-TB therapy (ATT) among HIV-AIDS patients suffering from tuberculosis. Forty patients were divided into two arms of the study; arm A was treated with ATT and arm B with Immunoxel + ATT. Immunoxel comprises of 27 immunological modulating herbal species. These include; aloe (*Aloe arborescens*), centaury (*Erythraea centaurium*), parsley root (*Petroselinum crispum*), rosehip (*Rosa laevigata*), highbush cranberry fruits (*Viburnum opulus*), hypericum (*Hypericum perforatum*), Chinese agrimony (*Agrimonia pilosa*), sea buckthorn berries (*Hippophae rhamnoides*), sage (*Salvia officinalis*), birch leaves (*Betula sp.*), marigold flower (*Calendula officinalis*), plantain (*Plantago major*), Siberian ginseng (*Eleutherococcus senticosus*), common wormwood (*Artemisia absinthium*), linden (*Tilia cordata*), juniper berries (*Juniperus communis*), rose root (*Rhodiola rosea*), ground ivy (*Glechoma hederacea*), oregano (*Origanum vulgare*), nettle leaf (*Urtica dioica*), licorice (*Glycyrrhiza sp.*), cornflower (*Echinacea purpurea*), wild thyme (*Thymus serpyllum*), equisetum (*Equisetum arvense*), wild strawberry (*Fragaria vesca*), chaga mushroom (*Inonotus obliquus*) and green tea (*Thea sinensis*). It was observed that addition of Immunoxel reduced opportunistic infections as well as improved clinical efficacy of ATT.17 Given the wide array of herbal species it is unspecified which phytochemicals are present and thus possibly active to stimulate the immune system either in isolation or in combination with other phytochemicals.

**Long term treatment of paediatric AIDS with herbal remedies in Romania**

In Romania, 10 children living with AIDS when treated with natural herbal remedies (Chan Bai San) showed improvement in CD4 count, decrease in mortality rate and good maintenance of quality of life. These health benefits were shown for those who kept taking the herbal medicines for 3 years, without any side-effect of the herbal medicine usage.18
Treatment with anti-oxidant herbs

Coupled with immune status, anti-oxidant status appears to be linked with lymphocyte levels in HIV. In a 24-month prospective study of 30 adults with symptomatic HIV and no anti-retroviral therapy, khaki weed *Alternanthera pungens* (AP) anti-oxidant herbal extract was provided as a tea thrice weekly (AP Group) vs. no tea control (Without AP Group).1 Venous blood samples revealed reduced oxidative damage (i.e. evidenced by reduced malondialdehyde concentration and a reduction in advanced oxidation protein end products), significant increase (p < 0.001) of CD4 and CD8 lymphocytes and the lack of biological hepatic and renal toxicity in the AP Group.

Zidovudine (a nucleoside analogue reverse-transcriptase inhibitor) was administered before and after an American ginseng extract (*Panax quinquefolius*) was administered to a study group comprising of 10 healthy volunteers, for two weeks. The study found a decrease in oxidative stress biomarkers (F2-isoprostan ratio = 0.79; 0.72-0.86 at P < 0.001 and 8-hydroxy-deoxyguanosine ratio = 0.74; 0.59-0.92 at P = 0.02) after ginseng extract administration. F2-isoprostan is a metabolite produced from the peroxidation of essential fatty acids (EFA) (primarily arachidonic acid), whereas 8-hydroxy-deoxyguanosine is indicative of *in vivo* DNA oxidative damage. The experiment also reported that ginseng extract did not interfere with pharmacokinetics of zidovudine.19

Mental health benefits from herbal medicine treatment of HIV-AIDS

Mental health is also a key issue in HIV-AIDS sufferers, who are often socially stigmatised. A study conducted in Thailand suggested that herbal medicines can improve the mental health aspect of quality of life (QoL) among HIV-AIDS infected subjects. In this study, 132 HIV-positive adults were given a self-administered questionnaire to assess dimensions of physical function (PF) and mental health (MH) in QoL. The data was also collected on the use of herbal medicine and socio-demographic and psychosocial characteristics related to HIV. Significantly better MH was observed among herbal medicine users vs. non-users, whereas, herbal medicine did not have a statistically significant association with PF scores. This improvement in MH score was higher among the socially vulnerable population.20 A placebo effect cannot be ruled out as a clinical trial of specific herbal extracts with standardised phytochemical concentrations is necessary to make a conclusive recommendation on the use of specific herbal medicine extracts in HIV-AIDS.

Action of a derivative of St John’s wort (Hypericum perforatum)

An isolated protein fraction, p27(SJ), derived from St John’s wort (*Hypericum perforatum*) (usually prescribed for depression and some anti-viral activity), reduced the transcription of the HIV-1 genome in primary culture of microglia and astrocytes. Trans-Activator

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**Table 1: Commonly used herbs in HIV-AIDS treatment**

<table>
<thead>
<tr>
<th>Skin immunity</th>
<th>Adaptogen</th>
<th>Anti-bacterial</th>
<th>Anti-inflammatory</th>
<th>Anti-viral activity</th>
<th>Anti-carcinogenic</th>
<th>Circulatory stimulant</th>
<th>Depurative</th>
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<td>• Ginseng (<em>Panax spp.</em>)</td>
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<td>• Golden Seal (<em>Hydrastis canadensis</em>)</td>
<td>• Dyer’s woad (<em>Isatis tinctoria</em>)</td>
<td>• Ginger (<em>Zingiber officinale</em>)</td>
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* Also denotes anti-viral activity.

Some indications shown above differ from TCM theory.

Adapted from (Lyons et al. 2005).
of Transcription (Tat) is a protein responsible for the enhanced efficiency of viral transcription (HIV dsDNA) and causes apoptosis in T-cells thus exacerbating HIV disease state. The p27(SJ) is associated with the transcription factor C/EBPβ and also Tat, changing their sub-cellular location (accumulation of C/EBPβ and Tat in the peri-nuclear cytoplasmic compartment), affecting DNA binding and hence transcriptional activity. In conjunction with conventional medication, herbal medicines proved to regulate transcription factors associated with HIV replication but also modulate immune function in HIV patients. St John’s wort traditionally is used for depression but also shows efficacy as an anti-viral, possibly via alteration of cytoplasmic location of C/EBPβ and also Tat.

Use of traditional herbal medicine with HIV-AIDS patients in South Africa

In a descriptive, prospective and follow-up study of 33 HIV-positive patients, the viral load decreased and CD4 counts increased after the consumption of traditional South African herbal medicines prior to meals in conjunction with conventional anti-retroviral drugs. The patients were able to increase their social activities such as work and had reduced prevalence of AIDS cachexia. This suggests that the combined therapy may be useful for the treatment and management of immune suppression and systemic inflammation during HIV infection.

Use of TCM treatments for HIV-AIDS

Studies have also shown that some TCM herbal formulations are useful in the management of HIV-AIDS related symptoms.

Evaluation of xiaomi granules

One experiment evaluated efficacy of xiaomi granules in 40 HIV-AIDS patients with oral candidiasis. The study had two groups; one treated with xiaomi granules (n = 40) and control group treated with anticandine. In both groups there were improvements in symptoms of: oral greasy-sticky, thirst, asthenia, abdominal distension and anorexia (p<0.05). Compared to the control group, there was significant improvement in symptoms of oral greasy-sticky and thirst in the xiaomi group (p<0.05). Efficacy rates were also much higher in the xiaomi group than in the control group (90.0% vs. 72.5%) and the 11.1% relapse rate in the xiaomi group was lower than the 31% in the control.

Evaluation of Chinese herbal pills

In a double-blind placebo study of 68 HIV-infected outpatients with a CD4 cell count <0.5 x 10^9/L, a treatment using Chinese herbal pills was investigated for observed changes in HIV-1 RNA plasma loads, CD4, CD8 cell counts and also quality of life scores. The patients taking Chinese herbs reported significantly more gastrointestinal disturbances (79% versus 38%; p = .003) than those receiving placebo, with no difference in HIV disease progression. It is worth noting that the authors stated the baseline levels of both the control and treatment group to be equivalent, even though the median CD4 counts were 25% lower in the treatment group at baseline and the median HIV-1 plasma viral loads 40% lower, creating a known bias in the study.

Evaluation of Zhongyan-4

Another study examined the Chinese herbal combination Zhongyan-4 (ZY-4), a herbal prescription containing Korean ginseng (Panax ginseng), astragalus (Astragalus membranaceus), goji berry fruit (Lycium barbarum), trichosanthes root (Trichosanthis kirilowii), Chinese violet (Viola mandshurica) and root of red-rooted sage or dānshēn (Salvia miltiorrhiza), showed positive results. The randomised double-blind, placebo-controlled study conducted among 72 patients showed a 5% increase in CD4 vs. placebo (24% decrease). The herbs in ZY-4 are all known for their adaptogenic properties. Although the efficacy of ginseng has not been tested as a single prescription in HIV, the ginsenoside Rh2, which is an active phytochemical in ginseng, has been shown to display immunoregulatory and anti-inflammatory properties in CTLL-2 cells; and the CD8(+) cytotoxic T-cell line which have protective effects against viral infection. It was observed that Rh2-B1 stimulated CTLT-2 cell proliferation and also IFN-γ production and thus anti-viral activity, explaining possible anti-viral activity seen in the trial using ZY-4. Sulfated Lycium barbarum polysaccharides (sLBPSs) have been shown to increase cultured chicken peripheral lymphocytes. Further, an in vivo trial using 14-day-old chickens (n=100) vaccinated with Newcastle disease vaccine showed that in the treatment group the chickens injected with the various sLBPSs had significantly higher lymphocytes proliferation and serum antibody titer, conferring immunological modulating capabilities. An ethanolic extract of Viola mandshurica W. Becker (VM) has been shown in the treatment of bronchial asthma in an ovalbumin (OVA)-induced asthmatic BALB/c mouse model to have significantly inhibited increases in total immunoglobulin E (IgE) and cytokines IL-4 and IL-13 levels in serum and bronchoalveolar lavage fluid (BALF), and thus may be of benefit for TB-related hypersensitivity of the lungs and bronchus. Several extracts of Salvia miltiorrhiza (Danshen) have been shown to display a neutralising effect on enterovirus 71 induced cytopathic condition in Vero cells, rhabdomyosarcomacells (malignant tumour from striated muscle) and MRC-5 cells in vitro and perhaps be responsible for the anti-viral effect seen in patients treated with ZY-4.
Evaluation of four different combinations of TCM herbs

In a study investigating four different combinations of TCM herbs administered to 60 AIDS or AIDS-related complex (ARC) patients who were individually prescribed one of four different combinations of TCM herbs, a decrease in viral load, an increase in CD4 and an increase in T-lymphocyte counts were reported. Using a TCM approach, patients with AIDS or ARC were observed to have ‘deficiencies’ of the lung or of the spleen and stomach; ‘insufficiency’ of both the spleen and kidneys, or mental confusion due to phlegm with excessive heat.

Evaluation of Qian-kun-nin

A Chinese herbal formulation known as Qian-kun-nin (乾坤宁), which consists of 14 herbs including Coptis chinensis, astragalus (Astragalus membranaceus), jasmine (Jasminum officinale), wolfiporia fungus (Wolfiporia extensa) (syn. Poria cocos), bur-reed (Sparganium stoloniferum), Polygonatum odoratum and Scrophularia buergeriana is traditionally used for its anti-infection, anti-tumour and immune-enhancing properties. In in vitro trials, Qian-kun-nin displayed ‘HIV-growth inhibition and immunomodulation’ effects. In a single blind pilot study over 24 weeks, this formula significantly decreased plasma virus load at the end of weeks 12 and 24 (p < 0.01), with increased plasma CD4 count (p < 0.01) and with no adverse effects. Plasma virus loads were also measured after four weeks from ceasing treatment, with viral loads still observed to be decreased. These results support claims that ‘Qian-Kun-Nin’ has the therapeutic potential to treat HIV-positive patients.

One ingredient of Qian-Kun-Nin; astragalus (Astragalus membranaceus) contains triterpene glycosides (e.g., astragalosides I-VII) and acts as an adaptogen and immune modulator. Furthermore, Polygonatum odoratum, contains saponin and flavonoid components which exhibit both anti-diabetic effect and anti-oxidant effects, and is traditionally used as a food by the Nu ethnic minority people of P.R. China. In addition, Scrophularia buergeriana (SB) modulates the immune responses via cytokine production. Traditionally, SB was used for fever and swelling, and in a human T-cell line (MOLT-4 cells), mouse peritoneal macrophages cytokines were increased after exposure to SB extract, via increase in the level of interleukin (IL)-2, IL-4 and interferon (IFN)-γ production. Thus, Qian-Kun-Nin contains herbs that influence CD4 count via immune modulation and cytokine production, which accords with its traditional use.

Impact of herbal medicine on adherence to conventional therapy

Although herbal medicines are seen as CAM therapies in the West, in Third World and developing nations, due to the cost of conventional anti-retroviral drugs, herbal medicines are a mainstay for the management and treatment of HIV-AIDS. Two studies examined the impact of complementary therapy on adherence to conventional therapies and whether the complementary medicine has an impact on adherence to highly active anti-retroviral therapies (HAART) amongst HIV-positive African-American women. The study included 366 women who were taking one of the complementary therapies including herbal medicine at enrolment. Women were considered non-adherent if they missed any dose of HAART in 30 days following baseline. According to a logistic regression model of assessment, women on complementary medicine were 1.69 times more likely to report missing their dose of HAART over the last 30 days vs. women not taking complementary medicine. Similarly, Jernewall et. al. conducted a study amongst 152 HIV-positive Latino gay and bisexual men. In this the study, those patients using complementary medicines were less likely to attend their doctors’ appointments, to follow the advice of the doctors or to adhere to pharmaceutical medicines prescribed.

In a study using a semi-structured interviewer-administered questionnaire of South African individuals with HIV infection or AIDS, it was revealed...
that a large proportion of the population consult with traditional health practitioners. Further, the majority experience negative interactions with anti-retrovirals (ARVs). Interestingly, herbal practitioners (HP) were interviewed, with 20% making a claim that they were able to cure the disease, with 88% manufacturing their own medications as aqueous plant extracts. In addition, of the HP, only 38% had received HIV-AIDS related training, with many believing that only traditional and herbal medicines should be used for HIV-AIDS treatment, while others believe there is no harm in taking both concurrently.14

Safety and efficacy of herbs used in HIV-AIDS treatment

There are few clinical trials available using herbs in the co-treatment of HIV-AIDS. There are also a number of safety issues regarding co-administration that have been raised in the literature.

