Volume 30 • Issue 1 • **2018**

Australian Journal of Herbal and Naturopathic Medicine

A publication of the NHAA

Australian Journal of Herbal and Naturopathic Medicine

naturopaths & herbalists association of australia

The NHAA is a peak professional association representing appropriately qualified naturopathic and Western herbal medicine practitioners. A foundation member of the World Naturopathic Federation and founded in 1920, it is a member-based association, the oldest professional association of complementary therapists in Australia and the only national professional association specifically concerned with the practice and education of Western herbal medicine (WHM) in Australia. Our mission is to support naturopaths and Western herbal medicine practitioners to deliver excellence in healthcare in Australia and our vision is naturopathy and Western herbal medicine for the health of Australia.

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Design of electronic platform and layout for hard copy Gordon McDade

Copy editing Rachel Hoare

ISSN 2209-119X ABN 25 000 009 932 PP 23692/00006

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Editorial: Developing intellectual capacity in Naturopathy and Herbal Medicine practice

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When we look back on these times, we are likely to recognise that this was a time of transition, of change for both herbalists and naturopaths. With minimum degree qualifications, our professions are moving towards academia, developing our critical thinking abilities, identifying our strengths and limitations, recognising different agendas, and becoming transparent, accountable, responsible and reliable. Academia brings a different type of rigour that complements our great artisan and technical skills — not only are we able to craft an ideal remedy, we are able to explain why from different perspectives, to demonstrate an in-depth understanding of how our practices fit into the *Improving the Health of All Australians* agenda, present our case, contribute to debate and shape health policy. Although academia may not be the only way forward, academic capacity is necessary in order to claim our place in the health care landscape as complete disciplines, as naturopaths and herbalists, and to prevent fracturing, or parts of our disciplines being claimed by others. And to meet other disciplines in similar roles on an even playing field.

As thinking human beings, we often find it easier to understand new ideas if we deconstruct the whole and identify core concepts as separate parts. Our understanding of the new kid on the block, academia, has been identified as a separate idea and is often contextualised separate to traditional wisdom. We sometimes identify as being practitioners that incorporate traditional knowledge and scientific evidence (the category in which academia tends to fall)[1]. But the reality of academia is actually more than just another separate part. It involves simultaneous combinations of traditional ideas and different types of evidence and methods of enquiry in much the same way as one of our unique practice characteristics, synergy (the overall effect being greater than the sum of parts). Academia at its core involves groups of people and developing an overarching, in-depth understanding, combining what is already known, testing new ideas and ultimately providing time and space to consider, contemplate, incorporate (or reject) ideas and develop holistic, complex, critiqued and documented solutions. This is the promise of academia and it brings a new formality to naturopathy and herbal medicine.

Academic thought is often structured using a 'problem-solving' model. First a problem is identified, a question is asked and then a solution is sought. The final solution accounts for human engagement and explains how the people involved might have influenced the process and the solution. This involves detailed description of bias including the cognitive biases or the values and beliefs of the question asker and the investigator. Methods of investigation are employed to mitigate all types of bias. These methods or strategies are critiqued by others that are often outside the boundaries of the discipline in question; comments from critique can develop new perspectives and add dimension to solutions. Identifying and declaring potential and actual bias and peer review is what makes an answer transparent. As human beings, we obviously influence the types of questions we ask and the way that we go about solving a problem, being transparent means declaring our inherent biases, using methods to mitigate our influence, seek inside and outside opinion and declare bias in the context of the solution. It doesn't necessarily mean that all ideas are rejected due to bias, it means that solutions are provided with bias in mind, and that readers or recipients can trust that the enquiry was undertaken without any hidden agenda other than revealing the truth. This transparency imbues trust.

It is interesting to reflect upon our cognitive biases as professions. One of our wise elders, Dr Karen Bridgeman, a teacher of naturopathic philosophy in the 1990s observed that we, as a profession, have defined ourselves as being alternative, as having different ideas that are separate to the mainstream[2]. People were attracted to naturopathy and herbal medicine as an alternative to mainstream; we flourished in an era that valued original and free thought, creativity and rebellion — pushed the limits. From here we can understand our resistance to mainstream ideas and ideals, developed within mainstream institutions; they go against the grain of our 'alternative' identity. This value of being alternative or different may inform one of our cognitive biases towards academia, that academia, as a mainstream method for developing thought, is not able to fulfil our aspirations of being different and may not preserve our unique identity, recognise and celebrate our individuality and complexity. And there has been resistance to the idea of building our capacity

via mainstream academic frameworks[3]. However, within an academic framework, other disciplines including nursing, pharmacy and medicine and those more diverse areas such as business[4], teaching[5], computer science[6] and law[7] have all embraced some of our alternative ideas. It is somewhat ironic that our contribution to discourse that has shaped the current world has been limited due to our lack of place in academia and yet some our ideas are shaping up as being central to defining this era in which we live. Our core ideas about holism and synergy are considered, critiqued and reviewed by peers and are becoming embedded within other disciplines. In order to engage, contribute and claim our place, it is imperative that we build our academic thought capacity. This means recognising and accounting for our inherent biases, demonstrating transparency and building trust.

The NHAA is unambiguous in supporting the development of academic capacity in naturopathy and herbal medicine. This is demonstrated by:

1. The NHAA international conference, which requires presenters to submit an abstract for peer review and critique prior to acceptance for presentation;
2. A journal where articles are peer reviewed by members and by those in diverse disciplines;
3. Maintaining a Conflict of Interest Register; and
4. Ensuring that future members are degree-qualified.

As the editor and in the interests of transparency I have a potential conflict of interest to declare. I have accepted a position with a college that delivers a Bachelor of Health Science (Naturopathy) degree. Although it is fairly common for editors of peer-reviewed journals to hold concurrent positions in academic institutions, there is a risk of bias inherent in the decision to publish articles from certain individuals or academic teams. In order to mitigate this bias, like other peer-reviewed journals, articles are subjected to critique and review before publication. The peer-review process includes the editorial board and review by others outside our disciplines. The peer-review process is documented and reported.

In this first issue of 2018, you will find a synopsis of the article "Evidence based practice in traditional and complementary medicine: An agenda for policy, practice, education and research" by academic naturopaths Matthew Leach and Rachel Canaway and GP Jennifer Hunter. This article is likely to be retrospectively viewed as instrumental in guiding the new direction of naturopathy. This issue further explores the role of herbal medicine and naturopathy in the management of three serious chronic diseases: hepatitis C, cancer and skin disease. I am very excited to publish the results of a much-anticipated investigation into the effectiveness of naturopathy and herbal medicine for people with chronic hepatitis C. This was an original research project and demonstrated significant effectiveness for a combined herbal treatment against a single herb and placebo for normalising the liver enzyme ALT and improving quality of life in people with chronic hepatitis C infection. It demonstrates a collaborative research effort, which involved naturopathic researchers and clinicians and medical teams. The investigation took place in hospital settings and this work sets the scene for the delivery of naturopathy as an integral component in health care for the management of people with chronic hepatitis C infection. The commentary on diets in cancer is another example of naturopathy being delivered within the context of conventional management. These presentations help us develop our place in health care. This edition includes a case study from a student of naturopathy about chronic skin disease in a stressed woman. This case explains what naturopathy can add to the management of complex conditions with physical, psychological and social components.

Jodie Tester has again been hard at work summarising the literature and has provided an interesting synopsis of 14 different studies. MedPlant has a focus on one of my (and perhaps your) favourite herbal medicines *Withania somnifera* (ashwagandha), and a few studies measured the effects of herbal medicines on improved central nervous system function, something at hand which may give us an edge in the process of developing our academic capacity. Enjoy.

References

1. Wardle JL *et al*. Current challenges and future directions for naturopathic medicine in Australia: a qualitative examination of perceptions and experiences from grassroots practice. BMC Complement Altern Med 2013;13(1):15.
2. Bridgeman DK. Clinical studies lectures, s.o.A.D.o.N. Australasian College of Natural Therapies, Clinical Studies Year four Editor. 1997.
3. Jagtenberg T *et al*. Evidence-based medicine and naturopathy. J Altern Complement Med 2006;12(3):323–328.
4. Pittaway L, Cope J. Entrepreneurship education: a systematic review of the evidence. International Small Business Journal 2007;25(5):479–510.
5. Rasiah RRV The Impact of Holistic Education Approaches on First-Year Experience of Business Undergraduates: Promoting Interactive and Creative Learning Environments. In Taylor's 7th Teaching and Learning Conference 2014 Proceedings. Springer; 2015.
6. Pullin AS, Knight TM, Watkinson AR. Linking reductionist science and holistic policy using systematic reviews: unpacking environmental policy questions to construct an evidence-based framework. J Appl Ecol 2009;46(5):970–975.
7. Singer JB. Dispute resolution and the post-divorce family: Implications of a paradigm shift. Fam Court Rev 2009;47(3):363–370.

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Post cancer diagnosis diets

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Abstract

Cancer is one of the main health burdens in developed countries. The increasing cancer survival rate has seen more people now living after cancer diagnosis and for longer. This brings with it a myriad of different requirements for these people. One area that is highly debated is the nutritional advice given to patients after cancer diagnosis and cancer treatment. Research on dietary regimens post-cancer treatment have had varied opinions, which can cause confusion for patients as well as health practitioners. Examining the research on post diagnosis has found that after people are diagnosed with cancer, it provides an opportunity for health practitioners to assist change, as it is seen as a 'teachable moment'. This means that a majority of cancer patients are open to change once they have been diagnosed. Health practitioners are very well placed to assist these patients to bring about changes in both their diet and lifestyle. However, having the current knowledge behind the correct dietary advice is extremely important. What has been well established is that the Western diet is detrimental and a healthy, unprocessed/prudent diet has been found to be beneficial.

Keywords: Cancer, diet, healthy diet, ketogenic diet.

Cancer consists of a diverse group of diseases, although it is commonly thought of as only one disease. Currently in Australia, it is estimated that 138,321 new cases of cancer diagnosis will occur in 2018, with approximately 50,000 deaths anticipated. The current survival rate from 2009 to 2013 is 68%, showing that more people are surviving cancer diagnosis and treatment[1]. According to the World Cancer Research Fund/American Institute for Cancer Research, a third of the most common cancers could be avoided through changing lifestyle and dietary habits in developed countries[2]. Certain dietary patterns have been well established to be preventative, such as increased vegetable and fruit intake[3]; however, it is the diet post-cancer diagnosis and treatment that most practitioners and patients focus on.

A cancer diagnosis for a majority of people creates a motivation for change and can be seen as a 'teachable moment' for dietary and lifestyle changes to reduce the risk of adverse health outcomes[4]. This motivation and moment creates an opportunity for health practitioners to assist patients to make sustainable and effective lifestyle changes which should increase their quality of life, reduce the risk of recurrence, co-morbidities and possible death[5].

For a majority of people, diet quality and quantity as well as certain lifestyle choices such as exercise, smoking and alcohol consumption are modifiable lifestyle factors[5,6]. Research on dietary interventions post-cancer diagnosis is important for each type of cancer as they are all different diseases; however, a number of common dietary recommendation factors cross all cancers. These include diets that reduce inflammation[7], avoiding a Western diet and consuming a healthy/prudent diet[8] and reducing blood glucose levels[9]. Therefore, increasing foods and culinary herbs that have anti-inflammatory properties and low glycaemic index are beneficial for people post-cancer diagnosis.

A recent laboratory-based *in vitro* study examined the inhibitory effects of culinary herbs and spices on the growth of a colorectal cancer cell line[10]. The culinary herbs chosen for this study included bay leaf (*Laurus nobilis*), rosemary (*Rosmarinus officinalis*), sage (*Salvia officinalis*), ginger (*Zingiber officinale*) and turmeric (*Curcuma longa*). The authors concluded from all the experiments they undertook that both individual and combinations of these herbs significantly inhibited the growth, via apoptosis, of the colorectal cancer cells. Combining several of these herbs could produce particularly beneficial growth inhibitory and anti-inflammatory effects on cancer cells[10].

The Western diet is also a main focus, with a recent prevalence study highlighting the consumption of highly processed foods and increased risk of cancer[8]. Highly or ultra-processed foods are described as foods with lower nutritional quality, containing additives, those that are packaged, and have compounds formed from production, processing and storage. This particular study examined 104,980 participants from 2009 to 2017 using repeated

24-hour dietary records with the foods categorised according to their degree of processing by the NOVA classification. The results found that consumption of ultra-processed food intake was associated with an overall cancer risk. A 10% increase in consumption of these foods increased the risk of overall and breast cancer by greater than 10%[8].

The majority of studies on the Western diet post cancer diagnosis has been conducted on prostate[11-13], breast[14,15] and colorectal cancer[16,17]. All studies found that diets based on healthy eating (called prudent diet) which were higher in plant-based foods, reduced the risk of cancer recurrence significantly when compared to the Western diet. The Western diet is defined in the medical dictionary as one high in saturated fats, red meats, 'empty' carbohydrates or calories (junk food), low in fresh fruits and vegetables, whole grains, seafood and poultry[18].

There are a number of major cancers such as breast, colorectal and prostate that have been a focus for diet research post diagnosis. A systemic review of clinical trials published in 2018 looked at overall dietary intake and prognosis after breast cancer[19]. Seven studies met their inclusion criteria and identified that a better quality, healthy/prudent dietary pattern, less inflammatory diet was associated with reduced breast cancer risk overall.

A review examining the adherence to a Mediterranean diet and risk of cancer found that an important inverse association between adhering to a Mediterranean diet and cancer mortality existed[20]. This indicated that those who followed this type of diet high in fruit and vegetables and whole grains had a much lower risk of recurrence and death, particularly for colorectal cancer. Similarly, another review on the effect of diet on mortality and cancer recurrence among cancer survivors found that adherence to a high-quality diet and healthy/prudent dietary pattern decreased the risk of recurrence among cancer survivors, whereas a Western diet significantly increased this risk[21].

Another diet that has been suggested for use in cancer patients is the ketogenic diet[22]. The ketogenic diet has been used for over 80 years for epilepsy, with it now being suggested that it may be a therapeutic strategy to selectively kill cancer cells[22]. However, this diet has caused controversy, with some researchers stating that the ketogenic diet is highly undesirable and may trigger and/or exacerbate cachexia development and increase the likelihood of unwanted weight loss[22]. Moreover, a diet high in fat has been found to be associated with increased cancer growth in breast and melanoma patients[23,24].

A systematic review on ketogenic diets and cancer found 10 studies that met their inclusion criteria. From these studies most were interventional except one prospective cohort study[22]. The duration from these trials varied from 5 days to 2 years and the main outcomes were focused on the acceptability of ketogenic diets in people with cancer, body weight and composition and blood profiles.

To date, evidence from randomised trials on a ketogenic diet for cancer is lacking. It is possible that it could be beneficial for certain cancers such as glioblastomas but further research is required. To really evaluate the clinical application of a ketogenic diet as an adjunct therapy for cancer patients, it first needs to be evaluated for its anti-tumour effect for each single type/genetic subtype of cancer in preclinical settings[25]. This is because the safety and efficacy of this diet would strongly depend on the tumour entity and its genotype. Information on this is lacking at present and further research is required.

As health practitioners, it is important to not focus on one type of diet for all cancers. As discussed, cancer consists of hundreds of different diseases and, hence, there is no single diet for all cancer types. What is important is the identification of the 'teachable moment' and knowing that we have a chance to positively influence patients' lives. Each patient needs to be considered as an individual to find the right type of diet for their circumstances using the research we have to date. Post diagnosis and cancer treatment provides a perfect opportunity to help steer people in the right direction. Keeping up with current research and knowing that different diets are appropriate for different type of cancers is an important point to remember when seeing patients with or after cancer.

References

1. Cancer Australia. All cancers in Australia. Affected by Cancer 2018 [cited 2018 21/2/2018]; https://canceraustralia.gov.au/affected-cancer/what-cancer/cancer-australia-statistics
2. World Cancer Research Fund International. Cancer preventability estimates for diet, nutrition, body fatness, and physical activity. 2017 [cited 2018 20 February]; https://wcrf.org/cancerpreventability-estimates
3. Tabung FK, Brown LS, Fung TT. Dietary patterns and colorectal cancer risk: A review of 17 years of evidence (2000–2016). Curr Colorectal Cancer Rep 2017;13(6):440–454.
4. Bluethmann SM *et al*. Grasping the 'teachable moment': time since diagnosis, symptom burden and health behaviors in breast, colorectal and prostate cancer survivors. Psychooncology 2015.
5. Demark-Wahnefried W *et al*. Lifestyle interventions to reduce cancer risk and improve outcomes. Am Fam Physician 2008;77(11):1573–8.
6. Chlebowski RT. Nutrition and physical activity influence on breast cancer incidence and outcome. Breast 2013;22(Suppl 2):S30–7.
7. Tabung FK *et al*. Changes in the inflammatory potential of diet over time and risk of colorectal cancer in postmenopausal women. Am J Epidemiol 2017;186(5):514–523.
8. Fiolet T *et al*. Consumption of ultra-processed foods and cancer risk: results from NutriNet-Sante prospective cohort. BMJ 2018;360:k322.
9. McCann SE *et al*. Reduction of dietary glycaemic load modifies the expression of microRNA potentially associated with energy balance and cancer pathways in pre-menopausal women. Br J Nutr 2013;109(4):585–92.
10. Jaksevicius A *et al*. Inhibitory effects of culinary herbs and spices on the growth of HCA-7 colorectal cancer cells and their COX-2 expression. Nutrients 2017;9(10).
11. Bishop KS *et al*. An investigation into the association between DNA damage and dietary fatty acid in men with prostate cancer. Nutrients 2015;7(1):405–22.
12. Nguyen JY *et al*. Adoption of a plant-based diet by patients with recurrent prostate cancer. Integr Cancer Ther 2006;5(3):214–23.

13. Yang M *et al*. Dietary patterns after prostate cancer diagnosis in relation to disease-specific and total mortality. Cancer Prev Res (Phila) 2015;8(6):545–51.
14. Pierce JP *et al*. Influence of a diet very high in vegetables, fruit, and fiber and low in fat on prognosis following treatment for breast cancer: the Women's Healthy Eating and Living (WHEL) randomized trial. JAMA 2007;298(3):289–298.
15. Thomson CA *et al*. Vegetable intake is associated with reduced breast cancer recurrence in tamoxifen users: a secondary analysis from the Women's Healthy Eating and Living Study. Breast Cancer Res Treat 2011; 2:519.
16. Meyerhardt JA *et al*. Association of dietary patterns with cancer recurrence and survival in patients with stage III colon cancer. JAMA 2007;298(7):754–764.
17. Fung TT *et al*. Post diagnosis diet quality and colorectal cancer survival in women. PLoS One 2014;9(12):e115377.
18. Western diet. (n.d.). Segen's Medical Dictionary 2011 [cited 2018 February 21]; https://medical-dictionary.thefreedictionary.com/Western+diet
19. Terranova CO, Protani MM, Reeves MM. Overall dietary intake and prognosis after breast cancer: A systematic review. Nutr Cancer 2018;70(2):153–163.
20. Schwingshackl L *et al*. Adherence to Mediterranean diet and risk of cancer: An updated systematic review and meta-analysis. Nutrients 2017;9(10).
21. Schwedhelm C *et al*. Effect of diet on mortality and cancer recurrence among cancer survivors: a systematic review and meta-analysis of cohort studies. Nutr Rev 2016;74(12):737–748.
22. Chung HY, Park YK. Rationale, feasibility and acceptability of ketogenic diet for cancer treatment. J Cancer Prev 2017;22(3):127–134.
23. Brennan SF, Woodside JV, Lunny PM, Cardwell CR, Cantwell MM. Dietary fat and breast cancer mortality: A systematic review and meta-analysis. Crit Rev Food Sci Nutr 2017 Jul 3;57(10):1999–2008. doi: 10.1080/10408398.2012.724481.
24. Clement E, Lazar I, Muller C, Nieto L. Obesity and melanoma: could fat be fueling malignancy? Pigment Cell Melanoma Res 2017 May;30(3):294–306. doi: 10.1111/pcmr.12584. Epub 2017 Apr 20.
25. Weber DD, Aminazdeh-Gohari S, Kofler B. Ketogenic diet in cancer therapy. Aging (Albany NY) 2018.

Hep573 Study: A randomised, double-blind, placebo-controlled trial of silymarin alone and combined with antioxidants to improve liver function and quality of life in people with chronic hepatitis C

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Abstract

Background: Chronic hepatitis C (CHC) is a viral liver disease characterised by oxidative stress and inflammation leading to fibrosis, liver injury, cirrhosis and increased risk of liver cancer and reduced quality of life (QOL). Antioxidant phytonutrients have potential to limit inflammation and reduce co-morbidities associated with CHC. This randomised, placebo-controlled trial investigated the effects of two naturopathic treatments consisting of antioxidant nutrients and herbal medicines against placebo on liver function and QOL in people with CHC.

Methods: A randomised, double-blind, placebo-controlled clinical trial was conducted in three Australian teaching hospitals in New South Wales. One hundred and eighteen participants with compensated CHC-related disease were recruited through liver outpatient clinics and randomised to one of three groups: silymarin; silymarin with 13 other antioxidants (SOX); or placebo. Study duration was 48 weeks: 24 weeks on active treatment or placebo, and 24 weeks follow-up post treatment. Outcome measures included alanine aminotransferase (ALT), F_2-isoprostanes (oxidative stress), HCV RNA (viral load), FibroTest (liver damage), and QOL.

Results: The use of silymarin with antioxidants (SOX) achieved a higher rate of ALT normalisation (primary outcome) than placebo (P=0.02) or silymarin alone (P=0.003) at week 24. In addition, there was significant improvement in the Hepatitis Quality of Life Questionnaire (HQLQ) Mental Component Summary (MCS) in the SOX group (P=0.002). There were no significant changes in F_2-isoprostanes, HCV RNA or FibroTest.

Conclusions: This study has shown that the use of a complex naturopathic herbal and nutritional treatment can normalise ALT and improve QOL in participants with compensated CHC-related disease.

Keywords: Silymarin, antioxidants, chronic hepatitis C, randomised, double-blind, placebo-controlled clinical trial, quality of life, vitality, naturopathy.

ANZCTR clinical register: ACTRN12614000966695

Acknowledgements

We wish to thank the medical staff, nursing staff and study participants of the three participating hospitals. We would like to acknowledge the generous financial support from the Vicki Kotsirilos Integrative Medicine Grant and the John Hunter Charitable Trust Grant. We are grateful to Phytomedicine Pty Ltd for the supply of the trial interventions; the company was not involved in the analysis or study design in any way. Thank you to Rhoslyn Humphreys, Dr Amie Steel (University of Technology, Sydney/Endeavour College of Natural Health) and Dr Viviane Morrigan for academic discussion and editing.

Sources of support

Grants: John Hunter Charitable Trust Grant and Dr Vicki Kotsirilos Integrative Medicine Grant.

Product support: Mr Bob Power and Mr Michael Power from Phytomedicine.

Conflicts of interest

There are no conflicts of interest by any of the contributing authors.

Introduction

Background

According to the World Health Organization (WHO), an estimated 71 million people have chronic hepatitis C (CHC) infection[1]. Annual global mortality rates are approximately 399,000 from hepatitis C-related liver diseases[1]. The number of people in Australia living with CHC increased from 210,000 in 2001 to 230,000 in 2012, and more recently the estimate has decreased slightly to 227,000 in 2015[2,3].

The hepatitis C virus (HCV) is a blood-borne virus. There are six distinct genotypes of the HCV, with many quasi-species[4-6] within each genotype. The most prevalent HCV genotype in Australia is genotype 1 (55%), followed by genotype 3 (33%), genotype 2 (8%), genotype 4 (3%), and other genotypes (1%)[7].

The HCV can cause both acute and chronic liver infection. Acute HCV infection is usually asymptomatic, and is only very rarely associated with life-threatening disease[1]. About 15–45% of infected people spontaneously clear the virus within six months of infection without treatment[1]. The remaining 55–85% of untreated infected individuals will develop chronic HCV infection[1]. Of those with CHC infection, 15–30% are at risk of developing cirrhosis of the liver within 20 years[1]. CHC can result in hepatic fibrosis, cirrhosis, hepatocellular carcinoma and, in some patients, end-stage liver disease[8-10]. Symptoms commonly experienced in people with CHC include fatigue, depression, reduced quality of life (QOL), infertility, cognitive impairment and pain.

There is a strong theoretical basis that oxidative stress (OS) contributes to disease progression in CHC patients[11-13]. The HCV infection is a direct cause of OS[38-41,59-63]. The immune response to HCV infection drives the inflammatory process, exacerbates OS and correlates with the severity of the disease[11-17]. CHC patients are reportedly deficient in a range of antioxidants including glutathione[18], trace elements and minerals[19]. OS causes damage to cellular proteins, lipids and DNA, leading to mitochondrial dysfunction, endoplasmic reticulum stress and modifications to signalling pathways. Consequences include an ineffective immune response and exacerbated inflammation via necrosis and fibrosis[17,20-23]. Yadav and colleagues[11], Duygy and colleagues[24], and Chuma and colleagues[25] all reported correlations between OS and disease progression. This was confirmed in an investigation including 247 CHC patients[14]. Researchers found a significant negative association between high whole blood glutathione and vitamin C levels and reduced hepatic inflammation (P=0.02) and fibrosis (P=0.02)[14]. Further studies have correlated low antioxidant levels[11,15,26,27] with increased fibrosis, elevated malondialdehyde[11,28] and elevated F_2-isoprostanes[12]. In addition, the endogenous antioxidant, glutathione was found to be depleted in the liver, blood, and lymph of CHC patients[29,30].

OS and inflammation are associated with other pathologies including depression which can independently worsen QOL in people with CHC. A number of studies emphasise the importance of effective treatment for depression in CHC. In a study including CHC patients, it was found that reduced QOL was independently associated with major depressive disorder (MDD) and significantly associated with elevated alanine aminotransferase (ALT)[31-33]. Other observational investigations have found significant associations between elevated ALT and depression in non-alcoholic fatty liver disease (NAFLD) (P< 0.001)[93]. A study of patients with major depressive disorder concluded that chronic low-grade inflammation, measured by C reactive protein (CRP), may be associated with a subtype of depression[95]. This is supported by evidence showing improved outcomes in mood disorder patients when anti-inflammatory agents are used as an adjunct to conventional therapy[97].

Conventional treatments

Since 2013–2014 direct acting antivirals (DAAs) became the gold standard of treatment for CHC, leading to sustained viral response (SVR) in 91% of CHC patients within the first 12 weeks of treatment[34]. However, response to treatment is variable and dependent upon the HCV genotype, duration of infection, degree of liver damage and history of previous treatment. Patients with non genotype 3 infection and minimal liver damage have the best prognosis[34-38].

Adverse events associated with DAAs treatment are generally mild, and include nausea, fatigue and

anaemia. Sofosbuvir (NS5B polymerase inhibitor), is contraindicated in patients with severe renal impairment, because of renal metabolism[39-41]. There is controversy as to whether direct acting antivirals increase the incidence or recurrence[42,43] of hepatocellular carcinomas[44-46] particularly in patients with cirrhosis. In addition, HCV genotype 3 infection may be resistant to treatment with these agents. Disease progression, debility and worsened QOL may explain why many people with CHC seek adjunct care such as complementary medicines[47].

NCCAM defines complementary medicine (CM) "as a group of diverse medical and health care interventions, practices, products, or disciplines that are not generally considered part of conventional medicine"[48]. Naturopathy, which includes herbal medicine and nutritional medicine in Australia[49] is based on six principles: the healing power of nature (*vis mediatrix naturae*), identify and treat the cause of disease (*tolle causam*), treat the whole person (*tolle totum*), first do no harm (*primum non nocere*), educate/teach the patient (*docere*) and disease prevention (*preventare*)[49]. There are no data specific to the use of CM in by people with HCV in Australia. However, the Australian 2016 survey investigating the prevalence of CM use by people with a similar chronic infectious condition, HIV, found that over 53% were regular users of ingestible CM (nutritional supplements and herbs)[50]. In an Irish cohort of CHC patients, 50% had consulted a CM practitioner compared to 24% of the general population. Within the CHC population, women, were three times more likely to use CM. Those with fibromyalgia or anxiety were 2.7 times and 1.4 times respectively more likely to use CM. Of interest, smokers were less likely to use CM[51]. The Irish cohort authors concluded that a more holistic approach to health care may better meet physical and psychological health needs of this group[51]. Research also suggests that other patient groups are using a more holistic approach than straight pharmaceutical medicine. The main reasons cited include: to enhance QOL, reduce fatigue and increase energy; improve immune function and symptom management[52]; address co-morbidities and reduce the possible side effects of conventional therapy[50]. Patients using CM feel empowered and more in control, enabling them to take a more active role in their health[53-56].

Using complementary medicine in liver clinics

Approximately 30–50% of patients presenting to liver clinics worldwide reportedly use CM for the purpose of better managing their disease[14,30,57-59]. In 2001, 41% of those attending hospital outpatient liver clinics in the USA indicated using CMs such as herbal medicines in the preceding month[57]. In 2008, 44% of participants in the USA Hepatitis C Antiviral Long Term Treatment against cirrhosis trial (HALT-C) reported previous or current CM use. Of those currently taking CMs, 195/269 (72%) were ingesting silymarin[58]. Findings of the HALT-C trial[58], demonstrated that users of silymarin experienced significantly less fatigue, nausea, liver pain, anorexia, muscle and joint pain[58].