Alternanthera pungens

In a study of the use of Alternanthera pungens herbal tea the treatment of HIV, a significant decrease in plasma levels of biomarkers of oxidative stress (p<0.001) (AOPP and MDA) and a significant increase in CD4 and CD8 lymphocytes (p<0.001) were shown. There were no toxicities related to kidney or liver in this 24-month prospective study consisting of 30 adults with symptomatic HIV and not receiving HAART.1

Jingyuankang

In a randomised double-blind trial (6 months) on Jingyuankang Capsule (JYK) + Leucogen analog + HAART drugs (n=58) and Leucogen + JYK analog + HAART drugs showed that JK increases leukocyte as effectively as Leucogen tablet.35 A list of herbs in this formula is found in Table 3.

Chinese herbal pills

Even though the quality of life was improved in many of the studies involving the use of herbal medicines in HIV-AIDS, in some instances it may pose a negative effect. In a placebo-controlled double-blind study of a Chinese herbal medicine (un-named practitioner devised pill comprising of 35 Chinese herbs) which was claimed to reduce the symptoms and also to improve the quality of life for HIV-infected persons over 6 months. A number of the herbal species are also used in Western herbal medicine. The large majority of actions displayed by the list are related to their anti-oxidant action

The formula contained the following herbs: lingzhi or reishi (Ganoderma lucidum), woad (Isatis tinctoria), Millettia reticulate, astragalus (Astragalus membranaceus), Snow fungus (Tremella fuciformis), Andrographis (Andrographis paniculata), Japanese honeysuckle (Lonicera japonica), agarwood (Aquilaria agallocha), horny goatweed (Epimedium macranthum), oldenlandia (Oldenlandia diffusa), cistanche (Cistanche salsa), Tibet goji berry (Lycium chinense), sea tangle (Laminaria japonica), dong quai (Angelica sinensis), Japanese knotweed (Polygonum cuspidatum), American ginseng (Panax quinquefolius), schizandra (Schizandra chinensis), Chinese privet (Ligusticum lucidum), Bai Zhu (Atractylodes macrocephala), rehmannia (Rehmannia glutinosa), dasanhen (Salvia miltiorrhiza), tumeric (Curcuma longa), violet herb (yedoensis), Mandarin orange (Citrus reticulatereticulata), paeonia (Paeonia lactiflora), polygonum (Polygonum multiflorum), eucommia (Eucommia ulmoides), amomum (Amomum villosum), Chinese liquorice (Glycyrrhiza uralensis), self-heal (Prunella vulgaris), cordyceps (Cordyceps sinensis), patchouli plant (Pogostemon cablin), Japanese hawthorn (Crataegus cuneata), Massamedicata fermentata, barley (Hordeum vulgare), rice (Oryza sativa) with fillers such as microcrystalline cellulose (filler), magnesium stearate (anti-adherent), silicon dioxide (desiccant), and gum acacia. Interestingly, gastrointestinal disturbances were the only effect of this Chinese herbal mixture with no significant differences in plasma viral loads, CD4 counts, symptoms, and psychometric parameters or HIV-1 RNA levels.12

IGM-1

In a fully-randomised, double-blind placebo, clinic-controlled study reviewing the short-term (12 week) safety and efficacy of a Chinese medicinal herb preparation (IGM-1) to treat HIV, there was revealed no significance differences between the placebo and the Chinese herbal medicine except for some reduction in symptoms (i.e. life satisfaction, perceived health, social function, and mental health).36 The species present in the Chinese / Kampo medicinal herb preparation included herbs prepared based on AIDS symptomology. Of 31 herbal ingredients in the 650-mg tablet, those present in significant concentration included lingzi or reishi (Ganoderma lucidum), woad (Isatis tinctoria), astragalus (Astragalus membranaceus), andrographis (Andrographis paniculata), Japanese honeysuckle (Lonicera japonica), evergreen wisteria (Milletia reticulata), oldenlandia (Oldenlandia diffusa), and dashi kombu (Laminaria japonica). These herbs have a range of immunomodulating, anti-viral, anti-cancer properties. Even though there was an improvement in symptoms, this alone could not be interpreted as a long term success with the use of this specific Chinese Medicine / Kampo herb formulation as presented for the treatment of HIV. Measures such as ‘quality of life’ can be subjective and open to bias such as placebo effect. Actual improvements in quantitative parameters such as CD4 counts were not recorded and/or not significant and thus it is unknown whether immune function had been affected or improved.
**Table 3: Details and major outcomes of reviewed research articles and epidemiological studies**

**Abbreviations:** AIDS: Acquired Immunodeficiency Syndrome; ARC: AIDS-related complex, ART: Anti-retroviral treatment/therapy, HZ: Herpes zoster (Shingles), HAART: Highly Active Anti-Retroviral Therapy, NASE: No adverse side effects, PVL: plasma viral loads, TB: Tuberculosis, ↑/↓: increase/decrease, PgP: P-glycoprotein.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Methodology</th>
<th>Subjects</th>
<th>Herbal Species</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arjanova et al.</td>
<td>2009</td>
<td>Open label study</td>
<td>A (n = 20) and B (n = 20) – TB/HIV</td>
<td>first-line anti-TB therapy (ATT) or ATT + Immunoxel (Dzherelo), respectively</td>
<td>Dzherelo had positive impact on the TB drugs and ↓ incidence of new opportunistic infections</td>
</tr>
<tr>
<td>Blonk et al.</td>
<td>2012</td>
<td>Open-label, randomised, two-period, crossover phase I trial</td>
<td>18 healthy volunteers</td>
<td>Ginkgo biloba extract + raltegravir</td>
<td>Although there was marginal increase in Cmax of raltegravir, it was of minor significance.</td>
</tr>
<tr>
<td>Burack et al.</td>
<td>1996</td>
<td>Randomised controlled trial</td>
<td>30 Adults with symptomatic HIV</td>
<td>Preparation of 31 Chinese herbs</td>
<td>Improvements in quality of life and symptoms No change in CD4+ count</td>
</tr>
<tr>
<td>Colebunders et al.</td>
<td>2003</td>
<td>Two questionnaire based surveys</td>
<td>European population</td>
<td>Assessed the use of anti-retrovirals, complementary or alternative medicines</td>
<td>Vitamins/minerals were most commonly used followed by homeopathic and herbal products. Complementary medicines are commonly used despite availability of pharmaceutical medicine.</td>
</tr>
<tr>
<td>Djohan et al.</td>
<td>2009</td>
<td>24 month prospective study</td>
<td>30 Adults with symptomatic HIV, no ART</td>
<td>Alternanthera pungens (khaki weed) extract as drink/tea; anti-oxidant containing herbal extract); thrice weekly or placebo</td>
<td>↓ oxidative damage, ↑ T-CD4 and CD8 lymphocytes (p&lt;0.001) No hepatic and renal toxicity in AP group</td>
</tr>
<tr>
<td>Duggan et al.</td>
<td>2001</td>
<td>Survey (USA based)</td>
<td>191-HIV positive outpatients</td>
<td>Use of various herbal medicines surveyed and recorded</td>
<td>67% used CAM at some point of time; 40% were receiving CAM at the time of survey. Exercise (43%) was the most common CAM used followed by lifestyle changes, dietary supplements, counselling, herbal medications, megavitamins, and prayer therapy. 74% used a protease inhibitor medication, 15% used a protease inhibitor sparing regime, and 11% had no current or prior anti-retroviral use. 70% of the patients felt improvement in QoL with CAM.</td>
</tr>
<tr>
<td>Han</td>
<td>2007</td>
<td>Various treatments</td>
<td>60 cases of AIDS or ARC</td>
<td>Four different TCM formulae depending on presentation.</td>
<td>86.7% patients; ↓ virus loading; ↑ CD4 T lymphocyte count.</td>
</tr>
<tr>
<td>Hennessy et al.</td>
<td>2002</td>
<td>0.15% St John’s Wort, 600 mg thrice daily/16 days</td>
<td>n=15 SJW n=7 placebo</td>
<td>St John’s work (<em>Hypericum perforatum</em>)</td>
<td>↑ PgP expression (4.2 fold) from baseline in SJW group, evidenced by rhodamine efflux. PgP efflux was inhibited in both groups by Ritonavir (5 µM).</td>
</tr>
<tr>
<td>Herrera-Arellano et al.</td>
<td>2009</td>
<td>Cross-sectional study of HIV patients / survey.</td>
<td>293</td>
<td>Use of various herbal medicines surveyed and recorded</td>
<td>29.7% using herbal medicine perceived benefit of quality of life</td>
</tr>
<tr>
<td>Homsy et al.</td>
<td>1999</td>
<td>Non-randomised, non-placebo controlled, observational study (2 phases). Phase 1: 3 mo follow up, Phase 2: 3 mo follow up.</td>
<td>Phase 1: 52 c/c Phase 2: 154 c/c</td>
<td>Herbal treatment according to healers’ prescriptions</td>
<td>Phase 1: HZ super-infection (18% vs. 42%, p &lt; 0.02) and keloid formation less common in herbal medicine vs. control. Phase 2: Faster pain resolution with herbal patients vs. control.</td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Methodology</td>
<td>Subjects</td>
<td>Herbal Species</td>
<td>Outcomes</td>
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<tr>
<td>Kisangau et al.</td>
<td>2007</td>
<td>Semi-structured questionnaire</td>
<td>30 herbal practitioners</td>
<td>Various African herbal medical species described.</td>
<td>Most common HIV-AIDS opportunistic infections were TB and oral candidiasis</td>
</tr>
<tr>
<td>Kusum et al.</td>
<td>2004</td>
<td>Open-label study</td>
<td>28</td>
<td>Glycyrrhiza glabra, Artemisia capillaris, Morus alba, Astragalus membranaceus, Carthamus tinctorius</td>
<td>Reduction of plasma HIV-1 RNA ↓ &gt; 0.5 log (treatment) and follow up period 4-10 (14.2-35.7%). Negative response ↓ plasma HIV-1 RNA &gt; 0.5 log were 2-4 (0-14.2%). No ↓ CD4 cell count.</td>
</tr>
<tr>
<td>Lee et al.</td>
<td>2008</td>
<td>Pharmacokinetic study</td>
<td>10 healthy volunteers</td>
<td>300 mg zidovudine orally before and after 2 weeks of treatment with American ginseng (Panax quinquefolius) extract 200 mg b.i.d.</td>
<td>Ginsenoside does not alter the pharmacokinetics of zidovudine. ↓ oxidative stress biomarkers (F2-isoprostane ratio = 0.79; 0.72-0.86; p&lt;.001; 8-hydroxy-deoxyguanosine ratio = 0.74; 0.59-0.92; p=0.02).</td>
</tr>
<tr>
<td>Maek-anantawat et al.</td>
<td>2003</td>
<td>Prospective open study 6 months</td>
<td>21 asymptomatic HIV patients</td>
<td>Jin Huang comprises of Curcuma longa, artificial Calcis bovis, Panax notoginseng, Aucklandia lappa, Rheum officinalis, Fritillaria cirrhosa, Borneolum Syntheticum</td>
<td>No changes to viral load or CD4 count Adverse reactions; increased bowel movements, vague taste.</td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
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<td>Herbal Species</td>
<td>Outcomes</td>
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<tr>
<td>Maek-a-nantawat et al.</td>
<td>2009</td>
<td>Open-labelled trial</td>
<td>18 asymptomatic HIV patients</td>
<td>CKBM-A01, a Chinese herbal medicine formulation composed of Panax ginseng</td>
<td>No significant changes in log viral load or CD4 cell counts</td>
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<td>Schisandra chinensis, Ziziphus jujube, Crataegus pinnatifida, Vigna radiata,</td>
<td>Adverse reactions; intermittent diarrhoea, skin rash/itching, increased</td>
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<td>Glycine max, Saccharomyces cerevisiae, apple, honey and water</td>
<td>bowel movement</td>
</tr>
<tr>
<td>Mbah et al.</td>
<td>2007</td>
<td>Interventional study</td>
<td>60 HIV-AIDS patients</td>
<td>Acetone-water Azadirachta indica (neem) leaf extract (IRAB)</td>
<td>50% had significant (159%) increase in mean CD4 cells (p &lt; 0.001).</td>
</tr>
<tr>
<td>Moltó et al.</td>
<td>2012</td>
<td>Open-label, fixed-sequence study</td>
<td>15 HIV infected patients</td>
<td>1500mg/d Echinacea purpurea root and 400mg etravirine.</td>
<td>Geometric Mean Ratio of etravirine co-administered with E. purpurea = 1.07; safe for co-administration.</td>
</tr>
<tr>
<td>Moltó et al.</td>
<td>2011</td>
<td>Open-label, fixed-sequence study</td>
<td>1500mg/d Echinacea purpurea root and 200mg darunavir-ritonavir (protease inhibitor)</td>
<td>Herbal medicine co-administered with darunavir-ritonavir resulted in slight decrease in the concentration of darunavir</td>
<td></td>
</tr>
<tr>
<td>Owen-Smith et al.</td>
<td>2007</td>
<td>Observational study</td>
<td>366 HIV-positive, mostly</td>
<td>CAM (Chinese herbs, mushrooms, garlic, ginseng or algae or multivitamins or</td>
<td>Women using CAM were 1.69 times more likely to report missing HAART doses</td>
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<td></td>
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<td></td>
<td>African-American women, aged</td>
<td>religious/psychic health or bodywork) use and HAART adherence among HIV+ women</td>
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<td></td>
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<td>18-50 years</td>
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<tr>
<td>Sugimoto et al.</td>
<td>2005</td>
<td>Survey</td>
<td>132 HIV-positive Thai adults</td>
<td>Herbal medicine</td>
<td>Significant improvement in mental health but no effect on physical health.</td>
</tr>
<tr>
<td>Tani et al.</td>
<td>2002</td>
<td>Long term study with herbal</td>
<td>10 children with pediatric AIDS</td>
<td>Chan Bai San – a formulation of 30 herbs undefined</td>
<td>Improvement in CD4 counts, mortality rates and quality of life. Treatment showed positive results after 1 to 3 years and dug resistant HIV strains did not emerge</td>
</tr>
<tr>
<td>Tshibangu et al.</td>
<td>2004</td>
<td>12-month follow-up study.</td>
<td>33 HIV-positive patients</td>
<td>Traditional South African herbal medicines undefined.</td>
<td>Anti-viral activity present</td>
</tr>
<tr>
<td>Vanlandingham et al.</td>
<td>2006</td>
<td>Analysis of data collected during the year 2000</td>
<td>412 HIV-AIDS patients</td>
<td>Bitter Cucumber (Momordica charantia) and other species used</td>
<td>74% reported using allopathic medicine with 31% reported using herbal treatments (3% overlap)</td>
</tr>
<tr>
<td>Vazquez et al.</td>
<td>2002</td>
<td>Prospective, single-centre, open-label study</td>
<td>27 AIDS patients with oral</td>
<td>Alcohol-based or alcohol-free Melaleuca alternifolia oral solution</td>
<td>60% of patients showed clinical response in 4 weeks.</td>
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<td></td>
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<td>candidias</td>
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<tr>
<td>Walwyn et al.</td>
<td>2010</td>
<td>Semi-structured questionnaire</td>
<td>Herbal practitioners</td>
<td>Various aqueous plant extracts</td>
<td>Only 38% had received HIV-AIDS related training</td>
</tr>
<tr>
<td>Wang et al.</td>
<td>2006</td>
<td>Randomised double-blinded and placebo-parallel-controlled trial</td>
<td>72 patients divided into treatment (n=36) and control (n=36)</td>
<td>Zhongyan-4 (ZY-4), a Chinese herbal preparation</td>
<td>↑ CD4 count (ZY-4) group (5%) vs. 24% ↓ in placebo group. ↑ CD(45) RA(+), &amp; CD(8)(+) count, HIV virus load, &amp; ↑ b.w.</td>
</tr>
<tr>
<td>Weber et al.</td>
<td>1999</td>
<td>Prospective, placebo-controlled double-blind study (6 mths).</td>
<td>68 HIV-infected adults</td>
<td>4 x 7 pills daily containing a standardised preparation of 35 Chinese herbs (listed in text above) versus placebo</td>
<td>Adverse reactions; gastrointestinal disturbances. No sig. ↑ HIV-1 RNA level, PVL, CD4 cell counts, psychometric parameters. Median CD4 cell counts (↓ 0.05 x 10^9/L); both groups.</td>
</tr>
</tbody>
</table>