There are limitations, however, in the evidence base for CM in people with CHC. In a review of 17 clinical trials from 1997–2010[60] investigating antioxidants in people with HCV infection (as adjunct interferon therapy), the majority of studies (12/17) had less than 50 participants and investigations were underpowered. To date no randomised controlled trials have investigated the efficacy and safety of silymarin and antioxidants for CHC patients.

This research (The Hep573 Study) sought to examine the efficacy of a complex naturopathic treatment consisting of oral silymarin and oral antioxidants for reductions in oxidative stress, inflammation, viral activity and improved quality of life against placebo in a well-defined CHC population. The study also aimed to determine if there were variations in response between HCV genotypes.

The intervention included a broad range of non-synthetic, phytochemical antioxidants. These interventions had multiple overlapping pharmacological actions including antioxidant, antiviral, anti-inflammatory and antifibrotic actions[61-68]. *Silybum marianum* was included as it has been the most researched herbal medicine in liver disease. A recent review of *S. marianum* identified that the antioxidant and anti-inflammatory effect of silymarin was due to a reduction of virus-related liver damage by immune modulation[69].

Materials and methods

This trial was registered on the ANZCTR clinical register ACTRN12614000966695. The study duration was 48 weeks. Interventions were administered for 24 weeks. Outcomes were assessed following a 24-week treatment period and at the end of the follow-up period at 48 weeks.

Participants

Participants were recruited from hospital outpatient liver clinics over 33 months. The participating hospitals were Royal Prince Alfred Hospital and Westmead Hospital, Sydney and John Hunter Hospital, Newcastle. The Hep573 Study was approved by four Human Research Ethics Committees (the three participating hospitals and the University of Newcastle Human Research Ethic Committees). Participants gave informed written consent.

The inclusion criteria were: people aged between 18 and 75 years; hepatitis C antibody and HCV RNA positive; abnormal alanine aminotransferase (ALT) tests on at least three occasions in the previous two years; and not taking any complementary medicines for 12 weeks prior to trial entry. The exclusion criteria were: alcohol-related liver disease; alpha 1-antitrypsin

deficiency; autoimmune hepatitis; drug-induced liver disease; haemochromatosis; hepatitis B and D virus infection; decompensated cirrhosis (Child-Pugh score >7); human immunodeficiency virus (HIV); antiviral therapy (pegylated interferon and ribavirin) in the past six months; platelet count ≤50 x 10^9/L; alcohol intake >70 grams per week; methadone >100 mg/day or unstable on methadone dose; non-prescription or recreational drugs >3 times per week; pregnant or currently breastfeeding women; potential drug-herb interactions and CM supplements within the past 12 weeks; and normal alanine aminotransferase (ALT) levels.

Participants were randomised to treatment in blocks of six in order of informed consent. In each block of six participants, two were allocated at random to the placebo group, two to silymarin and two to the silymarin and antioxidant (SOX) group. This randomisation scheme was designed by statistician Adrienne Kirby from the National Health and Medical Research Centre (NHMRC) Clinical Trials Centre at the University of Sydney to ensure the treatment groups remained 'balanced' with respect to number of patients. All investigators, study personnel and participants at the participating hospitals were blinded to the treatment allocation. The hospital pharmacy staff prepared the assigned treatment allocation for each patient identification number. The randomisation coordinator was the only person who had access to treatment allocation and this was concealed until all data was provided to the biostatistician.

Study interventions

The interventions were administered for 24 weeks. The SOX intervention contained phytochemical and nutritional antioxidants (Table 1). The silymarin intervention contained 60 grams of *S. marianum,* 70:1 seed extract standardised to contain 720 mg silybin per day. The placebo controls contained calcium hydrogen phosphate, cellulose microcyrstalline, sodium starch glycolate, magnesium stearate, hypromellose and coating colour. The intervention and placebo tablets were produced by Phytomedicine Pty Ltd (Sydney, Australia) and were identical in appearance and taste. All interventions were presented as tablets taken as two equal oral doses per day.

Table 1: Full List of Hep573 silymarin and antioxidant (SOX) trial interventions.

Hep573 SOX Trial interventions	Validated content of constituents per tablet	Rationale for inclusion
Silybum marianum[69,70] 60 grams/day (g/d)	720 mg silybin	Antioxidant, anti-inflammatory, hepatoprotective, antifibrotic
Andrographis paniculata[71] 3 g/d	34.8 mg andrographolide	Antioxidant, immunomodulator, hepatoprotective
Astragalus membranaceus[72] 3 g/d		Adaptogen, antioxidant, immunomodulator, antiviral, antifibrotic
Camellia sinensis[73-75] 4 g/d		Antioxidant, anti-inflammatory, antiviral, antifibrotic
Curcuma longa[76] 8 g/d	280 mg curcuminoids	Antioxidant, anti-inflammatory, antiviral, antifibrotic
Eleutherococcus senticosus[77-79] 3 g/d	1.2 mg syringaresinol diglucosides	Adaptogen, immunomodulator
Hypericum perforatum[80-84] 1.5 g/d	0.8 mg hypericin	Antioxidant, anti-inflammatory, antidepressant, antiviral
Phyllanthus amarus[85] 3 g/d		Antioxidant, anti-inflammatory, antiviral, hepatoprotective Immunomodulator
Vitis vinifera[86,87] *12 g/d*	80 mg procyanidins	Antioxidant, anti-inflammatory
Alpha lipoic acid[88] 200 mg/d		Antioxidant, anti-inflammatory
Lycopene[89] 80 mg/d		Antioxidant, anti-inflammatory
Selenomethionine[90] 40 mg/d	elemental selenium 200 mcg	Antioxidant, anti-inflammatory
Vitamin C[91] 400 mg/d	calcium ascorbate 400 mg	Antioxidant, anti-inflammatory
Zinc[92-94] amino acid chelate 20% 250 mg/d	elemental zinc 50 mg	Antioxidant, anti-inflammatory, antifibrotic

Outcome measures

Outcomes were assessed at 24 weeks and 48 weeks. The primary outcome measure was the proportion of patients who achieved alanine aminotransferase (ALT) normalisation (within normal reference ranges) from baseline at week 24. Alanine aminotransferase (ALT) is a hepatic enzyme, found primarily in the cytosol of the hepatocyte[95] and released from damaged hepatocytes into the blood after hepatocellular injury or death[96]. Given its predominant hepatic origin, ALT is regarded as a specific marker of liver injury[97], and serum elevations are considered the hallmark of hepatocyte necrosis[98-100]. In addition, ALT is inexpensive, accessible, widely used and to date, the most reliable and sensitive serum marker available for the screening[95,97,101], diagnosis[95,96,98] and evaluation of inflammatory liver disease[95,96]. There were some variations of the normal reference ranges of ALT at the three participating hospitals of this study. At John Hunter Hospital, the normal reference range for ALT was 0–40 U/L, at Royal Prince Alfred Hospital (5–55 U/L) and at Westmead Hospital (10–47 U/L, men and 7–33 U/L, women).

There is debate as to whether ALT is a true measure and predictor of disease progression. Evidence suggests that disease progression is less likely in patients with persistently normal ALT levels[98,102-106] than in those with persistently elevated ALT levels. Puoti suggests that progression of liver disease in patients with normal ALT still occurs, but at about half the rate of patients with elevated ALT[107].

Secondary outcome measures included: the changes over time in ALT, HCV RNA viral load, F_2-isoprostanes as a measure of oxidative stress, FibroTest as a measure of liver damage and quality of life (QOL). QOL was measured using the Medical Outcomes Trust validated *Hepatitis Quality of Life Questionnaire* (*HQLQ*™) (*QualityMetric*™, Version 1, 1999)[33,108,109]. The F_2-isoprostanes were measured using a method previously published[110], with minor modifications. In brief, 15-F_{2t}-IsoP-d_4 and 8-F_{2t}-IsoP-d_4 (5ng) were added to plasma (250 µl) as internal standards. Samples were purified by chromatography on a Certify II column (Varian), derivatised from the trimethylsilyl, pentafluorobenzylesters and analysed by gas chromatography-mass spectrometry on an Agilent 6890 gas chromatograph coupled to an Agilent 5973 mass-selective detector using electron capture negative ionisation. F_2-isoprostanes were detected by SIM monitoring: at m/z 569 for detecting 15-F_{2t}-IsoP, and at m/z 573 for 15-F_{2t}-IsoP-d_4 and 8-F_{2t}-IsoP-d_4.

The HCV genotype testing was performed by in-house INNO-LiPA HCV II or Versant HCV Genotype 2.0 Assay (LiPA).

Adverse effects

Adverse effects were assessed monthly by study investigators and by participants self-reporting any unpleasant symptoms or signs or as increased consultations with health or medical providers.

Statistical methods

A sample size of 49 per arm was calculated based on previous unpublished pilot data to have 80% power to detect a difference in the proportion of subjects with normalised ALT at 24 weeks (12% in the control group versus ≥36% in the treated group) (Chi-square test, two-tailed, 5% significance level).

Statistical analyses

Characteristics of participants were described using frequencies for categorical variables (age, gender, HCV genotype) and medians with lower to upper quartile ranges for continuous variables (ALT, F_2-isoprostanes, HCV RNA viral load, FibroTest, QOL: Physical Component Summary (PCS) and Mental Component Summary (MCS)). Baseline characteristics were assessed for differences between groups using Chi squared or Kruskall Wallis ANOVA tests as appropriate.

The proportion of patients with normalised ALT levels at 24 weeks and the associated 95% confidence interval (CI) were reported for each treatment arm. Fisher's exact test[111] was used to test for differences in proportion between treatments. Continuous variables were investigated with a Linear Mixed Effects Models (LMEs). These models account for the correlation between repeated measurements on the same patient. Two-tailed tests with a significance level of 5% were used throughout[112,113]. The LMEs considered treatment as a fixed effect, time as both a fixed and a random effect, and participant identifier as a random effect. The continuous variables (ALT, F_2-isoprostanes, HCV RNA viral load) with skewed distributions were logarithmically transformed prior to analysis. Parameter estimates were back transformed and reported as percentage changes. The FibroTest and *HQLQ™v1*data were normally distributed and did not require logarithmic transformation. Data were analysed using the statistical packages, SPSS Version 24 (IBM SPSS Inc, Chicago, IL) and S_PLUS Version 8 (Insightful Corp., Seattle, Washington). All withdrawals were included in an intention to treat analyses.

Results

One hundred and eighteen people with CHC were randomised to one of three study arms; silymarin plus antioxidants, silymarin alone or placebo (placebo, N=39, silymarin, N=40, and silymarin with antioxidants, N=39) (Figure 1). Four of the 118 participants who were randomised did not enter the study. Reasons are provided in Figure 1.

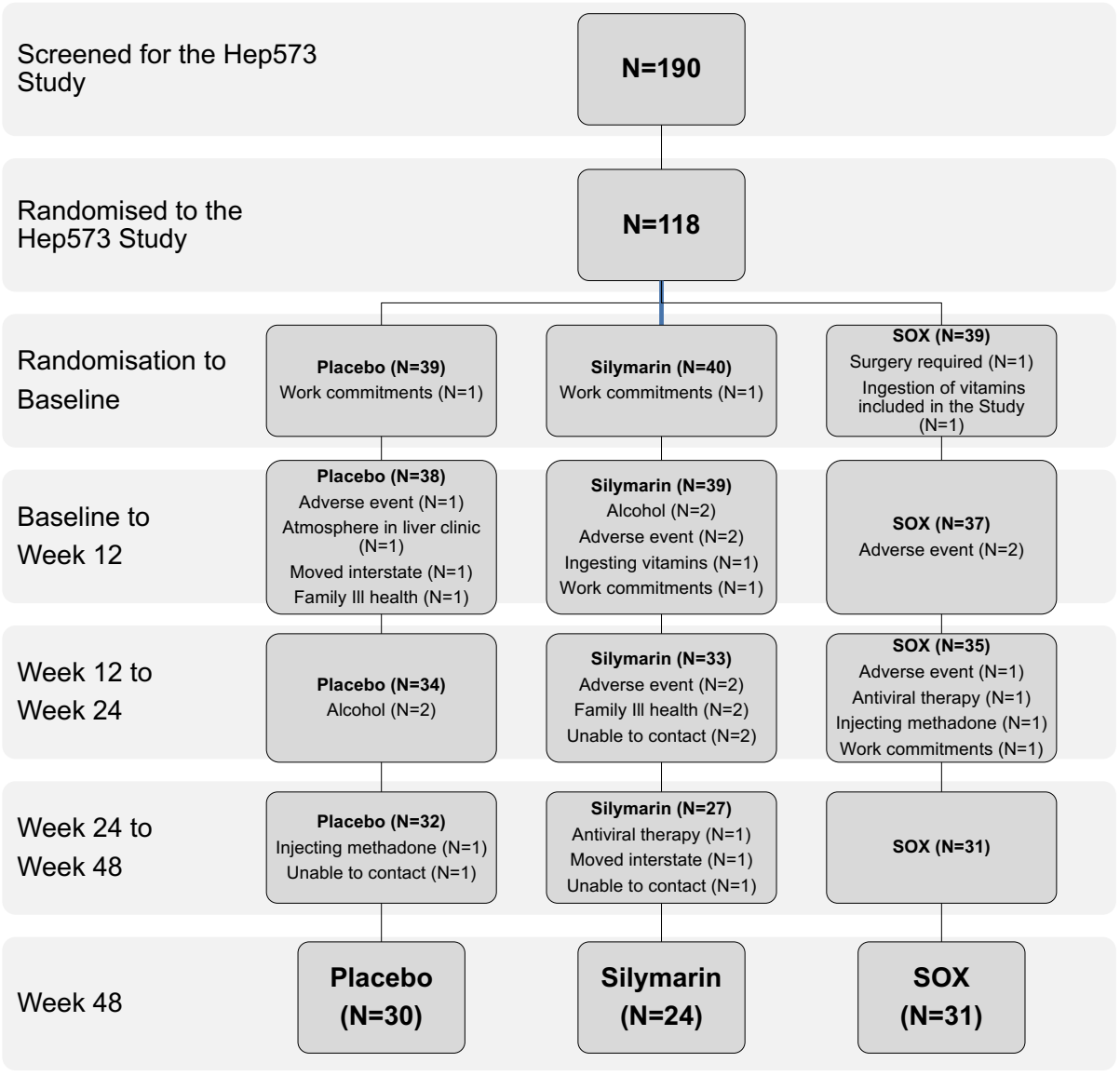

Figure 1: Hep573 Study flowchart

Baseline characteristics

With the exception of HCV RNA, no significant between group differences in baseline characteristics were detected. At baseline, the HCV RNA was significantly elevated in the silymarin group compared with the SOX and placebo (P=0.047) groups (Table 2).

Table 2: Baseline characteristics by treatment group

Variable	Placebo	Silymarin	SOX	P-value
Participant numbers (N)	39	40	39	
Gender (M vs F)	(30,9)	(23,17)	(27,12)	*P*=0.176
Age (years)	47 (37–53)	48 (42–52)	50 (44–54)	*P*=0.337
HCV genotype (1, 4, 6) vs (2 or 3)	(26,13)	(25,15)	(31,8)	*P*=0.234
ALT U/L	87 (56–126)	100 (60–133)	76 (57–112)	*P*=0.372
F_2-isoprostanes pmol/L	2118 (1605–2698)	2410 (1829–3946)	2141 (1768–2696)	*P*=0.262
HCV RNA 10^5 copies/ml	32.1 (10.6–83.6)	79.3 (30.4–132.2)	46.8 (24.0–117.7)	*P*=0.047*
FibroTest	0.54 (0.26–0.71)	0.64 (0.36–0.85)	0.55 (0.38–0.78)	*P*=0.455
PCS	43.6 (39.3–47.9)	41.7 (35.9–47.5)	43.4 (35.9–47.5)	*P*=0.183
MCS	41.5 (35.1–47.9)	44.1 (37–51.2)	41.4 (35.5–47.3)	*P*=0.119

Key:
ALT = Alanine aminotransferase
HCV RNA = Viral load
PCS = Physical Component Summary Score
MCS = Mental Component Summary Score

Primary outcome — ALT normalisation at week 24

A significantly higher proportion of participants receiving the SOX intervention demonstrated normalised ALT levels at week 24, compared to the placebo and the silymarin group (P=0.002) (Table 3). Ten of 39 (26%) participants in the SOX group were found to have normalised ALT compared to two of 39 (5%) taking placebo (*P*=0.02) and one of 40 (2.5%) taking silymarin alone (*P*=0.003).

Table 3: ALT normalisation from baseline at Week 24

ALT normalisation	Placebo	Silymarin	SOX	P value
N	2/39	1/40	10/39	0.002
Percentage (95% CI)	5% (1.4–16.9%)	2.5% (0.4–12.9%)	26% (14.6–41.1%)	

Key:
SOX = silymarin and antioxidant group
95% CI = 95% Confidence Interval
P value = Homogeneity (interaction) P value

Primary outcome — ALT normalisation according to HCV genotype at week 24

Nine out of 10 of those who had ALT normalisation in the SOX group had HCV genotype 1. Significant differences in the ALT normalisation rates amongst genotype 1 groups were significant (P=0.008).There was no significant difference between treatment groups and ALT normalisation rates in the other genotype groups (P=0.440).

Secondary outcomes at week 24

Quality of life

Mental-health status was significantly improved in the SOX group compared to silymarin alone and placebo (P=0.024) (Table 4). Two of the components of the MCS score that showed significant improvement in the SOX group from baseline at Week 24 were mental health (P=0.012) and vitality (P=0.001).

Table 4: Absolute change in HQLQ™v1 from baseline at week 24

SF-36 outcome	Absolute change	Placebo	Silymarin	SOX	Homogeneity *P*-value
MCS	Change	+1.3	–1.4	+5.2	0.024
	95% CI	(–2.0, +4.6)	(–4.8, +2.0)	(+2.0, +8.4)	
	P-value	0.443	0.422	0.002	

Key:
HQLQ = Hepatitis Quality of Life Questionnaire
MCS = Mental Component Summary score
95% CI = 95% Confidence Interval
P value = Homogeneity (interaction) P value

ALT, F_2-isoprostanes, HCV RNA and FibroTest

There were no statistically significant percentage changes over time in ALT, F_2-isoprostanes, HCV RNA and FibroTest from baseline at week 24 as shown in Table 5.

Table 5: Percentage change in ALT, F_2-isoprostanes, HCV RNA, FibroTest from baseline at week 24

Outcome Measure	Placebo	Silymarin	SOX	Homogeneity (interaction) *P*-value
ALT U/L	–5.0	+8.6	–13.1	*P*=0.113
95% CI	(–18.0, +9.9)	(–7.0, +26.6)	(–25.0, +0.3)	
P-value	0.490	0.291	0.055	
F_2-isoprostanes pmol/L	–7.0	+2.0	–12.0	*P*=0.071
95% CI	(–14.5, +0.4)	(10.0, +7.0)	(–18.4, –4.3)	
P-value	0.066	0.666	0.003	
HCV RNA 10^5 copies/ml	+13.0	–9.0	+21.0	*P*=0.542
95% CI	(–21.3, +63.1)	(–37.1, +32.5)	(–15.5, +73.6)	
P-value	0.504	0.633	0.300	
FibroTest	+19.7	+6.4	+5.4	*P*=0.674
95% CI	(–3.9,+43.4)	(–15.0, +27.8)	(–16.2, +26.9)	
P-value	0.105	0.560	0.626	

Key: 95% CI = 95% confidence interval

Secondary outcomes at week 48 (follow-up period from weeks 24 to 48)

ALT increased in all groups during the follow-up period (weeks 24 to 48). On average, there was a 9.6% increase in ALT in the six-month follow-up period. There were no statistically significant differences between groups in the percentage changes in ALT (P=0.810), HCV RNA (P=0.100) or FibroTest (P=0.906) in the follow-up period, as shown in Table 6.

Table 6: Percentage change in ALT, HCV RNA and FibroTest from week 24 at Week 48

Outcome measure	Treatment Group	Percentage change	95% confidence interval (CI)	*P*-value	Homogeneity (Interaction) *P*-value
ALT	Placebo	+5.0	(–10.4, +23.0)	0.549	0.810
	Silymarin	+11.8	(–4.4, +30.7)	0.162	
	SOX	+12.3	(–5.5, +33.4)	0.189	
HCV RNA	Placebo	+2.3	(–37.1, +66.4)	0.926	0.100
	Silymarin	–35.1	(–61.4, +9.3)	0.108	
	SOX	–28.0	(–55.2, +15.7)	0.178	
FibroTest	Placebo	8.1	(–20.9, +37.1)	0.587	0.906
	Silymarin	5.3	(–22.9, +33.6)	0.713	
	SOX	0.8	(–26.9, +28.5)	0.954	

Quality of life

In the follow-up period from week 24 to 48 only mental health (P=0.005) and MCS (P=0.042) showed statistically significant interactions between treatment and the change observed during follow-up. For both variables the SOX group demonstrated a significant negative change of –4.1 in mental health (P=0.004) and –4.0 in the MCS (P=0.021) while no significant changes were seen in either the placebo or silymarin group suggesting a return to baseline scores following cessation of the SOX intervention. Results for MCS are reflected in Table 7.

Table 7: Absolute change in *HQLQ™v1* from week 24 at week 48

SF-36 Outcome	Absolute change	Placebo	Silymarin	SOX	Homogeneity *P*-value
MCS	Change	+0.5	+2.1	–4.0	0.042
	95% CI	(–2.9, +3.9)	(–1.5, +5.7)	(–7.3, –0.6)	
	P value	0.787	0.251	0.021	

Key:
MCS = Mental Component Summary score

Adverse reactions

Similar numbers of participants experienced adverse effects in the three treatment groups; however, not all of these were related to the trial preparations. The only adverse effect directly linked to the trial preparations was an idiosyncratic reaction in one participant to silymarin (dry mouth, blurred vision, headache and 'hot feeling on upper chest') which resolved immediately when the dose was stopped. This participant and others with adverse reactions were withdrawn from the trial and data were included in the analyses (intention-to-treat).

Discussion

This randomised controlled trial, known as the Hep573 Study, shows that a complex naturopathic intervention, consisting of herbal medicines and antioxidant nutrients achieved a significant reduction in ALT and improved QOL at 24 weeks for people with CHC. The intervention appeared to have no effect on plasma F_2-isoprostanes, HCV RNA or the FibroTest at week 24. All significant treatment effects disappeared during the 24-week follow-up after treatment. This suggests benefit was due to treatment and that ongoing treatment may be of benefit.

As with conventional treatment, the results were genotype-specific. In this study the ALT normalisation was most evident in HCV genotype 1. Glutathione depletion, an indicator of OS, can be more marked in genotype 1 CHC patients compared to genotype 2 or 3 CHC patients and correlates with increased liver disease progression[18]. This may mean interventions, such as antioxidants, which maintain glutathione levels may have particular benefit to genotype 1 patients through reduction in OS[30,114,115]. CHC patients are deficient in a range of antioxidants including glutathione[18], trace elements and minerals[19,116-119]. It may be for this reason that the SOX group had positive findings compared to the silymarin only or placebo groups.

The Study population had significantly lower baseline scores for QOL compared to the Australian population. The inclusion of *Hypericum perforatum*, which has high level evidence as an effective treatment for depression, may have contributed to the improved well-being[80-84]. The overall QOL improvements found in the SOX group occurred in two of its four domains, mental health and vitality. Vitality is identified as an outcome of importance to people with CHC, an important predictor

of QOL status[120,121] and an important person-centred outcome for people with CHC seeking treatment from complementary practitioners. In this case vitality was measured as a component of the QOL tool (*HQLQ™v1*) with extra weighting placed on the vitality scale within the MCS measure. Significant improvements were found for the complex naturopathic treatment only. This may inform individual's self-care and clinicians treatment decisions for people with CHC seeking improved vitality. Investigations of efficacy for silymarin in CHC patients[30,76,77] suggest that clinical outcomes improve only if treatment is started early in the disease process[122].

This study demonstrates that complex naturopathic interventions targeted to address oxidative stress and inflammation may help reduce co-morbidities such as depression particularly when patients are deficient in antioxidants including the endogenous antioxidant glutathione[18], and trace elements and minerals[19]. Other patient groups this may be applicable to include non-alcoholic fatty liver disease (NAFLD)[123], diabetes, CVD and dementia. A reduction in the oxidative stress marker F_2-isoprostanes in the SOX group was observed; however, it did not reach statistical significance compared to silymarin alone or placebo controls. Although our results suggest anti-oxidation as the mechanism of therapeutic effect other factors may have contributed these outcomes.

Future research directions

Whilst there has been an unprecedented cure rate with the new direct acting antivirals in HCV, key questions remain regarding the recurrence and occurrence of hepatocellular carcinoma despite viral cure, resistance to treatment in patients with genotype 3 and effective treatment for comorbid conditions including depression and reduced QOL. This is the first rigorously designed study to investigate a complex naturopathic intervention against a single herbal medicine and placebo controls. We found that the use of a complex intervention significantly improved QOL and normalised a marker of liver damage (ALT). More research is needed to examine the robustness and generalisability of our findings.

Limitations

The calculated sample size of 147 (49 per treatment arm) was not reached. Time constraints resulted in a reduced sample size. The pre-specified wash-out period of 12 weeks not taking CMs hindered recruitment. A four-week wash-out period may have sufficed.

The complex nature of the naturopathic complex intervention means that it is not possible to identify exactly which ingredients were most efficacious. The observed reduction in F_2-isoprostanes in the SOX group did not reach statistical significance (P=0.071), possibly due to insufficient sample size to detect a significant change for this outcome measure.

Strengths of the study

This is the first RDBPCT study that investigated the effectiveness and safety of two naturopathic interventions, silymarin alone and silymarin plus antioxidants against placebo controls in CHC participants. The Hep573 Study was carried out for an extra 12 weeks' duration, compared to previous studies[124,125], and antioxidants were combined with silymarin, reflecting naturopathic clinical practice. The longer treatment and the addition of antioxidants may have contributed to the positive findings in QOL and ALT in this study.

Conclusion

This study has shown that a complex naturopathic intervention consisting of silymarin plus antioxidants may lead to ALT normalisation and improve QOL in those with CHC infection. The results were found primarily in those with HCV genotype 1, who have been previously found to be deficient in endogenous antioxidants. These results may translate to patient groups with free radical driven, inflammatory liver diseases such as HCV and NAFLD.

References

1. WHO. Hepatitis C. WHO; 2017 [updated October 2017; cited 15 November 2017]; [Fact sheet]. Available from: http://www.who.int/mediacentre/factsheets/fs164/en/.
2. The Kirby Institute. Hepatitis C. Sydney: UNSW MEDICINE; 2017 [cited 2017 24 September]; Available from: https://data.kirby.unsw.edu.au/hepatitis-c.
3. Commonwealth of Australia. Fourth National Hepatitis C Strategy 2014–2017. Canberra: Commonwealth of Australia; 2014.
4. Webster G, Barnes E, Brown D, Dusheiko G. HCV genotypes — role in pathogenesis of disease and response to therapy. Baillières Best Pract Res Clin Gastroenterol 2000 Apr;14:229–40.
5. Simmonds P, Bukh J, Combet C, Deléage G, Enomoto N, Feinstone S *et al*. Consensus proposals for a unified system of nomenclature of hepatitis C virus genotypes. Hepatology 2005 Oct;42:962–73.
6. Farci P, Bukh J, Purcell RH. The quasispecies of hepatitis C virus and the host immune response. Springer Semin Immunopathol 1997;19:5–26.
7. Dore GJ, Law M, MacDonald M, Kaldor JM. Epidemiology of hepatitis C virus infection in Australia. J Clin Virol 2003 Feb;26:171–84.
8. Thomas DL, Seeff LB. Natural history of hepatitis C. Clin Liver Dis 2005 Aug;9:383–98,vi.
9. Schuppan D, Krebs A, Bauer M, Hahn EG. Hepatitis C and liver fibrosis. Cell Death Differ 2003; Jan;10 Suppl 1:S59–67.
10. Hoofnagle JH. Course and outcome of hepatitis C. Hepatology 2002 Nov;36:S21–9.
11. Yadav D, Hertan HI, Schweitzer P, Norkus EP, Pitchumoni CS. Serum and liver micronutrient antioxidants and serum oxidative stress in patients with chronic hepatitis C. Am J Gastroenterol 2002 Oct;97:2634–9.
12. Jain SK, Pemberton PW, Smith A, McMahon RF, Burrows PC, Aboutwerat A *et al*. Oxidative stress in chronic hepatitis C: not just a feature of late stage disease. J Hepatol 2002 Jun;36:805–11.
13. Okuda M, Li K, Beard MR, Showalter LA, Scholle F, Lemon SM *et al*. Mitochondrial injury, oxidative stress, and antioxidant gene expression are induced by hepatitis C virus core protein. Gastroenterology 2002 Feb;122:366–75.
14. Bandara P, George J, McCaughan G, Naidoo D, Lux O, Salonikas C *et al*. Antioxidant levels in peripheral blood, disease activity and fibrotic stage in chronic hepatitis C. Liver Int 2005 Jun;25:518–26.
15. Choi J, Ou JH. Mechanisms of liver injury. III. Oxidative stress in the pathogenesis of hepatitis C virus. Am J Physiol Gastrointest Liver Physiol 2006 May;290:G847–51.