Table 3: Details and major outcomes of reviewed research articles and epidemiological studies (cont.)
Oral suspension SH

A study by Kusum et al. who examined oral suspension SH, a combination of five ‘Chinese herbs’, native to Asia, near-Asia and Europe. These herbs, namely licorice (Glycyrrhiza glabra), capillary wormwood (Artemisia capillaris) white mulberry (Morus alba), astragalus (Astragalus membranaceus), safflower (Carthamus tinctorius) were either provided as 5g solid or 30 mL tincture, divided into three doses daily. These herbs have phytochemicals present that display efficacy as anti-inflammatory, adrenal tonic, anti-oxidant, anti-viral, immune enhancement, adaptogenic and postprandial. The combination was administered daily in three divided doses post-meal amongst 28 subjects with HIV-AIDS. The participants also received sulfamethoxazole/trimethoprim (antibiotic pharmaceutical selective against Pneumocystis pneumonia in patients with HIV), 400/80 mg after breakfast with treatment provided for 12 weeks. The combination was shown to be safe and showed satisfactory outcomes in terms of viral load, whereas immunological response measured in terms of increase of CD4 cell count did not demonstrate a satisfactory outcome.37

Jin Huang

‘Jin Huang’ a Chinese herbal medicine combination showed no anti-viral effect although patients described a certain ‘improvement in personal well-being.38 Such measures as ‘well-being’ are subjective and open to bias a certain ‘improvement in personal well-being.38 Such shown no anti-viral effect although patients described increase of CD4 cell count did not demonstrate a satisfactory outcome.37

Table 3: Details and major outcomes of reviewed research articles and epidemiological studies (cont.)

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</thead>
<tbody>
<tr>
<td>Wujsiguleng et</td>
<td>2012</td>
<td>Ethnobotanical review</td>
<td>8 patients</td>
<td>Polygonatum macropodium, P. cytonema, P. filipes</td>
<td>Eaten as salad, green tea ethanol extract is used as adaptogen. In TCM P. odoratum reinforces “qi”, nourishing “yin” and moistening the lungs, strengthening kidney and spleen</td>
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<td>al.30</td>
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<tr>
<td>Zhan et al.28</td>
<td>2000</td>
<td>Pilot study, single blind placebo study (24 weeks)</td>
<td>8 patients</td>
<td>Qian-kun-Nin capsules, Coptis chinensis, Astragalus membranaceus, Gardenia jasminoides, Poria cocos, Sparganium stoloniferum</td>
<td>Sig. ↓ plasma virus load week 12 &amp; week 24, &amp; &gt;4 week after cessation of treatment cf. baseline. ↑ blood CD4 cell count, &amp; NASE</td>
</tr>
</tbody>
</table>

as shown in Table 3, and the ingredients’ appear to have anti-inflammatory and anti-oxidant actions.

CKBM-A01

Overall, the peer-reviewed literature suggests that except for ‘Qian-Kun-Nin’, various Chinese herbal medicine formulations showed no, or only limited, effectiveness for the treatment of HIV-AIDS, with some displaying adverse effects. This was also shown in a study on the use of a Chinese medicinal combination known as CKBM-A01, which had no effect on CD4 cell counts or HIV viral loading, but had improvement in cold and flu symptoms suggesting an immune-stimulant effect, but with intermittent diarrhoea observed in over half of the patients, together with skin rashes and increased peristalsis as side effects.40

Neem Leaf

A study41 assessed the efficacy of a neem leaf extract (Azadirachta indica) amongst 60 HIV-AIDS subjects (HIV I or II positive, CD4 cell count <300 cells/μL, and anti-retroviral naïve). Traditionally A. indica has been used, amongst other actions, for its anti-viral activity. In a study, the effect of an acetone-water neem leaf extract (IRAB), of 1.0 g daily for 12 weeks, on immunity and viral load were monitored. Of the 60 participants, 50 (83.33%) were compliant. There was significant improvement in CD4 cell count in these 50 patients (p<0.001) at 12 weeks. There was improvement in the erythrocyte sedimentation rate (64 mm/hr at baseline to 16 mm/hr at week 12). There was also a decrease in HIV-AIDS-related pathologies (120 at baseline to 5 at 12 weeks). Further, there was a significant increase in mean bodyweight, haemoglobin concentration and lymphocyte differential count observed. No major adverse effects were reported in the study.41

Melaleuca

Two studies evaluated the efficacy of oil derived from the genus melaleuca in fluconazole-refractory (anti-fungal pharmaceutical resistant) oral candidiasis amongst AIDS patients.42, 43 An alcohol-based and
alcohol-free melaleuca oral solution was evaluated for two to four weeks amongst AIDS patients with fluconazole-refractory oropharyngeal candidiasis (within mouth cavity) in a prospective, single-centre, open-label study. Forty-seven participants randomly received either alcohol-based or alcohol-free melaleuca oral solution four times daily at a 1:1 extract ratio. The primary study aim was the resolution of clinical lesions. Evaluation of clinical signs and symptoms of oral candidiasis and quantitative yeast cultures were performed at two and four weeks. At week four, clinical response was demonstrated in 60% of the participants. Evaluation of clinical signs and symptoms of oral candidiasis and quantitative yeast cultures were performed at two and four weeks. At week four, clinical response was demonstrated in 60% of the participants suggesting efficacy in oral candidiasis refractory to fluconazole in AIDS patients. Further, in a prospective, single-centre, open-labelled study (no blinding) which evaluated 12 patients with AIDS and oral candidiasis resistant to fluconazole. The patients were treated using a 15 ml melaleuca oral solution four times a day, administered as a mouth wash, for a period of two to four weeks. The participants were evaluated weekly both clinically and with quantitative yeast cultures. A total of 8 of the 12 patients responded positively in four weeks (2 cured, 6 improved with 4 not responding) to the prescribed therapy. Seven patients showed mycological response. Clinical relapse was not observed amongst cured patients during a follow-up of the cohort after a two to four week period after final evaluation.

**American ginseng**

Healthy patients consuming 200mg of a ginsenoside-enriched American ginseng (Panax quinquefolius) extract for two weeks have been observed to induce phase 2 (i.e. UDP-glucuronosyltransferases, sulfotransferases, N-acetylttransferases, glutathione S-transferases and methyltransferases) and antioxidant enzymes in vitro and thought to increase the clearance of zidovudine, an anti-retroviral drug at a 300 mg dosage. Clearance is thought to be due to increased quinoline reductase activity. However two weeks of the P. quinquefolius extract intake did not adversely alter zidovudine pharmacokinetics, but was shown to reduce oxidative stress markers, and thus a positive outcome for treatment of HIV-AIDS patients using the extract for its presumed adaptogenic properties.

**Micronutrients**

Interestingly, in a study of sub-Sahara African HIV-positive patients, it was observed that micronutrient deficiencies (i.e. micronutrients including vitamins A, C, and E, β-carotene, selenium, zinc, and food/tea polyphenols) are common. Due to HIV infection, there is an increased generation of reactive oxygen species (ROS). These anti-oxidant nutrients can be provided via an anti-oxidant rich-diet (i.e. fruit and vegetable based diets) or via dietary anti-oxidant supplements and may have a positive effect on CD4 and viral load in HIV-positive patients that are ineligible for anti-retroviral therapy. In a review of HIV-infected individuals, selenium was suggested to be beneficial due to its inhibitory effect in HIV in vitro and for increasing CD4 counts in vivo, and it has been observed as a deficient nutrient in cohorts with HIV infection. Thus, brazil nuts (Bertholletia excelsa), and burdock root (Arctium spp.), which contain higher levels of selenium, may be a beneficial inclusion in the diet of HIV-AIDS sufferers.

**Impact of CAM on the pharmacokinetics of conventional medicine**

In traditional Western herbal medicine St John’s Wort (Hypericum perforatum) is used for the treatment of mild depression and Echinacea spp. for their immunomodulation action. In a study investigating the safety of the use of echinacea (Echinacea purpurea) and its interaction with etravirine (non-nucleoside reverse transcriptase inhibitor of HIV), patients received 400 mg once daily of etravirine and also E. purpurea root (500 mg every 8 h) over a 14 day period. The etravirine pharmacokinetic parameters such as geometric mean ratio showed that the co-administration of E. purpurea with etravirine was safe and well-tolerated in HIV-infected patients. This observation was also noted in a study of co-administration of E. purpurea with darunavir-ritonavir (protease inhibitor, anti-retroviral drug), but there was a minor decrease in darunavir concentrations, which warranted the monitoring of darunavir concentrations in plasma to ensure the patient was receiving adequate dosage.

Conversely, St John’s wort (Hypericum perforatum) has been shown to increase the activity of p-glycoprotein (Pgp), which is a trans-membrane protein that excretes xenotoxins (i.e. pharmaceutical compounds or their conjugates) from cells such as anti-viral conjugates, especially indinavir and cyclosporine which are known substrates for cytochrome P450 3A4 (CYP3A4), and which theoretically may pose a threat to the efficacy of an anti-retroviral drug. Another placebo-controlled study also showed utility of St John’s wort to increase PgP expression (4.2 fold) from baseline.

The co-administration of Ginkgo biloba extract marginally increased C max (maximal plasma drug concentration in a tested area post-administration) of raltegravir, however there was no effect on raltegravir exposure. The change in C max of raltegravir was considered of minor significance owing to the large inter-subject variability of raltegravir.

Thus, some herbal medicines appear to be safe for co-use with anti-retroviral medicine, and provide immune-supportive action in the treatment of HIV-AIDS and present a valuable complementary treatment options for patients, but there are still questions about others due to possible interaction with anti-retroviral drugs and reduction in their efficacy i.e. reduction of C max.
Concluding remarks

Herbal medicines are commonly used all over the world in both developing and developed countries, especially in the management of chronic conditions. They are used for the treatment of HIV-AIDS and associated conditions such as opportunistic infections. Emerging evidence suggests some benefits of herbal medicines for immune modulating effects, but there are some concerns related to its use for example the possible reduced efficacy of antiretroviral drugs. Herbal medicines may be suited to immune-support by increasing CD4, rather than treatment of HIV-AIDS. However, there have not been an extensive number clinical trials (i.e. randomised clinical trials) carried out on the utility of herbal medicine as a direct treatment or in combination with anti-retroviral drugs, as revealed in our literature search for this review.

Studies indicate that some herbal medicines (single extracts and combination formulas) are safe and efficacious however in some instances safety issues arose, especially in relation to the ability of practitioners to administer a phytochemically relevant herbal extract or mixture. There is also the danger of contamination or adulteration with other materials such as heavy metals, pesticides, bacteria or pharmaceutical compounds which is a known concern for Chinese herbal medicines. Some studies showed efficacy of herbs in terms of immunological parameters, viral load and symptomatology however since the studies were not conducted on large populations and were not of a longitudinal cohort design, they are not conclusive enough to create a definitive answer relating to the use of herbal medicines in HIV-AIDS.

The main actions of herbal medicine for the treatment of HIV-AIDS are via immune modulation, anti-oxidant activity and some anti-retroviral activity of isolated fractions. Considering the primary evidence of efficacy from these small trials, and also selected in vitro cell culture, conducting further in vitro for mechanistic understanding, as well as clinical studies may be beneficial and may lead to a clearer recommendation on how and where in the treatment plan to use herbal medicines in HIV-AIDS treatment. Further, standardisation of extracts and validation using double-blind clinical trials are required with formalised complementary treatment protocols co-administered with anti-retroviral drugs.

Another issue that was revealed in this review is the significant incidence of people with HIV-AIDS using herbal medicine and not adhering to conventional medical treatment. This may be due to compliance issues or the availability and cost of modern anti-retroviral drugs. Thus, there is a need to educate patients, as well as herbal medicine practitioners across the globe, of the importance of conventional medicine and the need for extensive study of herb/drug interactions. Chinese herbal medicine, using combinations of up to 40 herbs, gave results suggesting minimal success other than immune supportive functions, as did African herbal medicine. In these traditional systems of medicine, which also appear as art forms rather than scientific practices, the practitioner relies on a static empirical belief system without considering a scientific understanding of the patient’s health. Conversely, this is also true of pharmacological intervention of HIV-AIDS. The main focus of traditional systems is to ‘re-balance’ patient health and bodily systems rather than to control or impede viral activity. Similarly, Western herbal medicine, both traditional and modern (as pharmacognosy), appears to be of benefit in immune support rather than ‘curing’ the condition per se. Clinical trials using phytochemically validated herbal medicines in conjunction with pharmacological intervention such as anti-retrovirals are required to assess potential benefits in such a complex condition which often has many confounding co-morbidities. There is potential for an integrative medicine system, enabling the patient to elect for either single or combined treatment from a pharmacological, pharmacognosy and traditional perspective and to include multiple modalities in the treatment plan which would include the use of herbal medicines.

In conclusion, herbal medicines are widely used in the treatment of HIV-AIDS and associated conditions. There are studies suggesting the safety and a degree of efficacy for some herbal medicines with, some studies suggesting a positive impact on viral load and immunological parameters. Herbal medicines may have great potential in the management of HIV-AIDS however rigorous research is required to determine safety and efficacy.

Conflict of Interest Statement

The authors have no conflict of interest to declare.

References

Herbal medicine usage by paramedical students of Delta State University Abraka, Nigeria

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Abstract

Introduction The use of herbal medicine predates recorded history and was the form of medication relied upon before the advent of conventional medicine. The focus of this study is to determine the use of herbal medicine among Delta State University students.

Methods A structured questionnaire was used to collect the data. A total of 193 students were given a questionnaire, from which 128 were retrieved. Data collected were analysed by using frequency counts and percentages.

Results Findings from the study indicated that 53.9% of the respondents had used herbal medicine, while 72.5% of the respondents consume herbal medicine orally. Findings of the study also showed that parents/family members (50%) were cited as the most common source of information for herbal medicine; it was also discovered that fear of being harmed by use, the lack of clinical data (48.4%), the diabolic nature of some herbal practitioners (35.9%), and lack of potency (27.1%) respectively, were identified as problems militating against the use of herbal medicine by students.

Conclusion This study shows that slightly more than half of the students utilised herbal medicine. The majority of respondents who used it consumed it orally and parents/family members were the most common sources of information for herbal medicine. Though many of the students used herbal medicine, concern about microbial contamination, fear of being harmed by use, lack of clinical data, poor quality control of herbal products, diabolic nature of some herbal practitioners, and lack of potency were identified as deterrents to herbal medicine use.

Keywords: Herbal medicine, students, Abraka, Nigeria

Introduction

Herbal medicine, also known as botanical medicine, is the use of herbs for their medicinal value.1 Herbs include plant materials such as leaves, flowers, fruits, seeds, stems, woods, bark, roots, rhizomes or other plant parts which may be entire, fragmented or powdered.2 The use of herbal medicine predates recorded history. Herbal medicine has been used by people of all cultures. A 60,000 year old Neanderthal burial site in northern Iraq has yielded large quantities of pollens from eight plant species, seven of which represent currently used herbal remedies.3 Egyptian4 and Assyrian5 texts detail the use of herbal therapies. Herbal medicine use also has been recorded in Europe. The first European herbal, De materia medica, written by Pednois Dioscorides in the first century AD, remains an authoritative herbal reference to date.6 In Africa, phytomedicine was in existence many centuries before colonial administration and is still in use today.7

The World Health Organisation estimates that 75% of the world’s population relies on herbs for their primary health needs.8 Herbal medicine use has increased since the late 1990s,9 which may be due to the emergence of diseases formerly thought to have been eradicated. Additionally, the rise of antibiotic resistant microbes may also contribute to an increase in use.

In America, one out of every three persons surveyed had used one form of alternative medicine.10 Studies have revealed that close to 70% of the population in Australia used at least one form of complementary and alternative medicine and 44.1% visited a traditional health practitioner in 2007.11 In China, traditional medicine accounts for 30-55% of the total population consumption.12 About 80% of Africans13 and 27 million South Africans (54%) have used herbal medicine.14 Traditional healers have been the main providers of primary health care, especially in rural areas.15 It has been observed that two thirds of patients with HIV/AIDS in developing countries use traditional medicine to obtain symptomatic relief, manage opportunistic infections and boost their immune system.16 The familiarity of traditional healers with patients and the communities in which they operate serve as an added advantage for HIV/AIDS patients. The use of traditional medicine and the services of traditional healers by millions in Africa have been noted by the WHO and in 1977 the World Health Assembly (WHA) drew attention to the potentials and efficacy of herbal medicine within the national health system. The WHA urged member countries to utilise traditional medicine to broaden the coverage of health care in their respective centres.17

Nigerians still rely on services of traditional healers for their health care needs. About 75% of Nigerians still
prefer to solve their health problems by consulting a traditional healer.18 Herbal use among Nigerians is well documented. Studies have revealed the use of herbal medicine among cancer patients, pregnant women, hypertensive patients, asthma patients and children.19-22 However, few studies on the pattern of use of herbal medicine among young people, especially university students, have not been reported to date.

The aim of this survey is to determine the use of herbal medicine among paramedical students. A case study of herbal medicine use in a population of young university students has been used to answer this question.

**Methodology**

The study was conducted among first degree paramedical students from Nursing, Pharmacology and Medical Biochemistry in the Faculty of Basic Medical Sciences, College of Health Sciences, Delta State University, Abraka, Nigeria.

A two-part structured questionnaire was employed in the survey. The first part was designed to obtain demographic data (age, sex and occupation). The second part consisted of items intended to obtain data on use, method of usage, reasons for usage, part of the plant normally used, means of awareness of herbal medicine and problems militating against usage.

The survey and administration techniques were approved by five independent assessors and only the recommended items were included in the final instrument.

A pilot study was carried out utilising ten students to check for readability and understanding of the questionnaire items. After revision, the questionnaire was distributed to a larger number of students. Results of the pretesting were not included in the final analysis of the data.

**Data Analysis**

Data were analysed using frequency counts and simple percentages.

**Results**

**Demographic Characteristics**

Out of the 193 students given copies of the questionnaire, 128 students completed and returned the questionnaire, giving a response rate of 66.3%. The age of the respondents ranged from 16-50 years old. A total of 53.9% were of the age range of 21-25 years old; 3.1% of the students combine studies with their job. Out of the 128 that returned the questionnaire, 67 (52.3%) were males, while 61 (47.7%) were females.

**Herbal Use**

Most respondents (n=69, 53.9%) had used herbal medicine before. Reasons mentioned for this usage included recommendation (40.6%), cost effectiveness (17.4%), the belief that herbal medicine is as potent as conventional medicine (7.2%) and safe (5.7%). Oral route (drinking 55.1%, chewing 17.4%) was the major means of herbal medicine intake compared with other ways herbal medicine was used such as topical application (13.0%). Attempt was also made to find out the part of herb/plant used. The leaf part of the plant (n=37, 56.9%) and stem/bark (n=23, 35.4%) were the most frequently used. Parents/family members (n=64, 50%), friend/coworker (n=39, 30.5%) and herbal practitioners (n=37, 28.9%) were the most common sources of information about herbal medicine.

Lack of clinical data (n=62, 48.4%), fear of being harmed (n=62, 48.4%), being unsure of quality (n=52, 40.6%), lack of standardisation of herbal products (n=47, 36.7%), diabolic nature of some of the herbal practitioners (n=46, 35.9%) and lack of pharmaceutical quality and information (n=22, 17.1%) were the most common concerns about herbal medicine.

A total of 59 (46.1%) respondents did not use herbal medicine. Reasons mentioned for non-usage included lack of specification of dosage (n=14, 23.7%), contamination of products (n=11, 18.6%), and adulteration of product (n=4, 6.8%). Others are lack of access to herbal medicine (n=3, 5.1%) and the belief that herbal medicine is not as effective (potent as conventional medicine (n=10, 17.0%).

**Discussion**

This study was carried out to determine the incidence of herbal use among university students. The students’ ages ranged from 16-40 years, which fairly represents a population of young adults having a common educational background. This study shows that the use of herbal
### Table 2: Use of Herbal Medicine

<table>
<thead>
<tr>
<th>Use of Herbal Medicine</th>
<th>Frequency</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Herbal medicine usage n = 128</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>69</td>
<td>53.9%</td>
</tr>
<tr>
<td>No</td>
<td>59</td>
<td>46.1%</td>
</tr>
<tr>
<td>2. Reasons for using herbal medicine n = 69</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lack of access to conventional medicine</td>
<td>3</td>
<td>4.3%</td>
</tr>
<tr>
<td>It was recommended</td>
<td>28</td>
<td>40.5%</td>
</tr>
<tr>
<td>It is potent/effective as conventional medicine</td>
<td>5</td>
<td>7.2%</td>
</tr>
<tr>
<td>It is very safe</td>
<td>4</td>
<td>5.7%</td>
</tr>
<tr>
<td>It is cheaper than conventional medicine</td>
<td>12</td>
<td>17.4%</td>
</tr>
<tr>
<td>Herbal medicine blends with human body</td>
<td>5</td>
<td>7.2%</td>
</tr>
<tr>
<td>Most conventional drugs are fake/counterfeit</td>
<td>3</td>
<td>4.3%</td>
</tr>
<tr>
<td>3. Methods of usage n = 69</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Topical application</td>
<td>9</td>
<td>13.0%</td>
</tr>
<tr>
<td>Bathing</td>
<td>10</td>
<td>14.4%</td>
</tr>
<tr>
<td>Chewing</td>
<td>12</td>
<td>17.4%</td>
</tr>
<tr>
<td>Drinking</td>
<td>38</td>
<td>55.1%</td>
</tr>
<tr>
<td>4. Parts of herbal medicine used n = 69</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leaf</td>
<td>37</td>
<td>56.9%</td>
</tr>
<tr>
<td>Stembark</td>
<td>23</td>
<td>35.4%</td>
</tr>
<tr>
<td>Latex</td>
<td>2</td>
<td>3.1%</td>
</tr>
<tr>
<td>Others specify</td>
<td>1</td>
<td>1.5%</td>
</tr>
<tr>
<td>No response</td>
<td>3</td>
<td>4.6%</td>
</tr>
<tr>
<td>5. Means of awareness of herbal medicine n = 128</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Through herbal practitioner</td>
<td>37</td>
<td>28.9%</td>
</tr>
<tr>
<td>Through television</td>
<td>22</td>
<td>17.2%</td>
</tr>
<tr>
<td>Through radio</td>
<td>14</td>
<td>10.9%</td>
</tr>
<tr>
<td>Through newspaper</td>
<td>13</td>
<td>10.2%</td>
</tr>
<tr>
<td>Through Internet</td>
<td>11</td>
<td>8.6%</td>
</tr>
<tr>
<td>Through parents/family members</td>
<td>64</td>
<td>50.0%</td>
</tr>
<tr>
<td>Through friends/colleagues</td>
<td>39</td>
<td>30.5%</td>
</tr>
<tr>
<td>Through handbills</td>
<td>12</td>
<td>9.4%</td>
</tr>
<tr>
<td>Other</td>
<td>4</td>
<td>5.8%</td>
</tr>
<tr>
<td>6. Concerns about herbal medicine n = 128</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lack or inadequate knowledge about existence or use of herbal medicine</td>
<td>36</td>
<td>28.1%</td>
</tr>
<tr>
<td>Fear of being harmed by use</td>
<td>62</td>
<td>48.4%</td>
</tr>
<tr>
<td>Diabolic nature of some of the herbal practitioner</td>
<td>46</td>
<td>35.9%</td>
</tr>
<tr>
<td>Lack of standardised herbal products</td>
<td>41</td>
<td>32.0%</td>
</tr>
<tr>
<td>Not sure of microbial quality</td>
<td>52</td>
<td>40.6%</td>
</tr>
<tr>
<td>Quality control of herbal products is poor</td>
<td>47</td>
<td>36.7%</td>
</tr>
<tr>
<td>Lack of clinical data</td>
<td>62</td>
<td>48.4%</td>
</tr>
<tr>
<td>Inappropriate labeling and/or advertisement</td>
<td>26</td>
<td>20.3%</td>
</tr>
<tr>
<td>The biopharmaceutical quality and behaviour of most herbal medicines is not well stated</td>
<td>22</td>
<td>17.1%</td>
</tr>
</tbody>
</table>
medicine is common among students of the Delta State University, Abraka, Nigeria. The respondents were not asked to list or mention particular herbs used as this was considered to be outside the scope of this study. The leaf and stem bark of herbs were frequently consumed orally compared to other parts of the plant. Herbal preparations are marketed as dry or fluid extracts which are made from dried plants by maceration or percolation.\textsuperscript{23} It can be self-prepared or pre-packaged and obtained from a herbal traditional healer.

Most students use herbal medicine due to a recommendation from family and friends, and believe that herbal medicine is a natural form of healthcare, which may have contributed to reason of usage.

A good number of respondents (46.1\%) had not used herbal medicine. Lack of usage by these respondents may be due to the method of herbal production used by traditional healers. Additionally, issues like low standards of hygiene, secrecy of actual herbal content, concern about some traditional healing methods and the absence of written records about patients \textsuperscript{24-26} may also reduce use. Lack of federal legislation to regulate the practice of traditional medicine in Nigeria \textsuperscript{27} may also be a factor. Dislike of herbal medicine and lack of potency was mentioned among those who had not used herbal medicine in our study. Similar findings were revealed by Enwere who reported lack of potency as the major reason for medical students not using herbal medicine.\textsuperscript{28} Herbal medicine was considered as unsafe in pregnancy and to have a slower onset of action compared to conventional drugs.\textsuperscript{28} Due to the slow action of some herbal medicines, it cannot substitute for highly effective modern drugs during emergency and life-saving situations.\textsuperscript{28} These aforementioned reasons indicate a lack of confidence by medical students as to the efficacy of herbal medicine and may contribute to the reasons for non-usage among these students.