16. Koike K, Miyoshi H. Oxidative stress and hepatitis C viral infection. Hepatol Res 2006 Feb;34:65–73.
17. Wang T, Weinman SA. Causes and consequences of mitochondrial reactive oxygen species generation in hepatitis C. J Gastroenterol Hepatol 2006 Oct;21(Suppl 3):S34–7.
18. Barbaro G, Di Lorenzo G, Soldini M, Parrotto S, Bellomo G, Belloni G *et al*. Hepatic glutathione deficiency in chronic hepatitis C: quantitative evaluation in patients who are HIV positive and HIV negative and correlations with plasmatic and lymphocytic concentrations and with the activity of the liver disease. Am J Gastroenterol 1996 Dec;91:2569–73.
19. Guo CH, Chen PC, Lin KP, Shih MY, Ko WS, Duygu F *et al*. Trace metal imbalance associated with oxidative stress and inflammatory status in anti-hepatitis C virus antibody positive subjects. Environ Toxicol Pharmacol 2012 Mar–Jul;33:288–96.
20. Filomeni G, Rotilio G, Ciriolo MR. Disulfide relays and phosphorylative cascades: partners in redox-mediated signaling pathways. Cell Death Differ 2005 Dec;12:1555–63.
21. Finkel T. Signal transduction by reactive oxygen species. J Cell Biol 2011 Jul 11;194:7–15.
22. Apte M. Oxidative stress: does it 'initiate' hepatic stellate cell activation or only 'perpetuate' the process? J Gastroenterol Hepatol 2002 Oct;17:1045–8.
23. Machida K, Cheng KT, Lai CK, Jeng KS, Sung VM, Lai MM. Hepatitis C virus triggers mitochondrial permeability transition with production of reactive oxygen species, leading to DNA damage and STAT3 activation. J Virol 2006 Jul;80:7199–207.
24. Duygu F, Koruk ST, Karsen H, Aksoy N, Taskin A, Hamidanoglu M. Prolidase and oxidative stress in chronic hepatitis C. J Clin Lab Anal 2012 Jul;26:232–7.
25. Chuma M, Hige S, Nakanishi M, Ogawa K, Natsuizaka M, Yamamoto Y *et al*. 8-Hydroxy-2'-deoxy-guanosine is a risk factor for development of hepatocellular carcinoma in patients with chronic hepatitis C virus infection. J Gastroenterol Hepatol 2008 Sep;23:1431–6.
26. Nakashima T, Sumida Y, Yoh T, Kakisaka Y, Nakajima Y, Ishikawa H *et al*. Thioredoxin levels in the sera of untreated viral hepatitis patients and those treated with glycyrrhizin or ursodeoxycholic acid. Antioxid Redox Signal 2000 Winter;2:687–94.
27. Sumida Y, Nakashima T, Yoh T, Nakajima Y, Ishikawa H, Mitsuyoshi H *et al*. Serum thioredoxin levels as an indicator of oxidative stress in patients with hepatitis C virus infection. J Hepatol 2000 Oct;33:616–22.
28. Ko WS, Guo CH, Yeh MS, Lin LY, Hsu GS, Chen PC *et al*. Blood micronutrient, oxidative stress, and viral load in patients with chronic hepatitis C. World J Gastroenterol 2005 Aug 14;11:4697–702.
29. Seronello S, Sheikh MY, Choi J. Redox regulation of hepatitis C in non-alcoholic and alcoholic liver. Free Radic Biol Med 2007 Sep 15;43:869–82.
30. Barbaro G, Di Lorenzo G, Asti A, Ribersani M, Belloni G, Grisorio B *et al*. Hepatocellular mitochondrial alterations in patients with chronic hepatitis C: ultrastructural and biochemical findings. Am J Gastroenterol 1999 Aug;94:2198–205.
31. Silva LD, Cunha CC, Cunha LR, Araujo RF, Barcelos VM, Menta PL *et al*. Depression rather than liver impairment reduces quality of life in patients with hepatitis C. Rev Bras Psiquiatr 2015 Jan–Mar;37:21–30.
32. Alt Y, Grimm A, Schlegel L, Grambihler A, Kittner JM, Wiltink J *et al*. The impact of liver cell injury on health-related quality of life in patients with chronic liver disease. PloS One 2016;11:e0151200.
33. Ware JE, Jr., Bayliss MS, Mannocchia M, Davis GL. Health-related quality of life in chronic hepatitis C: impact of disease and treatment response. The Interventional Therapy Group. Hepatology 1999 Aug;30:550–5.
34. Ioannou GN, Beste LA, Chang MF, Green PK, Lowy E, Tsui JI *et al*. Effectiveness of Sofosbuvir, Ledipasvir/Sofosbuvir, or Paritaprevir/Ritonavir/Ombitasvir and Dasabuvir regimens for treatment of patients with hepatitis C in the Veterans Affairs National Health Care System. Gastroenterology 2016 Sep;151:457–71 e5.
35. Sarrazin C, Zeuzem S. Resistance to direct antiviral agents in patients with hepatitis C virus infection. Gastroenterology 2010 Feb;138:447–62.
36. Costantino A, Spada E, Equestre M, Bruni R, Tritarelli E, Coppola N *et al*. Naturally occurring mutations associated with resistance to HCV NS5B polymerase and NS3 protease inhibitors in treatment-naive patients with chronic hepatitis C. Virol J 2015;12:186.
37. Asselah T, Thompson AJ, Flisiak R, Romero-Gomez M, Messinger D, Bakalos G *et al*. A Predictive Model for Selecting Patients with HCV Genotype 3 Chronic Infection with a High Probability of Sustained Virological Response to Peginterferon Alfa-2a/Ribavirin. PloS One 2016;11:e0150569.
38. Bertino G, Ardiri A, Proiti M, Rigano G, Frazzetto E, Demma S *et al*. Chronic hepatitis C: This and the new era of treatment. World J Hepatol 2016 Jan 18;8:92–106.
39. Banerjee D, Reddy KR. Review article: safety and tolerability of direct-acting anti-viral agents in the new era of hepatitis C therapy. Aliment Pharmacol Ther 2016 Mar;43:674–96.
40. Renard S, Borentain P, Salaun E, Benhaourech S, Maille B, Darque A *et al*. Severe pulmonary arterial hypertension in patients treated for hepatitis C with Sofosbuvir. Chest 2016 Mar;149:e69–73.
41. Chin-Loy K, Galaydh F, Shaikh S. Retinopathy and Uveitis Associated with Sofosbuvir Therapy for Chronic Hepatitis C Infection. Cureus 2016 May 03;8:e597.
42. Kozbial K, Moser S, Schwarzer R, Laferl H, Al-Zoairy R, Stauber R *et al*. Unexpected high incidence of hepatocellular carcinoma in cirrhotic patients with sustained virologic response following interferon-free direct-acting antiviral treatment. J Hepatol 2016 Oct;65:856–8.
43. Reig M, Marino Z, Perello C, Inarrairaegui M, Ribeiro A, Lens S *et al*. Unexpected high rate of early tumor recurrence in patients with HCV-related HCC undergoing interferon-free therapy. J Hepatol 2016 Oct;65:719–26.
44. Cheung MC, Walker AJ, Hudson BE, Verma S, McLauchlan J, Mutimer DJ *et al*. Outcomes after successful direct-acting antiviral therapy for patients with chronic hepatitis C and decompensated cirrhosis. J Hepatol 2016 Oct;65:741–7.
45. Kobayashi M, Suzuki F, Fujiyama S, Kawamura Y, Sezaki H, Hosaka T *et al*. Sustained virologic response by direct antiviral agents reduces the incidence of hepatocellular carcinoma in patients with HCV infection. J Med Virol 2017 Mar;89:476–83.
46. ANRS collaborative study group on hepatocellular carcinoma. Lack of evidence of an effect of direct-acting antivirals on the recurrence of hepatocellular carcinoma: Data from three ANRS cohorts. J Hepatol 2016 Oct;65:734–40.
47. Stedman C. Sofosbuvir, a NS5B polymerase inhibitor in the treatment of hepatitis C: a review of its clinical potential. Therap Adv Gastroenterol 2014 May;7:131–40.
48. NCCAM. Exploring the Science of Complementary and Alternative Medicine. USA: US Department of Health and Human Services,National Institutes of Health; [updated 24/09/201726/02/2018]; Available from: https://nccih.nih.gov/about/plans/2011/introduction.htm.
49. Seaton K. Naturopathic philosophy. In: Hechtman L, editor. Clinical Naturopathic Medicine. Sydney: Elsevier; 2011, pp. 2–13.
50. Braun LA, Forrester CA, Rawlins MD, Levy RW, Penm J, Graham MM *et al*. Complementary medicine use by people living with HIV in Australia — a national survey. Int J STD AIDS 2016 Jan;27:33–8.
51. Coughlan BM, Thornton LM, Murphy N, Tait MA, Flanagan PC, Kenny-Walsh EE *et al*. The use of complementary and alternative medicine in an Irish cohort of people with an iatrogenic hepatitis C infection: results from a health and lifestyle survey. Complement Ther Med 2014 Aug;22:683–9.
52. Rambaldi A, Jacobs BP, Gluud C. Milk thistle for alcoholic and/or hepatitis B or C virus liver diseases. Cochrane Database Syst Rev 2007;CD003620.

53. Reid R, Steel A, Wardle J, Trubody A, Adams J. Complementary medicine use by the Australian population: a critical mixed studies systematic review of utilisation, perceptions and factors associated with use. BMC Complement Altern Med 2016 Jun 11;16:176.
54. Carboon I. Rethinking the evidence imperative: why patients choose complementary and alternative medicine. Leuk Lymphoma 2008 Feb;49:181–2.
55. Ritenbaugh C, Nichter M, Nichter MA, Kelly KL, Sims CM, Bell IR *et al*. Developing a patient-centered outcome measure for complementary and alternative medicine therapies I: defining content and format. BMC Complement Altern Med 2011;11:135.
56. Bates A, Wilkinson J. Perceptions of patients with cancer attending a natural health retreat. JATMS 2009;I5:153–9.
57. Seeff LB, Lindsay KL, Bacon BR, Kresina TF, Hoofnagle JH. Complementary and alternative medicine in chronic liver disease. Hepatology 2001 Sep;34:595–603.
58. Seeff LB, Curto TM, Szabo G, Everson GT, Bonkovsky HL, Dienstag JL *et al*. Herbal product use by persons enrolled in the hepatitis C Antiviral Long-Term Treatment Against Cirrhosis (HALT-C) Trial. Hepatology 2008 Feb;47:605–12.
59. Bruguera M, Barrera JM, Ampurdanés S, Forns X, Sánchez Tapias JM. Use of complementary and alternative medicine in patients with chronic hepatitis C. Med Clin (Barc) 2004 Mar 13;122:334–5.
60. Choi J. Oxidative stress, endogenous antioxidants, alcohol, and hepatitis C: pathogenic interactions and therapeutic considerations. Free Radic Biol Med [serial on the Internet] 2012;52(7). Available from: http://www.sciencedirect.com/science/article/pii/S0891584912000366.
61. Wagoner J, Negash A, Kane OJ, Martinez LE, Nahmias Y, Bourne N *et al*. Multiple effects of silymarin on the hepatitis C virus lifecycle. Hepatology 2010 Jun;51:1912–21.
62. Yumei F, Zhou Y, Zheng S, Chen A. The antifibrogenic effect of (-)-epigallocatechin gallate results from the induction of de novo synthesis of glutathione in passaged rat hepatic stellate cells. Lab Invest 2006 Jul;86:697–709.
63. Skrzydlewska E, Ostrowska J, Farbiszewski R, Michalak K. Protective effect of green tea against lipid peroxidation in the rat liver, blood serum and the brain. Phytomedicine 2002; Apr;9:232–8.
64. Ak T, Gülçin I. Antioxidant and radical scavenging properties of curcumin. Chem Biol Interact 2008 Jul 10;174:27–37.
65. Holt AP, Salmon M, Buckley CD, Adams DH. Immune interactions in hepatic fibrosis. Clin Liver Dis 2008 Nov;12:861–82.
66. Marra F. Hepatic stellate cells and the regulation of liver inflammation. J Hepatol 1999; Dec;31:1120–30.
67. Cohen-Naftaly M, Friedman SL. Current status of novel antifibrotic therapies in patients with chronic liver disease. Therap Adv Gastroenterol 2011 Nov;4:391–417.
68. Schuppan D, Popov Y. Rationale and targets for antifibrotic therapies. Gastroenterol Clin Biol 2009 Oct–Nov;33:949–57.
69. Federico A, Dallio M, Loguercio C. Silymarin/Silybin and chronic liver disease: A marriage of many years. Molecules 2017 Jan 24;22.
70. Saller R, Brignoli R, Melzer J, Meier R. An updated systematic review with meta-analysis for the clinical evidence of silymarin. Forschende Komplementarmedizin 2008 Feb;15:9–20.
71. Tan WSD, Liao W, Zhou S, Wong WSF. Is there a future for andrographolide to be an anti-inflammatory drug? Deciphering its major mechanisms of action. Biochem Pharmacol 2017 Sep 1;139:71–81.
72. Shahzad M, Shabbir A, Wojcikowski K, Wohlmuth H, Gobe GC. The antioxidant effects of *Radix Astragali* (*Astragalus membranaceus* and related species) in protecting tissues from injury and disease. Curr Drug Targets 2016;17:1331–40.
73. Basu A, Betts NM, Mulugeta A, Tong C, Newman E, Lyons TJ. Green tea supplementation increases glutathione and plasma antioxidant capacity in adults with the metabolic syndrome. Nutr Res 2013 Mar;33:180–7.
74. Fukazawa H, Suzuki T, Wakita T, Murakami Y. A cell-based, microplate colorimetric screen identifies 7,8-benzoflavone and green tea gallate catechins as inhibitors of the hepatitis C virus. Biol Pharm Bull 2012;35:1320–7.
75. Steinmann J, Buer J, Pietschmann T, Steinmann E. Anti-infective properties of epigallocatechin-3-gallate (EGCG), a component of green tea. Br J Pharmacol 2013 Mar;168:1059–73.
76. Rahmani S, Asgary S, Askari G, Keshvari M, Hatamipour M, Feizi A *et al*. Treatment of non-alcoholic fatty liver disease with curcumin: A randomized placebo-controlled trial. Phytother Res 2016 Sep;30:1540–8.
77. Davydov M, Krikorian AD. *Eleutherococcus senticosus* (Rupr. & Maxim.) Maxim. (Araliaceae) as an adaptogen: a closer look. J Ethnopharmacol 2000 Oct;72:345–93.
78. Schmolz MW, Sacher F, Aicher B. The synthesis of Rantes, G-CSF, IL-4, IL-5, IL-6, IL-12 and IL-13 in human whole-blood cultures is modulated by an extract from *Eleutherococcus senticosus L*. roots. Phytother Res 2001 May;15:268–70.
79. Bleakney TL. Deconstructing an adaptogen: *Eleutherococcus senticosus*. Holist Nurs Pract 2008 Jul–Aug;22:220–4.
80. Tian J, Zhang F, Cheng J, Guo S, Liu P, Wang H. Antidepressant-like activity of adhyperforin, a novel constituent of *Hypericum perforatum L.* Sci Rep 2014 Jul 9;4:5632.
81. Rodriguez-Landa JF, Contreras CM. A review of clinical and experimental observations about antidepressant actions and side effects produced by Hypericum perforatum extracts. Phytomedicine 2003 Nov;10:688–99.
82. Solomon D, Ford E, Adams J, Graves N. Potential of St John's wort for the treatment of depression: the economic perspective. Aust N Z J Psychiatry 2011 Feb;45:123–30.
83. Linde K, Berner MM, Kriston L. St John's wort for major depression. Cochrane Database Syst Rev 2008 Oct 8;CD000448.
84. Apaydin EA, Maher AR, Shanman R, Booth MS, Miles JN, Sorbero ME *et al*. A systematic review of St John's wort for major depressive disorder. Syst Rev 2016 Sep 2;5:148.
85. Xia Y, Luo H, Liu JP, Gluud C. Phyllanthus species versus antiviral drugs for chronic hepatitis B virus infection. Cochrane Database Syst Rev 2013 Apr 30;CD009004.
86. Stankovic M, Tesevic V, Vajs V, Todorovic N, Milosavljevic S, Godevac D. Antioxidant properties of grape seed extract on human lymphocyte oxidative defence. Planta Med 2008 Jun;74:730–5.
87. Grases F, Prieto RM, Fernandez-Cabot RA, Costa-Bauza A, Sanchez AM, Prodanov M. Effect of consuming a grape seed supplement with abundant phenolic compounds on the oxidative status of healthy human volunteers. Nutrition J 2015 Sep 9;14:94.
88. Zembron-Lacny A, Gajewski M, Naczk M, Dziewiecka H, Siatkowski I. Physical activity and alpha-lipoic acid modulate inflammatory response through changes in thiol redox status. J Physiol Biochem 2013 Sep;69:397–404.
89. Ried K, Fakler P. Protective effect of lycopene on serum cholesterol and blood pressure: Meta-analyses of intervention trials. Maturitas 2011 Apr;68:299–310.
90. Himoto T, Yoneyama H, Kurokohchi K, Inukai M, Masugata H, Goda F *et al*. Selenium deficiency is associated with insulin resistance in patients with hepatitis C virus-related chronic liver disease. Nutr Res 2011 Nov;31:829–35.
91. Hong IH, Han JY, Goo MJ, Hwa SY, Ki MR, Park JK *et al*. Ascorbic acid deficiency accelerates aging of hepatic stellate cells with up-regulation of PPARgamma. Histol Histopathol 2012 Feb;27:171–9.
92. Chavez-Tapia NC, Cesar-Arce A, Barrientos-Gutierrez T, Villegas-Lopez FA, Mendez-Sanchez N, Uribe M. A systematic review and meta-analysis of the use of oral zinc in the treatment of hepatic encephalopathy. Nutrition J 2013 Jun 6;12:74.
93. Katayama K, Saito M, Kawaguchi T, Endo R, Sawara K, Nishiguchi S *et al*. Effect of zinc on liver cirrhosis with hyperammonemia: a preliminary randomized, placebo-controlled double-blind trial. Nutrition 2014 Nov–Dec;30:1409–14.