Herbal medicine has much to offer; not all ailments can be treated with conventional drugs and many conventional drugs were derived from herbal medicine. About 25\% of prescription drugs dispensed in the United States contain at least one active ingredient derived from plants materials. The use of herbal medicine in Nigeria may increase if traditional healers are educated on good manufacturing practices in cultivation, harvesting and production of herbal medicine. Presently, there is a growing local and international call to include information about traditional medicine in medical curriculum.\textsuperscript{24, 30} This would lead to a better knowledge of herbs, for both health professionals and the general public.

### Conclusion

This study indicated that the number of students who had used herbal medicine were slightly more than those that had not; that a majority of respondents who had used it consumed it orally, and that parents/family members were the most common sources of information for herbal medicine. Though many of the students used herbal medicine, problems such as quality, fear of being harmed by use, lack of clinical data, poor quality control of herbal products, diabolic nature of some herbal practitioners, and lack of potency were identified as deterrents to herbal medicine use.

Based on the findings of this study, the following recommendations are set forth in relation to herbal medicine practice and manufacture in Nigeria:

i. Herbal medical practitioners should ensure that clinical information is provided on every herbal product.

ii. Herbal medical regulatory agencies should ensure quality control of all herbal products. In this regard, the agencies should make every effort to get every herbal medical practitioners/product manufacturers to only sell/administer products that have been subjected to laboratory tests to verify their microbial quality.

iii. Efforts should be made to regularly advertise herbal products that are safe for consumption by regulatory agencies and licensed herbal practitioners/manufacturers.

iv. Traditional healers should apply standard methods of herbal preparation.

v. Students should be educated on the importance and efficacy of herbal medicine.

<table>
<thead>
<tr>
<th>Use of Herbal Medicine</th>
<th>Frequency</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>I just don’t like using herbal medicine</td>
<td>9</td>
<td>15.3%</td>
</tr>
<tr>
<td>Herbal medicine is not effective/potent</td>
<td>10</td>
<td>17.0%</td>
</tr>
<tr>
<td>I don’t know how to use it</td>
<td>3</td>
<td>5.1%</td>
</tr>
<tr>
<td>I don’t know how I can get access to herbal medicine</td>
<td>3</td>
<td>5.1%</td>
</tr>
<tr>
<td>Fear of contamination of products</td>
<td>11</td>
<td>18.6%</td>
</tr>
<tr>
<td>Lack of specification of dosage of most herbal products</td>
<td>14</td>
<td>23.7%</td>
</tr>
<tr>
<td>Adulteration of some herbal products</td>
<td>4</td>
<td>6.8%</td>
</tr>
<tr>
<td>Not sure of microbial quality</td>
<td>5</td>
<td>8.5%</td>
</tr>
</tbody>
</table>

Table 2: Use of Herbal Medicine (cont.)
Herbal medicine in the management and treatment of HIV-AIDS - A review of clinical trials


Female Hormonal Disorders:
Simple Strategies for Great Clinical Outcomes

What You Will Learn From Attending This Seminar:

- Learn about the major imbalances in progesterone, oestrogen and testosterone that commonly present in practice and how to effectively influence hormone levels for more successful treatment outcomes in your clinic.
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- Discover the important interaction of sex hormones with neurotransmission and how the inability of the nervous system to adapt to fluctuating hormones drives conditions such as premenstrual syndrome and menopausal hot flushes in your patients.
- Recognise the key nutrients critical for women through every life stage and how they serve as the foundation for promoting optimal hormonal balance.
- Discover the simple diet and lifestyle changes which can make profound differences for your patients with specific hormonal imbalances, such as polycystic ovarian syndrome and premenstrual syndrome.

Locations

QLD
- Caloundra: Wednesday 8th October
- Noosa: Friday 10th October
- Hervey Bay: Saturday 11th October
- Rockhampton: Monday 13th October
- Toowoomba: Tuesday 14th October
- Mackay: Wednesday 15th October
- Townsville: Friday 17th October
- Cairns: Saturday 18th October
- Brisbane: Sunday 19th October
- Gold Coast: Friday 31st October

NSW & ACT
- Ballina: Saturday 11th October
- Coffs Harbour: Sunday 12th October
- Port Macquarie: Tuesday 14th October
- Kingscliff: Thursday 16th October
- Parramatta: Saturday 18th October
- Manly: Sunday 19th October
- Newcastle: Monday 20th October
- Forster’s Beach: Wednesday 22nd October
- Leura: Thursday 23rd October
- Batemans Bay: Friday 24th October
- Goulburn: Saturday 25th October
- Wellington: Monday 26th October
- Wollongong: Saturday 21st October
- Cranulla: Monday 27th October
- Sydney: Saturday 2nd November

VIC
- St Kilda: Saturday 18th October
- Glen Waverley: Monday 20th October
- Geelong: Tuesday 21st October
- Albury: Friday 24th October
- Melbourne: Sunday 26th October

TAS
- Hobart: Thursday 16th October
- Launceston: Friday 17th October

SA
- Barossa: Saturday 24th October
- Adelaide: Saturday 25th October

WA
- Perth: Sunday 24th October
- Bunbury: Monday 27th October
- Albany: Tuesday 28th October

NT
- Darwin: Tuesday 28th October

ALL SEMINAR TIMES
- Registration: 2:30 to 3:00 pm
- Session 1: 3:00 to 4:30 pm
- Break: 4:30 to 5:00 pm
- Session 2: 5:00 to 6:30 pm
- Dinner: 6:30 to 7:30 pm

SPEAKERS
- Paul Mannion
- Angela Carroll
- Laurence Katsaras
- Erica Smith
- Andrew Thurgood
- Nicola Reid

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Reviews of articles on medicinal herbs

Jodie Tester, Tessa Finney-Brown

These abstracts are brief summaries of articles which have appeared in recent issues of herbal medicine journals, some of which may be held in the NHAA library.

**Nigella improves sperm quality in infertile men**


Infertility and childlessness is an increasing issue worldwide. Male factors contribute to over half of all cases of infertility, generally due to some problem with sperm quality. This may be due to a multiple of reasons, including congenital disease, hormone imbalance, genetic and nutritional defects. Many different strategies have been tried to address this, and there is no panacea.

*Nigella sativa* L. seed (NS) has been used in the traditional medicine system of Iran for treatment of infertility. Animal studies have reported use of the oil to have some effect on the reproductive traits of chickens and rats, but there has been no in vivo testing in humans.

This study looked at the effects of daily consumption of 5ml NS oil for infertile men with abnormal semen quality. 80 men were recruited from the Infertility Center of Mahdieh Hospital in Tehran, Iran, each of whom had initial semen samples showing sperm abnormal morphology > 30%; or sperm count < 20 × 106ml; or type (A) motility < 25% and type (B) motility < 50%) (as per WHO standard guidelines). They were randomised into two groups and each man took 2.5ml NS oil of 2.5ml placebo (mineral oil) twice daily for 2 months. Both researchers and participants were blinded (double-blind study).

At baseline and after 2 months, semen samples were obtained from all patients and the parameters of these formed the primary outcome measures.

At baseline, 12 patients in the NS group and 15 patients in the placebo group had abnormally low sperm counts, and 15 patients in each group had abnormal sperm morphology. 38 NS patients and 41 placebo group patients had low sperm motility. Following the administration of the active treatment, morphology, count and motility of sperm increased significantly, compared with the placebo group. Group semen round cells, volume and pH also improved significantly in the active treatment group. No adverse effects were seen.

Overall, 5ml NS oil administration for 2 months significantly improved all semen parameters in the infertile men in the study. Authors suggest that further research may be necessary to elucidate potential mechanisms of NS oil action, and whether conception occurred as a result of improved semen parameters.

**Mood modulation with skullcap**


Anxiety and mood disorders are highly prevalent conditions in our society, and in milder manifestations are emotional states that every human being experiences. Pharmacological strategies for treating these disorders include benzodiazepines (BZD), and antidepressants, which are medications with a number of side effects, and, in the case of BZD, the risk of tolerance and dependence. Natural and traditional medicines may offer a treatment alternative associated with lower risk of adverse effects. The major challenge at this stage is to show that they are effective, thus allowing herbalists, naturopaths and doctors alike to feel confident in their use.

*Scutellaria lateriflora* (SL) has traditionally been used for anxiety and related disorders in North America, and in vitro studies have shown it to contain phytochemicals with BZD and serotonin-7 (5-HT7) receptor binding affinity. One previous clinical trial has shown the plant to have acute anxiolytic effects, but other quality studies are lacking.

For this study, researchers designed a double-blinded, placebo-controlled crossover trial assessing the effects of SL on anxiety and multiple mood factors in healthy volunteers. 43 participants were enrolled, and although not compulsory, recruitment was on the basis of experiencing persistent stress, anxiety, mood swings, irritability, poor sleep or difficulty in coping. None had current or previous psychiatric diagnoses and none were taking medications affecting the CNS. Patients were randomised into two groups which each took 14 days of active or placebo capsule three times daily, followed by a 7 day washout with a further 14 days of the alternate treatment. The test herb were capsules containing 350mg of organic freeze dried aerial parts of SL. The placebo capsules contained 350mg of freeze dried *Urtica diocca folia* as this has no known effect on the CNS, yet is similar in appearance and smell to skullcap.

Effects of treatment were assessed via Becks Anxiety Inventory (BAI), the Profile of Mood States (POMS),...
measures of alanine aminotransferase (ALT), blood pressure (BP) and pulse (HR) at the end of each 14 day test period.

Of the 31 participants who completed the study, initial testing revealed that 11 were experiencing minimal anxiety, 14 were mildly anxious, 3 were moderately anxious and 3 had severe anxiety. For group one (the first to have placebo treatment), there was an enhanced within-group anxiolytic effect following active treatment. Despite randomisation, all patients with moderate-severe anxiety were in this group, which could account for the greater efficacy. Group 2 had much less response, which may have been due to their low baseline scores. Results on POMS mood scores showed no significant effect for SL treatment overall, but again there was an enhanced effect of SL treatment in Group 1, which suggests that it may also reduce the risk of depression in some individuals. Part of the POMS measures energy levels, and these were increased by 20% by treatment with SL in group 1 individuals.

Researchers also note that non-significant results for group 2 may be due to low baseline scores on anxiety and mood indices, as well as a carryover effect from the initial period of treatment with SL. This suggests that 7 days may not be a long enough washout period for a trial like this.

Results for ALT, BP & HR were unchanged and not abnormal following active treatment. Minor and infrequent side-effects were reported by 7 participants in the trial, including vivid dreams, mild digestive disturbance and feeling ‘spaced out’.

Limitations of the study included the use of an active placebo (although with no noted CNS effects), the allocation of all moderate-severely anxious individuals into one group and a short wash-out period with potential carryover effect of the herb.

Overall, the data from the study suggests that SL has some anxiolytic and mood enhancing effects without a reduction in energy or cognition. These were most profound in those who had more severe symptoms at baseline. Further studies should be conducted in those with more notable anxiety or mood disruption.

**Chamomile for PMS**


Premenstrual syndrome (PMS) is a common condition, affecting up to 75% of women during childbearing years. Whilst the aetiology of PMS is not completely understood, it is likely that prostaglandins are responsible for a number of PMS associated symptoms. Mefenamic acid (MA) has demonstrated efficacy in treatment of PMS in clinical studies through inhibition of enzymes involved in prostaglandin synthesis, however a number of side effects are associated with MA affecting the blood, gastrointestinal tract, kidney and skin.

*Matricaria chamomila* (chamomile) has been reported to be effective at improving some menstrual conditions including PMS and dysmenorrhea. A number of constituents of chamomile may have an effect including chamazulene with anti-inflammatory and antioxidant effects; apigenin with anti-inflammatory, angesic and antineoplastic effects; flavonoids with anti-inflammatory and anxiolytic activity; and alpha-bisabolol with anti-inflammatory and digestive effects.

The present study aimed to compare the effects of chamomile to MA on PMS intensity through a prospective, randomised, double blind clinical trial. Participants were students from an Iran university residing onsite in dormitories. For study inclusion, women were required to be single, aged 18-35 years, normal body mass index and diagnosed PMS with presence of at least five symptoms based on DSM-IV criteria. Participants were required to complete a daily PMS form consisting of 30 items, 15 physical and 15 psychological, for two consecutive cycles and rated the severity of daily symptoms from none, mild, moderate to severe. The participants were classified as mild, medium or severe based on the intensity of symptoms for the seven days prior to menstruation. In total, 118 participants who completed the daily questionnaire for the two cycles were randomly divided into 2 groups of 59 based on the symptom severity. One group received chamomile 100g capsule three times daily and the other group received 250mg MA capsule three times daily. Both therapies were only taken from 21st day til the onset of menstruation and were taken for two consecutive cycles with symptoms recorded.

Of the 118 participants, 90 were included in the analysis (45 participants in each group), with others excluded due to insufficient data, improper use of capsules and GI disorders amongst other reasons. The intensity of general, physical and psychological symptoms between groups prior to menstruation were similar before intervention was commenced. After the two courses of treatment over two cycles, chamomile was found to be more effective than MA at reducing the overall intensity of symptoms and particularly psychological symptoms associated with PMS. Both chamomile and MA provided effective relief of physical symptoms of PMS however there was no significant difference between the therapies. The incidence of side effects reported was comparable, however there was a non-significant increase in menstrual bleeding with chamomile.

Limitations of the study include the potential for data being inaccurate/biased as collected through self-report. The analysis was not performed on the intention to treat (ITT) population, rather only the data that the study received complete records for. Performing the analysis on the ITT group could have provided additional
information about dropout rates and safety side effects of both products as a number of the MA group discontinued due to GI problems, which may have changed the safety findings from the overall analysis. The study did not include a placebo-controlled group, which would have strengthened the findings. Finally, the article was poorly written, which may unfortunately negatively influence on its impact upon reading.

Despite these flaws in study design, the results demonstrated that chamomile treatment may alleviate general physical and psychological symptoms associated with PMS, and that treatment for approximately 7 days prior to the onset of menstruation was sufficient for benefit, thus not requiring medication for the entire cycle. Whilst these results are promising, further studies with improved study design, larger study numbers, and a placebo-controlled arm will provide further understanding of chamomile’s therapeutic effect in PMS and a greater understanding of the safety profiles.