94. Uddin MG, Hossain MS, Rahman MA, Uddin A, Bhuiyan MS. Elemental zinc is inversely associated with c-reactive protein and oxidative stress in chronic liver disease. Biol Trace Elem Res 2017 Aug;178:189–93.
95. Kim WR, Flamm SL, Di Bisceglie AM, Bodenheimer Jr HC, Public Policy Committee of the American Association for the Study of Liver Disease. Serum activity of alanine aminotransferase (ALT) as an indicator of health and disease. Hepatology 2008;47:1363–70.
96. Green RM, Flamm S. AGA technical review on the evaluation of liver chemistry tests. Gastroenterology 2002;123:1367–84.
97. Ruhl CE, Everhart JE. Elevated serum alanine aminotransferase and gamma-glutamyltransferase and mortality in the United States population. Gastroenterology 2009 Feb;136:477–85 e11.
98. Pradat P, Alberti A, Poynard T, Esteban JI, Weiland O, Marcellin P *et al*. Predictive value of ALT levels for histologic findings in chronic hepatitis C: a European collaborative study. Hepatology 2002 Oct;36:973–7.
99. Gopal DV, Rosen HR. Abnormal findings on liver function tests. Interpreting results to narrow the diagnosis and establish a prognosis. Postgrad Med 2000 Feb;107:100–2, 5–9, 13–4.
100. Hanada K, Tanaka Y, Mizokami M, Gojobori T, Alter HJ. A reduction in selective immune pressure during the course of chronic hepatitis C correlates with diminished biochemical evidence of hepatic inflammation. Virology 2007 Apr 25;361:27–33.
101. Kaplan MM. Alanine aminotransferase levels: what's normal? Ann Intern Med 2002 Jul 2;137:49–51.
102. Persico M, Persico E, Suozzo R, Conte S, De Seta M, Coppola L *et al*. Natural history of hepatitis C virus carriers with persistently normal aminotransferase levels. Gastroenterology 2000;118:760–64.
103. Poynard T, Ratziu V, Charlotte F, Goodman Z, McHutchison J, Albrecht J. Rates and risk factors of liver fibrosis progression in patients with chronic hepatitis C. J Hepatol 2001 May;34:730–9.
104. Puoti C, Castellacci R, Montagnese F, Zaltron S, Stornaiuolo G, Bergami N *et al*. Histological and virological features and follow-up of hepatitis C virus carriers with normal aminotransferase levels: the Italian prospective study of the asymptomatic C carriers (ISACC). J Hepatol 2002 Jul;37:117–23.
105. Martinot-Peignoux M, Boyer N, Cazals-Hatem D, Pham BN, Gervais A, Le Breton V *et al*. Prospective study on anti-hepatitis C virus-positive patients with persistently normal serum alanine transaminase with or without detectable serum hepatitis C virus RNA. Hepatology 2001 Nov;34:1000–5.
106. Collier JD, Woodall T, Wight DG, Shore S, Gimson AE, Alexander GJ. Predicting progressive hepatic fibrosis stage on subsequent liver biopsy in chronic hepatitis C virus infection. J Viral Hepat 2005 Jan;12:74–80.
107. Puoti C, Bellis L, Guarisco R, Dell' Unto O, Spilabotti L, Costanza OM. HCV carriers with normal alanine aminotransferase levels: healthy persons or severely ill patients? Dealing with an everyday clinical problem. Eur J Intern Med 2010 Apr;21:57–61.
108. Ware JE, Kosinski M. Interpreting SF-36 summary health measures: a response. Qual Life Res 2001;10:405–13; discussion 15–20.
109. Bayliss MS, Gandek B, Bungay KM, Sugano D, Hsu MA, Ware JE, Jr. A questionnaire to assess the generic and disease-specific health outcomes of patients with chronic hepatitis C. Qual Life Res 1998 Jan;7:39–55.
110. Mori TA, Croft KD, Puddey IB, Beilin LJ. An improved method for the measurement of urinary and plasma F_2-isoprostanes using gas chromatography-mass spectrometry. Anal Biochem 1999 Mar 1;268:117–25.
111. Wacholder S, Weinberg CR. Paired versus two-sample design for a clinical trial of treatments with dichotomous outcome: power considerations. Biometrics 1982 Sep;38:801–12.
112. Batey RG, Bensoussan A, Fan YY, Bollipo S, Hossain MA. Preliminary report of a randomized, double-blind placebo-controlled trial of a Chinese herbal medicine preparation CH-100 in the treatment of chronic hepatitis C. J Gastroenterol Hepatol 1998 Mar;13:244–7.
113. Reinert DF, Allen JP. The alcohol use disorders identification test: an update of research findings. Alcohol Clin Exp Res 2007 Feb;31:185–99.
114. Jahan S, Khaliq S, Ijaz B, Ahmad W, Hassan S. Role of HCV Core gene of genotype 1a and 3a and host gene Cox-2 in HCV-induced pathogenesis. Virol J 2011;8:155.
115. Khadem Ansari MH, Omrani MD, Kheradmand F. Oxidative stress response in patients infected by diverse hepatitis C virus genotypes. Hepat Mon 2015 Feb;15:e22069.
116. Kolachi NF, Kazi TG, Afridi HI, Kazi NG, Mughal MA, Khan S. Effects of selenium and zinc status in biological samples of hepatitis C patient after herbal and pharmaceutical supplements. Biol Trace Elem Res 2013 May;152:187–94.
117. Riboli E, Norat T. Epidemiologic evidence of the protective effect of fruit and vegetables on cancer risk. Am J Clin Nutr 2003 Sep;78:559S–69S.
118. Tavani A, La Vecchia C. Fruit and vegetable consumption and cancer risk in a Mediterranean population. Am J Clin Nutr 1995 Jun;61:1374S–7S.
119. Steinmetz KA, Potter JD. Vegetables, fruit, and cancer. I. Epidemiology. Cancer Causes Control 1991 Sep;2:325–57.
120. Spiegel BM, Younossi ZM, Hays RD, Revicki D, Robbins S, Kanwal F. Impact of hepatitis C on health-related quality of life: a systematic review and quantitative assessment. Hepatology 2005 Apr;41:790–800.
121. Foster GR. Quality of life considerations for patients with chronic hepatitis C. J Viral Hepat 2009 Sep;16:605–11.
122. Roberts SK, Weltman MD, Crawford DH, McCaughan GW, Sievert W, Cheng WS *et al*. Impact of high-dose peginterferon alfa-2A on virological response rates in patients with hepatitis C genotype 1: a randomized controlled trial. Hepatology 2009 Oct;50:1045–55.
123. Guo CH, Chen PC, Ko WS. Status of essential trace minerals and oxidative stress in viral hepatitis C patients with non-alcoholic fatty liver disease. Int J Med Sci 2013;10:730–7.
124. Huber R, Futter I, Lüdtke R. Oral silymarin for chronic hepatitis C — a retrospective analysis comparing three dose regimens. Eur J Med Res 2005 Feb 28;10:68–70.
125. Gordon A, Hobbs DA, Bowden DS, Bailey MJ, Mitchell J, Francis AJ *et al*. Effects of *Silybum marianum* on serum hepatitis C virus RNA, alanine aminotransferase levels and well-being in patients with chronic hepatitis C. J Gastroenterol Hepatol 2006 Jan;21:275–80.

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MET5534 - 02/18

Australian Journal of Herbal and Naturopathic Medicine **2018** 30(1)

The role of nervous system support in naturopathic treatment of skin disorders: A case study

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Abstract

A significant proportion of patients who present with skin disorders have concomitant psychopathology. It has been suggested that besides its primary physiological roles, the skin may also be an organ of expression or outlet for anxiety and emotional issues, and psychological stress may manifest on the skin in the absence of any identifiable skin disease.

This case study describes the treatment of skin pathology of unknown aetiology where the manifestation corresponds with periods of emotional and psychosocial stress. It demonstrates the importance of a naturopathic treatment strategy that incorporates emotional health considerations and treatment with herbal formulations. The skin condition in this case was successfully treated and the beneficial effects of herbal medicine extended to improved nervous system function, with better sleep and emotional health and digestive tract function with reduced bloating. This case illustrates a naturopathic approach for the successful treatment of a perplexing skin condition.

Keywords: Anxiety, psycho-emotional, psychosocial, naturopathic medicine, skin disorders, herbal medicine.

Introduction

Besides its principal physiological roles, the skin can be an organ of emotional expression, functioning as an outlet for anxiety and psycho-emotional issues[1]. At least one in three people presenting with skin diseases have associated psychosocial factors[1]. Further, emotional and psychosocial stress has been linked to the first onset of certain chronic dermatologic conditions[2]. Psychopathology may manifest on the skin in the absences of any identifiable skin disease[1], whilst emotional stress is also known to exacerbate existing primary skin disorders including psoriasis, atopic dermatitis and acne[2]. Gupta and colleagues[3] present a more detailed hypothesis and discuss the link between emotional regulation and the skin, whereby the skin reacts to incidences of trauma and stress associated with an individual's compromised capacity to cope. States of chronic hyperarousal and acute psychological stress may have a direct effect on the skin, causing physical symptomatology[3].

The concept of a "brain–skin axis" has been described as "the interactions between psyche, immune system, and cutaneous inflammation" by Kleyn and colleagues[4], who discovered that concentrations of Langerhans' cells (LCs) (located in the epidermis and play a role in regulating cutaneous immune responses) were reduced after episodes of acute social stress. Further, Kim and colleagues[5] discuss the direct link between the skin and the nervous system where stress alters hypothalamic–pituitary–adrenal (HPA) axis hormones as well as cytokine profiles and the secretion of stress-related neuropeptides, illustrating the possibility of HPA axis hormones interacting with some cytokines and neuropeptides causing increased or exacerbated localised inflammation[5].

It is common place for patients to consult health care practitioners for physical symptoms, but to overlook their psychological associations, perhaps due to lack of awareness or due to the social stigma around mental and emotional health[1]. A substantial proportion of people with psychopathology have reported feeling stigmatised as a significant barrier to seeking treatment for mental health conditions[6]. Gordon-Elliott and Muskin[2] suggest the naturopathic practitioner may be one of the few health care providers who the client might trust, due to holistic principles of practice and capacity to integrate several aspects of an individual's physical, psychological

and emotional health into the case analyses. Therefore, an essential component of effective naturopathic case management is being able to recognise and address the impact of psychosocial and emotional issues, within their case understanding, and within their scope of practice. Comprehensive and compassionate case taking could help identify key issues during naturopathic consultations. Psychological issues are not always what the patient directly complains about[7]; however, it is essential to understand the impact of the client's psychology in order to rectify the presenting skin complaint.

The purpose of this case study is to highlight the complex interplay between the nervous system and the skin, providing insight into important considerations on which to base a treatment for people with skin conditions of unknown aetiology. We discuss the potential benefit of herbal medicine support for the nervous system, reducing anxiety, and regulating the physiological stress response in the treatment of non-specific skin disorders.

The case overview

'Kay' presented to the Wellnations student clinic on 7th March 2017 for treatment of a chronic skin condition. Kay is a 27-year-old female with a five-year history of a dry, bumpy rash on her chin and upper lip, treated with antibiotics and steroid cream with no lasting result. The rash was worse for touch, by eating too much sugar, or when Kay felt overly stressed or anxious.

Kay's bowel motions fluctuated between diarrhoea and constipation; however, her general pattern was 1–2 soft stools per day. She experienced bloating in the morning, eased by taking apple cider vinegar, and she reported diarrhoea after eating fatty foods in some instances.

Kay revealed that she was in an abusive relationship for three years, where she felt manipulated, criticised, insulted and isolated from her social networks. She reported that she had "moved past stressed to just feeling numb" and that she was having difficulty remembering anything. Kay had a history of abusive relationships. Further, she was grieving due to her grandmother's recent passing, with whom she lived for 22 years and who was a consistent support. She has experienced nightmares and disturbed sleep. Kay's fingernails were short, bitten and picked at.

Kay expressed that she generally consumed a wholefood diet, with limited processed foods, refined grains and sugar. Her meals often consisted of a lean protein source (for example, chicken) with a variety of fresh vegetables; however, her diet was lacking in fibre and nutrients from plant-based foods.