**Acute dosing of Bacopa for stress reactivity and mood**


*Bacopa monniera* (BM) has been used in traditional Ayurvedic medicine to treat a broad range of psychiatric and physical conditions, including anxiety, depression and poor cognition. Recent scientific research has shown it to have proven no-tropic effects, but little human research has been conducted into the adaptogen, anxiolytic, antidepressant or sedative actions of the herb. Murine models have shown promising results.

This study looked at the ability of varying acute doses of BM on mood, cognition, anxiety and stress at an earlier time point than previous acute BM studies. 17 healthy volunteers (mainly female) were enrolled in a double-blind, placebo-controlled, cross-over design study. Researchers used a 320mg or 640mg dose of BM (KeenMind©) standardised to no less than 55% of total bacosides. Standardisation was important as the main psychoactive components of BM are the steroidal saponins Bacoside A and Bacoside B. They act in the CNS as antioxidants, to enhance kinase activity, restore synaptic activity and ultimately nerve transmission.

Prior to the first study visit, each participant undertook a practice session where they undertook the same cognitive assessment (MTF) and mood and anxiety measures (Bond-Lader VAS & State Anxiety subscale STAI-S) that they would undertake on the study days. On each study visit (3 in total) each participant completed the MTF and provided a saliva sample for cortisol testing. Scores on mood and anxiety measures were taken before and after the MTF to assess the impact that it had on their emotional state. They then took the requisite dose or placebo and repeated these procedures 1hr and 2hr post-dose. At each study visit the participants took a different dose of BM or the placebo capsule.

Neither the BM treatment nor the placebo affected MTF scores differentially. There was an increase in MTF scores from baseline with all treatments. It was considerable greater in the group treated with 640mg of Bacopa, compared with the placebo group, but this did not reach statistical significance. After treatment, alertness was significantly greater in the 320mg group 2hr post-administration compared to placebo.

Accounting for the effects of the MTF, the change from baseline of score of anxiety and mood showed a considerable effect of BM treatment (especially 640mg after 1 hr), but the trend did not reach significance. Cortisol levels also showed a significant main effect of the condition, significantly greater for the 640mg group compared to 320mg and placebo. No adverse effects were reported during the trial.

Overall, results suggest that acute dosing of BM improved performance on cognitive tasks in comparison with placebo (with the effects lasting longer with higher doses). However, this did not increase enough to reach statistical significance. Self-rated alertness was also improved 1hr post-administration of 320mg, and increased levels of contentedness and lower cortisol were also seen for the 640mg group. Again, there were no significant differences.

This general pattern indicates that BM may be useful to improve mood and reduce anxiety in cognitively stressful settings, but higher doses may be required, and further studies might derive better results from exposing the participants to novel stressors rather than a repeated test. Researchers also suggest that temporally sensitive brain imaging measures may be used in future trials to assess which brain regions are acutely affected by the administration of BM.

**Panax ginseng’s immune modulation in influenza**


Influenza A virus is an important respiratory tract pathogen causing significant morbidity and mortality. Mechanisms involved in the process of influenza may include production of reactive oxygen species (ROS), which can stimulate cytokine/chemokine production, epithelial cell death, airway inflammation and pulmonary damage. Epithelial dysfunction in influenza may be influenced by hypercytokinemia and epithelial cell apoptosis. Additionally, the severity of human respiratory disease by viral infection has been suggested to be associated with pro-inflammatory hypercytokinemia.

*Panax ginseng* is a commonly used herbal medicine.
known to enhance the immune system by stimulating natural killer cells, T-cells, B-cells and dendritic cell-independent immune response, as well as inhibit ROS-induced oxidative stress and modulate the antioxidant defense system. The potential therapeutic effect of ginseng in protection against inflammatory viral infection have not been well demonstrated, hence the authors aimed to investigate red ginseng extract (RGE) as a preventative agent in influenza A virus infection.

The study had two components: an in vitro study assessing cell survival, cytokine expression and cellular oxidative stress upon human epithelial cells infected with influenza virus, and an in vivo study evaluating the potential immunomodulatory functions of RGE upon influenza A virus infection in a mouse model. The ginseng used was a concentrated commercial product of dried, 6 year old red ginseng root boiled in water with the supernatants concentrated to create the RGE.

For the in vitro study, human alveolar epithelial A549 cells were infected with H1N1 influenza virus in the presence or absence of RGE treatment. All cells were continuously treated with RGE for 24 hours prior to infection with the virus at which point, cells were treated with or without RGE for another 48 hours. The influenza H1N1 was found to induce severe cytopathogenic effects in a dose-dependant manner, however the cells treated with RGE displayed decreased viral cytopathogenic effects and reduced cell death caused by the virus. Additionally, human epithelial cells infected with influenza A virus significantly increased expression of IL-6 and IL-8 and were associated with a significant amount of ROS generation due to the virus. The RGE significantly diminished the generation of ROS and inhibited IL-6 and IL-8 production induced by influenza A virus-infected human epithelial cells.

In the in vivo component, BALB/c mice were orally administered with RGE at a dose of 25mg/kg for 30 days. RGE-treated and untreated mice were intranasally infected with a mouse-adapted influenza A H1N1 virus. Lung and BAL samples were collected at day 5 post infection to determine cytokine levels. In the RGE treated mice, cytokine IL-6 from RGE exposed mice were moderately lower than or similar, IFN-γ was significantly higher and the cellularity of CD8 T cells and CD11c⁺ were moderately increased when compared to the untreated control. In the control mice, influenza virus infection resulted in severe inflammation of the bronchioles and appeared to be flooded and surrounded with inflammatory cells. The RGE treatment group experienced significantly decreased inflammation in the bronchioles as measures with inflammatory exudate.

Overall the authors concluded the RGE may improve viability of human epithelial cells, suppress inflammatory responses in lung alveolar epithelial cells and may interfere with oxidative stress events upon H1N1 influenza A virus infection. Additionally, oral RGE treatment for 30 days prior to influenza virus infection significantly decreased the inflammation of the bronchioles compared to non-exposure. Whilst the exact underlying anti-viral mechanisms of ginseng is unknown, authors proposed that ginseng may be able to affect influenza virus disease by antioxidative and immunomodulatory effects.

**Turmeric: More than curcumin**


Alzheimer’s disease (AD) is a chronic, progressive neurodegenerative disorder accounting for 50-60% of all dementia cases. Prevalence is less than 1% below 60-64 years of age but increases exponentially with age to a prevalence of between 25-33% at the age >85 years in the western world. The economic burden of AD was estimated to be $US608bn in 2010 and this, combined with an ageing population and an increasing number of AD cases, means that therapeutics that offer effective, safe and cost-effective treatment with potential to delay disease progression are required.

*Curcuma longa* (turmeric) has a number of medicinal properties including being an antioxidant, anti-inflammatory, anticarcinogenic, hepatoprotective, thrombosuppressive, cardioprotective, vasodilator, antispasmodic, bronchodilator, antidepressant, neuroprotective, hypoglycaemic and anti-arthritic. Whilst numerous compounds have been isolated and studied from turmeric, studies on the curcuminoids have provided the most insight into the understanding of turmeric’s effects in AD. The combination of 3-5% bisdemethoxycurcumin, 15-20% demethoxycurcumin and 75-80% curcumin make up the curcuminoids or curcuminoid mixture. The study highlights the clinical studies demonstrating the neuroprotective potential of the curcuminoids and highlights the contribution of the different curcuminoid constituents. The authors also bring awareness to the fact that some reference to curcumin can vary between studies at times referring to the individual constituent and at other times, making reference to the curcuminoid mixture.

The studies of both curcumin and curcuminoids have revealed numerous effects on different target sites that may have the potential to ameliorate symptoms of AD. In summary, curcumin and curcuminoids have been demonstrated to clear the neurotoxic amyloid-β (Aβ) by promoting its uptake in cell culture systems, inhibit Aβ fibril formation, prevent the cellular insult induced by the Aβ peptide, and have a non-inflammatory phagocytic activity. Additional potential neuroprotective effects of curcumin and/or the curcuminoids include as an antidepressant; protection against aluminium-induced neurotoxicity, ethanol-induced brain damage, sodium-arsenite toxicity, 3-nitropipronic acid-induced toxicity, MPTP toxicity, traumatic brain injury, lead-
induced neurotoxicity, glutamate toxicity and brain focal ischemia; memory improvement by HIV glycoprotein; anti aging; reversal of amyloid pathology and ethanol-induced neurotoxicity; and restoration of the synaptic plasticity.

Only a few studies have investigated the individual components of the curcuminoid mixture finding variable efficacy and potency in different models with no clear supremacy of curcumin over the other two components. Several studies found better results with bisdemethoxycurcumin and demethoxycurcumin compared to curcumin, highlighting the importance of each individual component. Importantly, there is very limited research comparing the efficacy of the curcuminoid mixture to the individual components. Whilst curcumin is the most extensively studied component of turmeric, authors emphasize that no single compound can be a true representative of a plant, reminding of the synergy of constituents.

The authors provide a diagrammatic summary of the potential targets of the curcuminoids in AD which highlights targets against amyloid precursor protein and Aβ activity through reduced apoptosis, inhibition of Nf-kB activation, decreased inflammatory stress, and improvements in neuronal survival; decrease in neurofibrillary tangles and improved cognition via attenuation of muscarinic insufficiency.

The article provides a detailed overview of studies and potential therapeutic targets of curcuminoids in AD, and highlights the distinct differences in activity of the individual compounds of the curcuminoid mixture. As curcumin in clinical studies in AD patients has been investigated with no significant improvement observed, future studies are required to assess the clinical efficacy of the curcuminoid mixture which may produce different outcomes with the different clinical activities of the individual constituents.

Ginger and Sumitriptan go head to head

Migraines are a chronic neurological condition with a high cost to the individual and the healthcare system, not only from medication expenses, but also lost worker productivity and impaired personal function. With a prevalence of 12%, migraines are one of the most common chronic pain disorders.

Although pharmacological management of the condition has improved, many patients prefer to relieve headaches by non-chemical means or OTC due to concerns regarding side effects or apprehensions of dependency.

Zingiber officinale (Ginger) is a native herb of Southeastern Asia that has been widely cultivated abroad. It has many roles in the traditional medicine of various cultures, and has been shown to have inhibitory effects of prostaglandin production and platelet aggregation amongst other properties. Previous studies have shown that OTC medications including ginger alleviated migraine completely in 48% and partially in 34% of sufferers within 2 hours of taking the medication. Case reports have also suggested that ginger may prevent the onset of headache when taken upon the onset of visual aura.

This was a randomised, double-blind clinical trial comparing the efficacy of ginger with sumatriptan in treatment of migraine. 100 study participants who suffered from the condition were enrolled and randomised to two groups. After completing an introductory questionnaire they were given a box of 5 capsules containing 250mg of ginger or 50mg of sumitriptan. Participants were instructed to take one capsule upon headache onset. With each attack they then had to fill in questionnaires assessing timing of onset, severity, timing of drug taking, and self-assessment of response after 30, 60, 90, 120 minutes and 24 hr. The entire study duration was one month, after which patients evaluated overall satisfaction with treatment efficacy and willingness to continue given treatments.

Average number of migraines across the month was 5.8 and 4.9 in the sumatriptan and ginger treated groups respectively. Average time from headache onset to drug taking was around 20 minutes for both groups. Before taking the medication 22% of the sumatriptan group and 20% of the ginger group had severe headaches. Frequency of mean headache severity 2hr after use demonstrated similar effectiveness for sumatriptan and ginger. Pain was reduced from 5.5 and 5.2 (out of 6) in severity down to 3 and 2.5 after 30 min, 1.2 and 1 after 90 min and 0.9 and 0.6 after 2hr for sumatriptan and ginger. Subjective side effects of sumatriptan included dizziness, sedation, vertigo and heartburn. The only adverse effect of ginger reported was dyspepsia. 86% of sumatriptan users reported high or superior satisfaction with treatment, as did 88% of ginger users. 88% and 72% respectively would be inclined to continue use of the product after the trial period.

Overall this study demonstrates that both sumatriptan and ginger powder reduce the severity of migraine headaches significantly within 2 hours of use. The efficacy of ginger was comparable to that of sumatriptan with less adverse effects reported.
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Reviews of medical journal articles

Jodie Tester, Tessa Finney-Brown

These abstracts are brief summaries of articles in recent issues of medical journals. Articles selected are of a general nature for the information of practitioners of herbal medicine. A dominant theme is often present throughout the journals which will be reflected in the reviews.

Safety of antiepileptic medication in breastfeeding

Veiby G, Engelsen B & Gilhus N. 2104. Early child development and exposure to antiepileptic drugs prenatally and through breastfeeding: a prospective cohort study on children of women with epilepsy. JAMA Neurology 70 (11); 1367-1374.

Antiepileptic medications are known to have deleterious effects on the foetus when used in the antenatal period. Mounting evidence implicates these drugs in adverse cognitive, motor and behavioural outcomes of children born to mothers who use them. That said, the costs and benefits of using a medication must always be weighed up, and there are good reasons for women to resume taking these medicines post-birth. Breastfeeding for at least 6 months is well-established as a practice that has beneficial outcomes for the infant. Given all of these factors it is important to examine the effect that antiepileptic medications may have on an infant if a mother takes them whilst breastfeeding.

Researchers took data from the Norwegian Mother and Child Cohort Study (MoBa), which had 108 976 enrolled. Mothers of these children reported on their child’s development at ages 6, 18 and 36 months of age (using standardised and validated scales), and provided detailed information on breastfeeding during the first year.

Of these children, 974 had mothers or fathers with epilepsy. The remaining children of parents without epilepsy served as the reference group. Mothers who had epilepsy provided data about the use of antiepileptic drugs during pregnancy and breastfeeding. Statistical analyses then categorised children according to prenatal and postnatal exposure.

Data 6 months after delivery included 503 children from 490 pregnancies by 441 women with epilepsy. Exposure during pregnancy was reported in 223 children (majority with lamotrigine monotherapy). Another 471 children had a father with epilepsy; 37.6% of whom had used antiepileptic drugs in the 6 months prior to conception.

Referrals to a specialist owing to developmental delay (particularly for fine motor skills and social skills) were increased for children of mothers who used antiepileptic drugs. Risk rates were similar between monotherapy with lamotrigine, valproate and carbamazepine. There was a higher risk with polytherapy. However, continuous breastfeeding during the first 6 months was associated with a tendency toward better developmental outcomes in all domains regardless of maternal antiepileptic drug treatment. Additionally, breastfeeding whilst taking antiepileptic medication was not associated with adverse developmental outcomes at ages 6-36 months.

Although an early study, this suggests that there was no deleterious outcome on development from breastfeeding whilst taking antiepileptic medications. At present, professional recommendation generally recommends caution or avoidance, but practitioners should be aware that this may change over the coming years, as more research data is published in the area.

Maternal fasting glucose in obese women not altered by probiotics


Over the last few years there have been a number of studies suggesting that probiotics may have a beneficial effect on maternal glycaemia in healthy pregnant women. As impaired glucose tolerance (IGT) and gestational diabetes (GDM) are more common in obese women, this is an important population to study. Gestational diabetes has detrimental outcomes for both mother and infant, including pre-eclampsia, shoulder dystocia, neonatal hypoglycaemia and increased risk of type 2 diabetes and cardiovascular disease. Even small reductions in maternal hyperglycaemia may provide significant benefits to pregnancy outcomes and the future health of the infant.

Researchers in Dublin designed a placebo-controlled, double blind, randomised trial of 175 obese pregnant women (BMI 30-39) in order to investigate the effects of a probiotic capsule on fasting glucose concentrations. Those enrolled were randomised to receive a daily probiotic or placebo capsule from 24 to 28 weeks of gestation in addition to regular antenatal care. The composition of the probiotic capsule was 100mg Lactobacillus salivarius UCC118 to achieve a target dose of 109 CFU. This strain has previously demonstrated an ability to transit and persist in the human gastrointestinal tract, and to influence the immune system. Women were instructed to take the capsules after a meal of their choice.

At baseline and again at 28 weeks, maternal fasting glucose was measured as the primary outcome measure...
of the study. This was assessed by intention to treat, and then subsequently via analysis that excluded non-compliers and antibiotic users. Women also undertook an oral glucose tolerance test at the end of the study period. Other outcomes assessed included the incidence of GDM and neonatal anthropometric measures. In addition, women were asked to complete 3 day diet diaries and a lifestyle questionnaire during the study period.

At the conclusion of the study intent-to-treat analysis was performed for 138 subjects. There was no significant difference between the active treatment group and the placebo. In addition, outcomes were similar for each group with regards to incidence of GDM or IGT and neonatal anthropometric measures.

Given that the two previous trials investigating probiotics and maternal glycaemia were conducted in glucose-tolerant non-obese women, the researchers hypothesise that the women in this trial may have had a degree of insulin resistance prior to enrolment. There may also have been genetic differences in response between the Finnish and Irish cohorts. Previous trials used a different probiotic strain, and had longer durations of treatment, both of which are likely to have made a difference to outcomes. One of the previous trials combined a probiotic with dietary counselling which was not provided here – this would have undoubtedly had some effect.

In conclusion, this study did not demonstrate effects of a probiotic intervention on maternal glycaemia in obese women, despite previous studies demonstrating positive results in non-obese women. Clinicians should be cautious about attempting to translate the results of clinical trials between metabolically different populations.

**Vitamin C supplementation for pregnant smokers and neonatal outcomes**


It is well established that maternal smoking has adverse effects on offspring, including lifelong decreases in pulmonary function and increased asthma risk. The nicotine in cigarette smoke crosses the placenta, upregulating nicotinic receptors in the foetus and contributing to altered lung development. As 50% of smokers who become pregnant continue to smoke (corresponding to 12% of pregnancies), it is important to develop strategies to minimise effects on the foetus. Whilst the ideal solution is smoking cessation, this may not be possible for all women. Studies in non-human primates have shown that vitamin C has the potential to decrease the effects of maternal smoking on newborn pulmonary function test results. This is the first trial in humans to examine the same intervention.

The study was a randomised, double-blind, placebo-controlled comparison of 500mg/d of vitamin C vs placebo in179 pregnant smokers. A group of pregnant non-smokers was prospectively studied as a reference group. Each pregnant woman in the trial smoked more than 1 cigarette daily and had declined smoking cessation. Each pregnancy was a singleton of 22 weeks or less, and there were no major foetal anomalies or concurrent alcohol or illicit drug use. Participants were randomised to take 500mg ascorbic acid or placebo once daily. This dose was chosen as data indicated that it was likely to saturate receptors and maximise plasma concentrations. All groups also took a prenatal vitamin containing 60mg Vitamin C.

The primary outcome of the study was newborn pulmonary function tests (PFTs) (within 72hrs of birth), with secondary outcome measures including the respiratory outcomes of the infants through 1 year and pulmonary function tests at 1 year. The incidence of wheezing was also determined. Newborn PFTs were completed during quiet sleep, supine position and breathing through a face mask using a standard operating procedure. Statistical analyses were based on intention to treat.

The newborns delivered to smokers taking vitamin C demonstrated a significantly increased peak tidal expiratory flow to expiratory time (TPTEF:TE) ratio and passive respiratory compliance per kg (Crs/kg) compared to placebo. Their results approached (but did not match) those of neonates born to non-smokers. Clinical respiratory follow-up for secondary outcomes was obtained for 92% of the infants. The incidence of wheezing the first year was 21% compared with 40% in the active vs. placebo groups, and fewer infants of those treated with vitamin C required medication for wheezing. After one year, respiratory compliance was higher in the infants of the treatment group (compared to placebo), but did not reach statistical significance, and no other parameters were significant different. This may mean that effects of supplementation on PFT was transient, however, one of the key effects of maternal smoking on infant PFTs is a reduction in forced expiratory flows, which were not measured in this study.

After the study was underway, a subgroup of mothers were genotyped for 2 nAChR and 3 glutathione transferase polymorphisms associated with smoking and lung disease. Maternal genotype for rs16969968 significantly affected offspring pulmonary function. In this subgroup, infants of mother randomised to Vitamin C had significantly less incidence of wheezing in the first year compared to those on placebo (14% v 48%). However, there were a relatively small number of women who were homozygous for this polymorphism.

The researchers suggest that vitamin C may act as an antioxidant, thus blocking free radical stimulation of...
abnormal patterns of airway cell proliferation that lead to abnormal airway geometry and narrowed airways.

Whilst it is clearly important to counsel pregnant women on smoking cessation, this study suggests that vitamin C supplementation may be an inexpensive and simple approach to ameliorate some of the effects of smoking on neonatal pulmonary function and infant respiratory morbidities.

**Insomnia and subsequent risk of stroke**


Patients rarely present to a clinician with a sole complaint, and insomnia and cardiovascular disease (CVD) commonly coexist. Research is just beginning to examine the correlations between sleep and CVD outcomes, but has focused mainly on sleep apnoea and sleep disordered breathing, along with sleep duration. Some small studies have displayed correlations between insomnia and stroke, but were not longitudinal, making it difficult to determine whether insomnia was an antecedent to the development of stroke.

This research was designed as a longitudinal analysis (over 4 years) of Taiwanese health data to assess the influence of insomnia on subsequent hospitalisation for stroke. Different patterns of insomnia were also evaluated.

This was a retrospective cohort study, and included a case cohort (of those who suffered insomnia) and a comparison cohort (3 people matched for age and sex for each of those in the case cohort), based on claims made in the Longitudinal Health Insurance Database 2000. Those with sleep apnoea were excluded, in attempts to avoid confounding effects. Each individual in the study was tracked from their index enrolment date until death or the end of the 4 year follow-up. Insomnia diagnosis was made using the International Classification of Diseases, Ninth Revision, Clinical Modification. Those with the condition were then categorised into the following subgroups:

- Persistent insomnia (>180 days)
- Relapse in insomnia
- Insomnia in remission

The primary outcome measure was hospitalisation for acute stroke (haemorrhagic or ischaemic), transient ischaemic attack or acute but ill-defined cerebrovascular disease.

Overall the study examined the data of 21 438 subjects with insomnia and 64 314 crossmatched subjects without insomnia. Mean age was 51-52. During the 4 years of follow-up there were 583 stroke admissions among the insomniacs and 962 among non-insomniacs. Adjusted for the amount of people in the cohort, this correlated to a 54% higher chance of developing stroke in insomniacs (adjusted hazard ratio, 1.54; 95% confidence interval, 1.38–1.72). The incidence rate ratio (IRR) for stroke in insomniac-to-noninsomniacs decreased as age advanced, with the higher IRR in those aged 18 – 34.

Subgroup analysis showed that persistent insomniacs had a higher 3 year cumulative incidence rate of stroke than those with insomnia in remission. However, these hazard rations were attenuated and became similar after adjusting for comorbidities, socioeconomic status, sex and older age. The highest ratios of incidence varied by type of stroke, being highest in TIA, followed by unspecified stroke, ischaemia and haemorrhage.

This study is one of the first to point to suggest that insomnia may be an antecedent to stroke. This risk may be higher with increasing severity of insomnia, but further research is needed to confirm associations. Potential pathophysiological explanations of the correlation may include increased inflammation, endocrine or metabolic dysregulation or increased SNS activity in insomnia.

Limitations to the study include the possibility that some of those with insomnia had not sought treatment for it, and thus the true effect might be greater than identified. Also, given that this was using a pre-existing dataset there may have been coding errors in the initial entries, thus skewing research results. Finally, some data that has an impact on stroke risk was not available from the NHI Research Database, including smoking status, physical inactivity and work stress.

This research identifies an interesting link between insomnia and CVD, and provides increased incentive for practitioners to identify and treat insomnia in their clients. Further investigation is needed to determine the effects such preventative health activity has on the end-point outcomes of CVD, notably stroke and myocardial infarction.

Conclusions: Insomnia predisposes individuals to increased risk of stroke and this association is profound among young adults. Our results underscore the clinical importance of identifying and treating insomnia. A novel behavioral intervention targeting insomnia that may prevent stroke should be explored.

**Micronutrients for adults with ADHD**


The prevalence of attention-deficit hyperactivity disorder (ADHD) in adults is estimated to be between 4-5%. Response to ADHD medications is typically lower in adults compared to children, and comorbid conditions may lower the therapeutic response further. An expanding evidence base around the role of micronutrients in the pathophysiology and management of psychiatric symptoms of mood, stress and autism support a potential role in ADHD treatment, however most research has looked at individual nutrients. This study presents the
first double-blind, placebo-controlled, parallel-group randomised controlled trial investigating the efficacy and safety of a broad-spectrum micronutrient formula in medication-free adults with ADHD.

Participants over 16 years were recruited from Canterbury, New Zealand and were required to meet criteria for ADHD according to the DSM-IV if over 18, and if under 18 (n=7) criteria to the Schedule for Affective Disorders and Schizophrenia for School-Aged Children – Present and Lifetime Version. In total, 80 participants were allocated to receive either micronutrients (EMPowerplus) or placebo and were to titrate their dose up over a week to 15 capsules per day, in three doses of 5 capsules, taken with food and water. Only individuals not taking psychiatric medications were considered. Participants were allowed to continue psychological therapies and other nutritional supplements if the dose and intensity remained constant throughout the duration of the study. Medications for physical conditions were considered individually but generally allowed (n=2 birth-control pills; 1= thyroid; 1=statin). Exclusion criteria included neurological disorders involving brain or central nervous system function, pregnancy or breastfeeding, untreated or unstable thyroid disease, conditions of abnormal mineral metabolism, abnormal baseline biochemistry or serious risk of suicide or violence. Participants with other Axis I disorders according to the DSM-IV-TR Axis I Disorders, which assesses whether another psychiatric disorders could account better for the ADHD symptoms, were also eligible for inclusion in the trial. Participants were followed up at weeks 1, 2, 4, 6 and 8 (end of study) after baseline at which points a clinician completed a range of assessment measures. At baseline and 8 weeks, patients completed a self-report and patients were requested to have an observer (family, spouse or friend) also complete a report at baseline and 8 weeks.

The study found that the micronutrient treatment resulted in statistically significant improvements in several indices from ADHD symptoms to global assessment of functioning compared with placebo. Participants taking the micronutrient formula reported greater improvement in both inattention and hyperactivity/impulsivity with observers also noting improvement in hyperactivity/impulsivity. Clinicians did not find differences between the groups using ADHD-rating scales, however rated those receiving micronutrients as more improved than placebo both globally and on ADHD symptoms. A post-hoc analysis also found a significant benefit of micronutrients for adults with moderate to severe depression. The micronutrient formula was well tolerated with good compliance rates overall.

The study highlights some of the challenges in reporting improvements of functioning with ADHD symptoms and a strength of the study is having the three reports from the patient, the clinician and the reporter. The authors note that a recent meta-analysis found that self-ratings were more consistent across studies than observer ratings in ASHD studies and therefore, despite clinicians generally being viewed as having the greatest objectivity, one should not discount the findings of the participants. This study reflects a true-clinical setting experience, which gives relevance and meaning to its findings. The inclusion of participants with other Axis I disorders limits its generalisability to individuals with uncomplicated ADHD, however is more in line with real world clinical experiences.

Whilst the results should be interpreted with caution given the inconsistencies across raters, this study provides a good basis for undertaking further trials on multi-nutrient treatment for a variety of psychiatric symptoms including adults with ADHD. Future trials of longer duration and varying dosing schedules will provide more useful information. Details on multivitamin formula used in the study can be found here: https://store.truehope.com/_documents/EMPower_Capsules_Facts_Sheet.pdf

**Mechanism for microbiota influence of cholesterol metabolism and weight**

Joyce SA, MacSherry J, Casey PG, Kinsella M, Murphy EF, Shanahan F, Hill C, Gahan CG. 2014. Regulation of host weight gain and lipid metabolism by bacterial bile acid modification in the gut. PNAS. In press. DOI:10.1073/pnas.1323599111

Alterations in gastrointestinal microbiota have been implicated in obesity in mice and humans and is known to influence adiposity and weight gain in the host. The key mechanism by which gut microorganisms influence host metabolism and adiposity remain unclear. Whilst significant advances have increased understanding of the genetic content of the human gut microbiome, there is a great challenge in categorising both gut-specific and gut-enriched microbial activities.