No pathological reports were available.

Rationale for the naturopathic treatment

The naturopathic treatment strategy in this case was based on the consideration of the skin being an organ of emotional expression[1], in the way that chronic stress may increase gut permeability[9], and that disorders of the skin may manifest and remit secondarily to digestive capacity and intestinal permeability[10]. We identified a multi-directional link between Kay's nervous system, gastrointestinal system and integumentary system. Prolonged activation of the HPA axis and the sympathetic nervous system (SNS) was possibly suppressing secretion of digestive enzymes and potentially compromising digestive capacity[8]. Chronic stress may also have been contributing to increased gastrointestinal permeability[9] and subsequently complicating an inflammatory skin condition, which may be an underlying expression of psychological stress and anxiety[1].

Brief stimulation of the sympathetic nervous system in response to stress (real or perceived) elicits a stress response that is considered to be a healthy coping mechanism[11]; however, long-term stimulation is more likely to result in a decline of health, which may eventually impact several body systems including the gastrointestinal (GI) tract and heart[11]. The HPA axis can become dysregulated and when this occurs, it may have a negatively adaptive effect on the central nervous system[12], and sustained suppression of the parasympathetic nerves and follow-on dysfunction of the GI tract[13] and other serious health complications[11].

Herbal medicines

Medicinal plants traditionally known as 'adaptogens' may alter the body's stress response by regulation of the HPA axis[12]. This may enhance resistance to physical, biological and mental stress. *Asparagus racemosus* (Shatavari) has been used historically as a tonic and adaptogenic herb[14] and antidepressant[15], anxiolytic[16] and adaptogenic[17] effects have been recently demonstrated in animal studies. Investigations exploring the mechanism of action of Shatavari have shown physiological modulation of the HPA axis and the sympathetic–noradrenergic system in animals[16]. This mechanism of action aligns with its traditional application as an adaptogen.

Anxiolytics and nervine herbal medicines may also be prescribed to reduce physical and psychological manifestations of stress[18] and may work synergistically with adaptogens. *Passiflora incarnata* (Passionflower) has an extensive traditional use to improve sleep and reduce anxiety. Clinical trials including people with insomnia and in stressful circumstances have demonstrated passionflower's effectiveness for stress reduction and safety[19-21]. *Avena sativa* (Oats green) is another traditional nervine tonic with anxiolytic and restorative effects in people with nervous exhaustion[22].

Naturopathic herbal formulations are often underpinned by bitter tonics used to promote digestive function and general health[23]. Bitter taste receptors are found at the back of the tongue and throughout the gastrointestinal tissue[24]. Bitter herbs (for example *Gentiana lutea*) may stimulate these receptors and activate parasympathetic vagal nerve fibres and stimulate secretions of the digestive system and promote healthy diversity and ecology of microflora[25]. The vagal stimulation may thereby facilitate digestion,

assimilation and absorption of essential nutrients and improve immune balance[25]. Medium to long-term use[23] of herbal bitters may be beneficial to sustain optimal digestive capacity, and improve general health and well-being (Moorhead, 1915, cited by[25]).

Cynara scolymus (Globe artichoke) contains bitter constituents and has a bitter action[25] as well as a choleretic action (stimulates bile acid secretion). It has been used traditionally for beneficial effects in the digestive system, biliary tract, and liver[26] and for reducing dyspeptic symptoms[26]. Significant benefits have been demonstrated in the treatment of people with irritable bowel syndrome (IBS)[27,28]. In adults suffering dyspepsia with alternating constipation/diarrhoea, bowel patterns have been observed to shift towards normal after treatment with globe artichoke[29].

Similar to bitters, herbal medicines containing pungent, warming constituents such as those in *Zingiber officinale* may have a stimulatory and tonic effect on the gastrointestinal tissue[25].

Ulmus rubra (Slippery elm (SE)) is a herbal medicine which has localised anti-inflammatory activity and may also improve integrity of the digestive ecology and reduce gastrointestinal permeability[25].

The herbal prescription

We provided two herbal mixtures (tonics) for treatment of Kay's skin condition (Table 1). Herbal tonic one contained *Avena sativa*, *Cynara scolymus*, *Passiflora incarnata* and *Asparagus racemosus* aimed to address the deep underlying nervous system support. Herbal tonic two was a digestive herbal combination of *Gentiana luteum* and *Zingiber officanale* provided in combination with slippery elm separately with the aim of supporting and regulating gastrointestinal function.

Table 1: Prescription

Herb		Dosage
Herbal mix 1	weekly dose	7.5mL to be taken twice daily in a small amount of water
Avena sativa 1:2 (oats green)	20 mL	
Cynara scolymus 1:2 (globe artichoke)	15 mL	
Passiflora incarnata 1:2 (passionflower)	40 mL	
Asparagus racemosus 1:1 (Shatavari)	30 mL	
	105 mL	
Herbal mix 2 equal parts *Zingiber officinale* (Ginger) *Gentiana luteum* (Gentian)		6 drops to be taken in a small amount of water about 10 minutes before meals
Ulmus rubra (Slippery elm) powder		1 heaped teaspoon to be mixed into a glass of water and taken daily away from meals by at least an hour

Treatment outcome

Kay missed the two-week follow-up appointment. At follow-up on 4th April 2017, the rash on Kay's chin had cleared and was no longer visible. Kay reported a significant reduction in stress, which she noticed soon after starting the naturopathic treatment. She was feeling calmer and more aware of herself in her relationship and was at a "crossroads" and feeling more capable of considering her options and what she wanted. Kay reported a marked improvement in digestion, she was no longer feeling bloated. She reported constipation when she stopped taking SE powder; however, her water intake was low, which may have limited its efficacy in bowel function normalisation.

Her prescription was repeated for a further two weeks with the additional use of a meditation app for daily meditation and an Australian bush flower essence mix for emotional support.

Over a course of 10 weeks, Kay attended three follow-up appointments where she was in varying degrees of mental and physical health and well-being. The rash on her chin did not re-appear; however, her digestive and mental health varied depending on life circumstances and compliance to treatment. Better well-being apparently depended on good compliance with the naturopathic treatment. She gained increased awareness of the connections between periods of non-compliance and slipping back into old states of poor mental and physical health. This empowered Kay's understanding of the connections between her skin and physical manifestations and stress, and the ability to make better decisions about her life and relationships when she felt well.

Discussion

This case highlights a multi-directional naturopathic approach linking the nervous system, GI system and integumentary system, and addressing underpinning emotional stress as a causative and complicating factor. The case presented here corroborates the naturopathic understanding that skin is an organ of expression for emotional unrest and psychological stress.

It has been suggested that pathogenic mechanisms of skin disease are due to systemic disruption such as dysbiosis or increased intestinal permeability, even where GI signs are absent[30]. Psychological stress plays a pivotal role, and may alter intestinal secretions, microflora diversity and barrier functions[31]. Chronic stress exposure may cause significant dysfunction of the intestinal barrier throughout the small and large bowel[32] and increased permeability between the digestive lining and blood and lymphatic circulatory systems. This may have ultimately manifested on the skin. Another possible pathogenic mechanism was a direct effect of sustained

sympathetic nervous excitation, described as the "brain–skin" axis. This may be causing local inflammation by altering skin cell and cytokine profiles[4,5].

The naturopathic treatment approach was informed by the findings of Kim and colleagues[5] that HPA axis hormones may negatively interact with some cytokines and neuropeptides, leading to an association between acute stress and skin inflammatory symptoms. Evidence from a clinical trial that examined the effects of marital relationships on inflammatory cytokines found that hostile and abrasive behaviours increased the frequency and intensity of pro-inflammatory cytokines[33]. These findings support the principle of the "brain–skin" axis concept[4,34]. Although the mechanism behind this concept is not fully understood, the consideration of a "brain–skin" axis may be important to successful management of inflammatory skin conditions.

The case provides insight into the naturopathic management of skin presentations by holistic treatment, incorporating strategies to improve nervous system and digestive function to treat a skin condition. It demonstrates the synergistic use of herbal medicines to restore the emotions and tonify the nervous system and GI system during times of acute and chronic stress, and improved health literacy and self-efficacy for the client to make positive self-help decisions.

One of the limitations to this case study is the difficulty in attributing the clinical changes to single components of the naturopathic treatment. Counselling is an incidental component of naturopathic consultations and this may have provided a therapeutic effect in itself. Naturopathic consultations are long by nature and there is opportunity for patients' self-reflection through the process of telling the 'story' of their health. This self-reflection may have contributed to the progress made by the client in this case. A further limitation of the case study is the issue of generalisability. As a single case study, it is not possible to estimate the probability of the benefits occurring in other people.

This study demonstrates the defining differences of naturopathic and herbal medicine practice from a methodologically, ideologically, humane perspective and how these practices uniquely meet the complex and holistic health needs and desires of patients. Overall, the case demonstrates the potential of naturopathy in holistic treatment of skin disorders where there is underlying emotional disturbance.

Conclusion

This case study demonstrated a direct interplay between the nervous system, the digestive tract and the skin. These links highlight the relevance of investigating emotional health when treating patients with skin disorders and that nervous system support as a component of naturopathic care with an individualised herbal medicine prescription have been an effective treatment strategy.

References

1. Sharma B, Sudarsanan B, Bhatnagar M. Skin and psyche: diversionary symbiosis. Med J Armed Forces India 2005;61(2):163–166.
2. Gordon-Elliott JS, Muskin PR. Managing the patient with psychiatric issues in dermatologic practice. Clin Dermatol 2013;31(1):3–10.
3. Gupta MA. Emotional regulation, dissociation, and the self-induced dermatoses: Clinical features and implications for treatment with mood stabilizers. Clin Dermatol 2013;31(1):110–117.
4. Kleyn CE *et al*. The effects of acute social stress on epidermal Langerhans' cell frequency and expression of cutaneous neuropeptides. J Invest Dermatol 2008;128(5):1273–1279.
5. Kim J *et al*. Expression of hypothalamic–pituitary–adrenal axis in common skin diseases: evidence of its association with stress-related disease activity. Acta Derm Venereol 2013;93(4):387–396.
6. Haugen PT *et al*. Mental health stigma and barriers to mental health care for first responders: A systematic review and meta-analysis. J Psychiatr Res 2017;94:218–229.
7. Seaton K. Naturopathic philosophy. In: L Hechtman, editor. Clinical naturopathic medicine Sydney: Churchill Livingstone Elsevier; 2012, pp. 3–13.
8. Gruner T, Sarris J. Stress and fatigue. In: J Sarris, J Wardle, editors. Clinical naturopathy: an evidence based guide to practice, Sydney: Churchill Livingstone Elsevier; 2014, pp. 350–370.
9. Pigrau M *et al*. The joint power of sex and stress to modulate brain–gut–microbiota axis and intestinal barrier homeostasis: implications for irritable bowel syndrome. Neurogastroenterol Motil 2016;28(4):463–486.
10. Steel A. Inflammatory skin disorders — atopic eczema and psoriasis. In: JSJ Wardle, editor. Clinical naturopathy: an evidence based guide to practice Sydney: Churchill Livingstone Elsevier; 2014, pp. 543–557.
11. Pratte M *et al*. An alternative treatment for anxiety: a systematic review of human trial results reported for the ayurvedic herb ashwagandha (*Withania somnifera*). J Altern Complement Med 2014;20(12):901–908.
12. Panossian A *et al*. Adaptogens exert a stress-protective effect by modulation of expression of molecular chaperones. Phytomedicine 2009;16(6):617–622.
13. Daley J. The gastrointestinal system. In: L Hechtman, editor. Clinical naturopathic medicine Sydney: Churchill Livingstone Elsevier; 2012, pp. 152–209.
14. Bone K. A clinical guide to blending liquid herbs. Missouri: Churchill Livingstone; 2003.
15. Singh G *et al*. Antidepressant activity of *Asparagus racemosus* in rodent models. Pharmacol Biochem Behav 2008;91(3):283–290.
16. Garabadu D, Krishnamurthy S. *Asparagus racemosus* attenuates anxiety-like behavior in experimental animal models. Cell Mol Neurobiol 2014;34(4):511–521.
17. Krishnamurthy S, Garabadu D, Reddy N. *Asparagus racemosus* modulates the hypothalamic–pituitary–adrenal axis and brain monoaminergic systems in rats. Nutr Neurosci 2013;16(6):255–261.
18. Sarris J, McIntyre E, Camfield D. Plant-based medicines for anxiety disorders, part 2: a review of clinical studies with supporting preclinical evidence. CNS Drugs 2013;27(4):301–319.
19. Akhondzadeh S *et al*. Passionflower in the treatment of generalized anxiety: A pilot double-blind randomized controlled trial with oxazepam. J Clin Pharm Ther 2001;26(5):363–367.
20. Movafegh A *et al*. Preoperative oral *Passiflora incarnata* reduces anxiety in ambulatory surgery patients: a double-blind, placebo-controlled study. Anesth Analg 2008;106(6):1728–1732.
21. Ngan A, Conduit R. A double-blind, placebo-controlled investigation of the effects of *Passiflora incarnata* (Passionflower) herbal tea on subjective sleep quality. Phytother Res 2011;25(8):1153–1159.
22. Singh R, De S, Belkheir A. Avena sativa (Oat), a potential neutraceutical and therapeutic agent: an overview. Crit Rev Food

Sci Nutr 2013;53(2):126–144.
23. Sinclair J, Hechtman L. Herbal medicine. In: L Hechtman, editor. Clinical naturopathic medicine. Sydney: Churchill Livingstone Elsevier; 2012, pp. 103–149.
24. Ekstrand B, Young J, Rasmussen M. Taste receptors in the gut — A new target for health promoting properties in diet. Food Res Int 2017.
25. Bone K, Mills S. Principles and practice of phytotherapy, modern herbal medicine, 2nd ed. Edinburgh: Churchill Livingstone Elsevier; 2013.
26. Salem M *et al*. Pharmacological studies of artichoke leaf extract and their health benefits. Plant Foods Hum Nutr 2015;70(4):441–453.
27. Walker A, Middleton R, Petrowicz O. Artichoke leaf extract reduces symptoms of irritable bowel syndrome in a post-marketing surveillance study. Phytother Res 2001;15(1):58–61.
28. Marakis G *et al*. Artichoke leaf extract reduces mild dyspepsia in an open study. Phytomedicine 2002;9(8):694–699.
29. Bundy R *et al*. Artichoke leaf extract reduces symptoms of irritable bowel syndrome and improves quality of life in otherwise healthy volunteers suffering from concomitant dyspepsia: a subset analysis. J Altern Complement Med 2004;10(4):667–669.
30. Craig J. Atopic dermatitis and the intestinal microbiota in humans and dogs. Vet Med Sci 2016;2(2):95–105.
31. Li Y *et al*. Chronic social stress in pigs impairs intestinal barrier and nutrient transporter function, and alters neuro-immune mediator and receptor expression. PLoS One 2017;12(2):e0171617.
32. Gareau M, Silva M, Perdue M. Pathophysiological mechanisms of stress-induced intestinal damage. Curr Mol Med 2008;8(4):274–281.
33. Kiecolt-Glaser J *et al*. Hostile marital interactions, proinflammatory cytokine production, and wound healing. Arch Gen Psychiatry 2005;62(12):1377–1384.
34. Hunter H, Momen S, Kleyn C. The impact of psychosocial stress on healthy skin. Clin Exp Dermatol 2015;40(5):540–546.