Bile acids are the main functional component of bile secretions, which play a significant role in the emulsification of dietary lipids, whilst also acting as signalling molecules in the host. The gastrointestinal microbiota composition is influenced by bile salts and in turn, bile salts themselves are chemically modified in the gut by bacterial enzymes such as bacterial bile salt hydrolase (BSH). It is thus suggested that bile acids can be considered as a mediator of reciprocal microbe-host cross talk.

BSH enzymes in the gut play an important role in the metabolism of bile acids, cleaving an amino acid to generate unconjugated bile acids which then undergo further bacterial modification to produce secondary bile acids. Previous research has demonstrated that BSH activity is unique to gut-associated microbiota. Authors of the present study aimed to gain further understanding of BSH activities and its influence on host metabolism and weight gain, through a series of in vivo experiments in mouse models.

The research found that the gut-specific bacterial...
enzyme, BSH, is capable of directing local and systemic gene-expression profiles in metabolic pathways that influence weight gain and adiposity in the host. By selectively elevating BSH levels in conventionally raised mice with a normal microbiota, the study demonstrated BSH can modify plasma bile acid profiles which can influence pathways governing lipid metabolism, metabolic signalling events, circadian rhythm and immune function. Additionally, elevated BSH activity was seen to reduce weight gain, serum cholesterol and liver triglycerides in the mouse models.

This study provides a greater understanding into the role of BSH and its ability to impact on host metabolism and weight. Prior to this study, the functional impact of individual bacterial bile acid modifications on the host were not well understood, and this research provides insight into some of the physiological consequences that may arise from dysbiosis of the microbiota. As a major regulator of host physiological processes and mediator of a microbe-host interaction, BSH activity may represent a target for obesity related therapies.

From a clinical practice perspective, the authors rationalise that as many probiotic bacteria possess potent BSH activity, the current work provides reason for the inclusion of probiotic bacteria in treatment for control of obesity, hypercholesterolemia and metabolic syndrome. Whilst more studies are required demonstrating these effects in humans, the appropriate use of probiotics for these conditions is worthy of consideration.

**Fast food intake and asthma, rhinoconjunctivitis and eczema in childhood**


The International Study of Asthma and Allergies in Childhood (ISAAC) is a multicentre, multiphase, cross-sectional study to investigate asthma, rhinitis and eczema in childhood. Previous analyses of data from the ISAAC study have revealed an association of sugar consumption in the perinatal period and symptoms of severe asthma in 6-7 year old children; frequent consumption of fruit, vegetable and fish to be associated with lower lifetime prevalence of asthma; high burger consumption associated with higher lifetime asthma prevalence; and a strong association of high calorie intake from cereal and rice and protein from cereal and nuts with decreased symptom prevalence. The current study aimed to investigate the associations between the prevalence of current and severe symptoms of asthma, rhinoconjunctivitis and eczema and food intake over the past year in two age groups of school children, specifically 6-7 year olds and 13-14 year old adolescents.

Subjects were selected from a random sample of schools in a defined geographical area and used standardised core written questionnaires as well as optional environmental questionnaires (EQ) to test a number of specific aetiological hypotheses. The EQ diet questions focused on foods that were possibly protective/risk factors based on previous ISAAC findings. Questionnaires were self-completed by adolescents and by the parents of the children. Final analyses were adjusted and covariates and other potential confounders.

Data for 319,196 adolescents from 107 centres in 51 countries and 181,631 children from 64 centres in 31 countries was available for dietary analysis, however different multivariate analyses involved differing numbers based on the amount of complete data available for the specific outcome and diet variables.

For adolescents, fruit intake was inversely associated with current wheeze, severe asthma, severe rhinoconjunctivitis and severe eczema; milk intake was inversely associated with current wheeze, severe asthma and current and severe rhinoconjunctivitis; and vegetable consumption was inversely associated with current wheeze. A positive association was observed for all three conditions (current and severe) with intake of butter, fast food, margarine and past ≥3 times per week, with the strongest association being found with fast food. Seafood showed a positive association with severe asthma, current and severe rhinoconjunctivitis, and current and severe eczema.

For children, consumption of eggs, fruit, meat and milk ≥3 times per week were inversely associated with all three conditions (current and severe). Vegetable consumption at least once of twice per week was inversely associated with current and severe wheeze and rhinoconjunctivitis, and ≥3 times per week was inversely associated with severe eczema. Fast food at least once or twice per week was positively associated with current wheeze, and ≥3 times per week with current and severe rhinoconjunctivitis and severe eczema.

After controlling for potential confounders, fast food intake was consistently positively associated across all centres and both age groups with current and severe symptom prevalence of wheeze, rhinoconjunctivitis and asthma whilst regular fruit and vegetable consumption seemed to have a protective effect. The authors proposed several biologically plausible mechanisms for the inverse relationship between fast food consumption and asthmatic and allergic disease including higher saturated fatty acids, trans fatty acids, sodium, carbohydrate and sugar levels of fast foods and possibly preservatives.

The size of these scale with its high numbers are a strength of the study, however numerous weaknesses require the results to be interpreted with caution. If the findings however can be further investigated to establish a causal association between fast food intake and the prevalence of symptoms of asthma, rhinoconjunctivitis
and eczema, the results are of major public health significance.

**Paracetamol use during pregnancy**


Acetaminophen (paracetamol) is one the most commonly used over the counter (OTC) medications for pain and fever, and since product marketing commenced in the 1950’s, its use as a safe OTC drug during pregnancy has continuously increased. More than 50% of pregnant women from USA and Denmark report use of acetaminophen during pregnancy. Despite its high use throughout pregnancy, recent studies have suggested that acetaminophen has endocrine-disrupting properties. Prenatal exposure to endocrine disrupters may affect neurodevelopment and contribute to behavioural dysfunction.

The aetiology of attention-deficit/hyperactivity disorder (ADHD) and hyperkinetic disorder (HKD), a severe form of ADHD, is not well understood but genetic and environmental factors are thought to contribute. Given the increasing prevalence of childhood neurodevelopment disorders including ADHD, this study evaluated the risk for developing ADHD-like behaviours at age 7 years, including a HKD diagnosis or use of ADHD medications on more than two occasions, after foetal exposure to acetaminophen.

The Danish National Birth Cohort (DNBC) was used to identify the study population. The DNBC is a nationwide cohort of pregnancies and children established to study causes of pregnancy complications and diseases in offspring in early life, with a focus on adverse events from medications and infections. Using pregnancies from the DNBC, acetaminophen use during pregnancy was assessed prospectively via three computer-assisted telephone interviews during pregnancy and 6 months after childbirth. Telephone interviews were conducted at 12 and 30 weeks gestation and 6 months after birth. Parental reports of children’s ADHD-like behaviours were based on the standardised Strengths and Difficulties Questionnaire (SDQ) based on the information mothers/caregivers had provided about their 7 year olds’ behaviour as part of the DNBC follow up. HKD diagnosis was identified for children on or after their fifth birthday, as per Danish National Hospital records and the Danish Psychiatric Central Registries. ADHD medication was identified using national prescribing data for children that had filled two or more scripts for ADHD medications including methylphenidate, atomoxetine or modafinil.

Of the 101,041 pregnancies enrolled in the DNBC, 64,322 were included for the cohort for analyses of HKD diagnosis and ADHD medication and a total of 40,916 pregnancies included in the cohort for analysis with reported SDQ behavioural outcomes available as reported by primary caregiver. More than half of the mothers reported ever use of acetaminophen during pregnancy for both cohorts. An increased risk for ADHD-like behaviours at age 7 years was observed with maternal use of acetaminophen use during pregnancy. Prenatal exposure to acetaminophen also increased the risk of an HKD diagnosis or ADHD medications. The associations were stronger for acetaminophen use in more than one trimester, with exposure response trends with increasing frequency of use throughout pregnancy. Confounding factors were considered and accounted for in the analyses and results did not appear to be influenced by maternal inflammation, infection during pregnancy, maternal mental health, or other confounders evaluated.

Strengths of the study include the large numbers of subjects available and the information collected in a prospective manner to minimise recall and selection bias. Additionally, the multiple endpoints of parent’s assessment of behaviour combined with hospital diagnosis of HKD and ADHD medication use add strength to the study. Limitations include data about dosage or number of pills taken, or specific week or gestation exposure in some accounts not being available for inclusion in the analysis, which would have provided greater understanding. Despite adjusting for potential confounders, the possibility of other factors including ADHD-genetic factors, exposure to other medications, and residual confounding for the indication of acetaminophen use in the ADHD developments cannot be dismissed.

This is an important and relevant study and if the results do indeed reflect a causal association, acetaminophen should not be considered as a safe drug in pregnancy. Authors concluded that exposure to acetaminophen may increase the risk for HKDs and ADHD-like behaviours in children, however investigations to further understand the association are needed.
AJHM based CPE Questionaire

The AJHM based CPE questionnaire system is a voluntary system designed to assist members in the accumulation of NHAA CPE points. Questions are divided into the appropriate subject categories (herbal medicine and medical science) and each question refers to an article in this issue of the Australian Journal of Herbal Medicine. Points accumulated through completion of these questions should be recorded in the NHAA CPE diary. Each completed question is worth one mark in the relevant category. Your completed CPE diary should be returned with your membership renewal at the end of the financial year. For further information please see the NHAA CPE Member’s Manual on the NHAA website www.nhaa.org.au.

Herbal medicine questions – AJHM 26(3)

1. With reference to the study on curcuminoids in Alzheimer’s disease, which of the following statements is incorrect?
   a) Therapeutic activity of curcuminoids in AD may target amyloid precursor protein and Aβ activity, decrease in neurofibrillary tangles and improved cognition via attenuation of muscarinic insufficiency
   b) Curcuminoids are the combination of 3-5% bisdemethoxycurcumin, 15-20% demethoxycurcumin and 75-80% curcumin
   c) Research into the individual curcuminoid components have found variable efficacy and potency with no clear supremacy of curcumin over the other two components
   d) No studies as yet have found better results with bisdemethoxycurcumin and demethoxycurcumin compared to curcumin

2. In the study reporting the immunomodulatory effects of ginseng against influenza A virus infection, which of the following statements is incorrect?
   a) RGE may improve viability of human epithelial cells, suppress inflammatory responses in lung alveolar epithelial cells and may interfere with oxidative stress events upon H1N1 influenza A virus infection
   b) The study concluded the underlying anti-viral mechanisms of ginseng in its affect against influenza virus disease is by antioxidative and immunomodulatory effects
   c) Oral RGE treatment for 30 days prior to influenza virus infection significantly decreased the inflammation of the bronchioles compared to non-exposure
   d) RGE was administered to mice at a dose of 25mg/kg for 30 days

3. With reference to the study investigating curcumin in major depressive disorder, which of the following statements is correct?
   a) Curcumin was provided as a 500mg capsule containing curcumin and volatile oils only from C. longa rhizomes
   b) Highest response was in the fluoxetine/curcumin group at 77.8% compared to fluoxetine 64.7% and curcumin 62.5%, which was found to be statistically significant
   c) Curcumin was found to be equivalent to fluoxetine in terms of change in HAM-D17 scores
   d) The fluoxetine/curcumin group reported a higher number included a reported case of serotonin syndrome associated with combination therapy

4. The study comparing Chamomilla matricaria (chamomile) to mefenamic acid (MA) for premenstrual syndrome found:
   a) Chamomile to be more effective than MA on reducing the overall intensity of symptoms and particularly psychological symptoms associated with PMS
   b) Chamomile to be equally effective as MA on reducing the overall intensity of symptoms, psychological symptoms and physical symptoms associated with PMS
   c) Chamomile to be more effective than MA on reducing the overall intensity of symptoms and particularly physical symptoms associated with PMS
   d) Chamomile to be less effective than MA on reducing the overall intensity of symptoms and particularly psychological symptoms associated with PMS

Medical science questions – AJHM 26(3)

1. The double-blind, placebo controlled trial on micronutrient supplementation in adults with ADHD found:
   a) A post-hoc analysis also found a significant benefit of micronutrients for adults with mild to moderate depression
   b) The inclusion of participants with other Axis I disorders limits its generalizability to individuals with uncomplicated ADHD
   c) Clinicians found differences between the groups using ADHD-rating scales
   d) Observers reported that those taking the micronutrient formula had greater improvement in both inattention and hyperactivity/impulsivity

2. With reference to the study investigating the influence of the microbiota on cholesterol metabolism and weight, which of the following statements is incorrect?
   a) BSH is capable of directing local and systemic gene-expression profiles in metabolic pathways which influence weight gain and adiposity in the host
   b) The gastrointestinal microbiota composition is influenced by bile salts and bile salts themselves are chemically modified by bacterial enzymes in the gut, including bacterial bile salt hydrolase
   c) BSH can modify plasma bile acid profiles which can influence pathways governing lipid metabolism, metabolic signalling events, circadian rhythm and immune function
   d) Elevated BSH activity was seen to reduce weight gain, serum cholesterol, fasting blood sugar levels and liver triglycerides in the mouse models
3. Regarding the ISAAC study investigating asthma, rhinitis and eczema in childhood and food, which of the following statements are correct (more than one may apply)?
   a) Milk intake was inversely associated with current wheeze, severe asthma and current and severe rhinoconjunctivitis in adolescents
   b) For children, consumption of eggs, fruit, meat and milk ≥1 times per week were inversely associated with all three conditions (current and severe)
   c) Milk intake was positively associated with current wheeze, severe asthma and current and severe rhinoconjunctivitis in adolescents
   d) For children, consumption of eggs, fruit, meat and milk ≥3 times per week were inversely associated with all three conditions (current and severe)

4. In the Danish study reviewing acetaminophen use during pregnancy, which of the following points is incorrect?
   a) More than half of the mothers reported use of acetaminophen during pregnancy
   b) An increased risk for ADHD-like behaviours at age 7 years was observed with maternal use of acetaminophen use during pregnancy
   c) Prenatal exposure to acetaminophen also increased the risk of an HKD diagnosis or ADHD medications
   d) A causal association between acetaminophen and ADHD behaviours was established and as such, acetaminophen should not be considered as a safe drug in pregnancy
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