Australian Journal of Herbal and Naturopathic Medicine **2018** 30(1)

Synopsis of: Leach M, Canaway R, Hunter J (2018) Evidence based practice in traditional and complementary medicine: An agenda for policy, practice, education and research, Complementary Therapies in Clinical Practice, 31 pp.38-46

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Synopsis of: Leach M, Canaway R, Hunter J (2018) Evidence based practice in traditional and complementary medicine: An agenda for policy, practice, education and research, Complementary Therapies in Clinical Practice, 31 pp.38-46

In November 2015, a facilitated roundtable 'Complementary Medicine Products Evidence Forum' was convened in Sydney. Through the Forum, the conveners[1] aimed to bring together 'great minds' in complementary medicine for discussion on how evidence for complementary medicine products is (or should be) 'thought about' now and in the future. Seventeen participants attended. The discussion on 'evidence' quickly broadened from 'products' to examine notions of evidence in many applications relevant to traditional and complementary medicine (T&CM). Analysis of the Forum transcript led to development of a framework for setting a broad agenda for strengthening the evidence-base for T&CM in Australia (pending publication). Also arising was a specific agenda for understanding and advancing evidence-based practice in T&CM. The resulting publication is available in the journal *Complementary Therapies in Clinical Practice* (vol 31, pp.38-46) – its central themes and highlights are summarised below.

Four central themes relating to evidence-based practice in T&CM were outlined: understanding evidence; drivers of change; interpersonal interaction; and 'moving forward'. The discussion teases out philosophic, cultural, political, educational and regulatory issues, and the need for leadership collaboration and effective communication to overcome barriers and drive change. The authors provide a relational thematic depiction of the four main themes and their 15 sub-themes – each discussed in turn. They follow with three 'broad calls to action': defining clear and consistent terminology (e.g. evidence, traditional and complementary medicine); defining an EBP approach for T&CM; and fostering social movement (i.e. a peoples' movement – change through societal pressure, encouraging social debate).

Highlights of the article include the need to revisit the original 'triad' of evidence-based medicine which teams *best available* evidence with clinical expertise and patient preferences – a conceptualisation that can easily be applied to T&CM. Rather than preferencing and discarding certain information based on where it sits in the 'evidence hierarchy' (academic hierarchy that preferences certain types of research evidence over others), use of 'totalities of evidence' can enable contemplation of 'evidence' from all types of research and knowledge (e.g. traditional knowledge), thus building a larger 'totality' of understanding. This relates well with the original EBM triad (acceptance of the *best available* evidence) and raises the need to discuss the suitability of traditional knowledge to provide evidence of safety, and to honour clinical expertise and the 'art' of healthcare applied alongside its science. Shifting research focus for T&CM away from efficacy (and randomised controlled trials) towards better understanding of T&CM safety (and clinically relevant evidence) was considered critical to the agenda.

To drive the agenda forward, the authors describe the need to harness a 'more politicised discourse' and make more use of the 'consumer voice' to create a 'peoples' movement' to educate and lobby. Perhaps publication of the agenda for EBP in T&CM will be enough to prompt traditional and complementary medicine practitioners to take note and become catalysts of change. It is more likely though, that leadership to drive the described actions is yet to crystallise. I await with anticipation to see whether this agenda and its suggested actions can prompt movement and stewardship towards strengthening EBP in T&CM – in a way that honours generations of accumulated knowledge and the preferences of the countless many who benefit from T&CM.

About the author: Rachel Canaway was a Forum participant, co-author of the article, is a long-time member of NHAA, is a (currently non-practising) naturopath and massage therapist, manages a primary care practice-based research network based at the Department of General Practice, The University of Melbourne, and is a Visiting Fellow at the Australian Research Centre in Complementary and Integrative Medicine, UTS.

Reference

1. NICM (National Institute of Complementary Medicine – Western Sydney University) and ASMI (Australian Self-Medication Industry)

Reviews of articles on medicinal herbs

Jodie Tester

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.

Ashwagandha in mild cognitive impairment

Choudhary D, Bhattacharyya S, Bose S. Efficacy and safety of ashwagandha (*Withania somnifera* (L.) dunal) root extract in improving memory and cognitive functions. *J Diet Suppl* 2017;14(6):599–612.

Cognitive function decline and mild cognitive impairment (MCI) are often associated with ageing processes, with MCI characterised by memory problems without significant functional disruption in activities of daily living. Ashwagandha (*Withania somnifera*) has traditionally been used in a variety of conditions including memory and cognitive deficit following injury, illness, or old age. Clinical research has explored the potential of ashwagandha extract in experimental models of neurodegenerative disorders including Alzheimer's disease and Parkinson's disease, as well as in bipolar disorder. This research was designed to investigate effect of ashwagandha on cognitive function in humans with symptoms of MCI.

The 8-week study was a prospective, randomised, double-blind, placebo-controlled study with subjects recruited from different outpatient clinics in Pune, India. Participants were aged 35 years or older with mild, subjective memory impairment, a previous diagnosis of dementia or MCI, or score of ≥19 on the Mini-Mental State Examination (MMSE). Exclusion criteria included MMSE score <19 (indicative of moderate to severe memory impairment), known neuropsychiatric conditions, persistent endocrine disorders, uncontrolled hypertension or diabetes, drug or alcohol use or dependence, psychotropic drugs or treatments for memory enhancement. The use of nootropic agents or anti-cholinesterase drugs were prohibited through the study.

Subjects were randomly allocated to receive either 300mg of ashwagandha root aqueous extract capsule (Ixoreal Biomed, California) twice daily or matching placebo for eight weeks. Physical examination, BMI, vitals, the MMSE questionnaire and cognitive assessments were undertaken at baseline and after 8 weeks intervention. Cognitive function assessments for memory, visuospatial, executive function and attention were included.

In total, 50 subjects were enrolled in the study with baseline characteristics and cognitive impairment levels (as determined by MMSE) similar across groups. After eight weeks of intervention, both groups demonstrated some improvement in immediate memory. Ashwagandha treatment was associated with significantly enhanced scores compared to placebo in the general memory and immediate memory subsets at 8 weeks.

Executive function, attention, and information processing speed were significantly improved with ashwagandha intervention at both 4 weeks and 8 weeks compared to placebo. The working memory index produced inconclusive results and no statistically significant effect was observe for visuospatial processing and response.

Strengths of the study include its prospective design and use of a variety of tools to assess different aspects of cognition. However, its small size and duration limit the interpretability of the findings. Furthermore, a single-dose regime makes it difficult to assess optimal dosing patterns. Future studies which address these limitations and assess the impact of both clinical efficacy and safety over a longer term are required.

Cranberry for prevention of UTI recurrence in otherwise healthy women

Fu Z, Liska D, Talan D, Chung M. Cranberry reduces the risk of urinary tract infection recurrence in otherwise healthy women: A systematic review and meta-analysis. *J Nutr* 2017. In print. doi: https://doi.org.10.3495/jn.117.254961

Urinary tract infection (UTI) is one of the most common urological conditions worldwide, causing significant health economic burden. The most common form of UTI is cystitis, a sporadic uncomplicated UTI in the bladder of otherwise healthy individuals. Uncomplicated UTIs are more common in women, and there is increased risk in those with a past history of UTI. Common therapeutic approaches to UTIs are with antibiotics, prophylactic treatment sometimes used in women with recurrent UTIs. With increasing rates of antibiotic resistance, interest in non-antibiotic methods for UTI prevention are of interests. Cranberry (*Vaccinium spp*) has been studied for its potential in UTI with in vitro research demonstrating that compounds in cranberry may interfere with bacterial adhesions to urinary tract epithelial cells amongst other actions. Published meta-analyses assessing the efficacy of cranberry in UTI have been conflicting and have included both complicated and uncomplicated UTIs. To better understand the literature, the authors of the current study aimed to assess the effect of cranberry on the risk of UTI recurrence in otherwise healthy women.

The authors searched the MEDLINE and EMBASE databases for literature published from January to July 2017 and used two previously published systematic reviews for literature previously published. The analysis

included randomised controlled trials (RCTs) conducted in healthy non-pregnant women aged 18 years or older, with a history of UTI, compared a cranberry intervention to a placebo or non-treatment control, and reported outcomes as the number of participants experiencing a UTI. Exclusion criteria included studies non-published as peer-reviewed full text articles. Conducted in special groups, institutionalised subjects, and participants with diagnosed disease or complicated UTI. The quality of evidence was assessed as was bias risk.

In total, seven RCTs were included for qualitative synthesis, three of which were included in the previous meta-analyses and four of which were published afterwards, representing new data. The studies were relatively small with only two studies having more than 300 participants. Pooling the data resulted in 1498 participants for analysis. The meta-analysis found a 26% reduction in risk of UTI recurrence for healthy women who received cranberry compared to those who did not. Cranberry supplementation used in the studies ranged from cranberry juice (n=5), powder capsules (n=1), or juice + tablets (n=1). Length of treatment varied from 6–12 months. Subgroup analysis also showed that cranberry significantly reduced the risk of UTI recurrence by 35% in women who were free of UTI at enrolment. No statistically significant reduction in risk was found for women with an active UTI episode at time of enrolment and then treated with antibiotics before UTI recurrence assessment.

Quality assessment of the studies highlighted the ongoing need for high quality research with a number of studies not providing randomisation information, having high rates of loss to follow-up, risk of bias, lack of information on UTI diagnosis or poor compliance.

The authors concluded that the meta-analysis suggests cranberry can be a potential non-pharmacological approach for generally healthy women to prevent an uncomplicated recurrent UTI. Larger high-quality studies are needed to confirm these findings.

Withania somnifera in a rat model for anxiety and neuroinflammation

Kaur T, Kaur G. *Withania somnifera* as a potential candidate to ameliorate high fat diet-induced anxiety and neuroinflammation. *Journal of Neuroinflammation* 2017;14:201. doi 10.1186/s12974-017-0975-6.

Obesity is an ongoing global health problem contributing to significant morbidity, mortality and economic burden. Obesity has been recognised as an inflammatory condition, characterised by increased production and secretion of proinflammatory cytokines including TNFα and IL-6. Whilst low-grade inflammation is implicated in various metabolic disorders, including cardiovascular disease, type 2 diabetes, and asthma, its role is also being considered in the context of neuropsychiatric disorders. It is suggested that peripheral inflammatory signals cross the blood–brain barrier and enter the CNS, causing neuroinflammation and affecting neuroendocrine and neurotransmitter activity. *Withania somnifera* is used for a variety of conditions in Ayurveda therapies. The current study aimed to investigate whether a dry leaf powder of *W. somnifera* has anxiolytic and anti-neuroinflammatory potential in diet-induced obesity in a rat model.

Young female rats aged 3–4 months were used for experiments and were randomised into four groups: low fat diet, high fat diet group, low fat diet plus extract group, and high fat diet supplemented with extract group. The intervention was a dry powdered extract of *W. somnifera* leaf (ASH) at a dose of 1mg/g body weight. Anxiety was assessed through an elevated plus maze (EPM) test. After the EPM test, animals were sacrificed and used for immunohistological staining, Western blot analysis, and quantitative real-time PCR analysis to study inflammatory markers.

The results of trial demonstrated ASH played a role in weight management with the supplemented groups, both low fat and high fat, gaining significantly less weight than their control counterparts. Overall the rats supplemented with ASH demonstrated less anxiety levels as per the maze test when compared to high-fat controls. The ASH supplemented groups were similar to anxiety levels of the low-fat diet control. At a biochemical and molecular level, ASH ameliorated the HFD-induced reactive gliosis and microgliosis and suppressed the expression of inflammatory markers such as PPARγ, iNOS, MCP-1, TNFα, IL-1β and IL-6. Further research demonstrated that ASH supplementation reduced leptin and insulin resistance and prevented HF-induced apoptosis.

The study provides interesting results regarding the potential of *W. somnifera* as an anxiolytic and anti-neuroinflammatory agent and investigated possible mechanisms of action. Whilst studies in animal models are valid and beneficial, more research to better understand and evaluate the potential of *W. somnifera* as an anxiolytic and to counter neuroinflammation in humans are needed.

Silymarin in mice model of NASH

Marin V, Gazzin S, Gambara SE, Dal Ben M, Calligaris S, Anese M *et al.* 2017. Effects of oral administration of silymarin in a juvenile murine model of non-alcoholic steatohepatitis. *Nutrients* 2017; 9:1006. In print. doi:10.3390/nu9091006

Non-alcoholic fatty liver disease, encompassing both simple steatosis and non-alcoholic steatohepatitis (NASH) is increasing in prevalence and is a common cause of liver disease in Australia. There is no consensus on pharmacological treatment for NASH with treatment mainstays including lifestyle modification, diet and physical activity; however, compliance for these approaches remains challenging. Silymarin, an isolated compound from *Silybum marianum*, has been traditionally used in various liver disorders due to potential hepatoprotective effects including anti-inflammatory, immunomodulatory, anticholesterolaemic properties. In the current study, the authors assessed the protective effects of silymarin in a juvenile NASH model and the in vitro effects on fat-laden human hepatocytes.

In the animal model, mice pups were initiated on a high fat high carbohydrate (HFHC) diet for a total of eight weeks. The HFHC induces alterations in the blood lipid profile by increasing total cholesterol, LDL and HDL. At this time, the mice were divided into 4 groups where one group of mice continued with HFHC silymarin (33mg/kg)-enriched diet (HFHC-SIL), the third group was switched from HFHC to control diet (HFHC → CTRL) to alimentary lifestyle changes, and the final group switched from HFHC to CTRL enriched with silymarin (HFHC →CTRL + SIL). The experiment was continued for a further 12 weeks when the mice were sacrificed. Secondly, the direct effect on human hepatocytes was assessed in vitro, by using stabilised hepatic cell lines.

The HFHC diet supplemented with silymarin resulted in improved glycaemia, visceral fat, lipid profile, and liver fibrosis. It also reduced both in vivo and in vitro ALT, hepatic inflammation, oxidative stress, and apoptosis. Differences in response were noted between female and male mice. Insulin resistance was only induced in male rats and whilst silymarin was associated with a slight reduction in glucose, there was no observed reduction in insulin and thus, no improvement insulin resistance. Conversely, the HFHC diet induced hepatic oxidative stress only in females with the silymarin intervention demonstrating ability to reduce the induced oxidative stress. The authors commented their most interesting finding within the study was the regression of liver fibrosis following the addition of silymarin to the HFHC diet. It has recently been described that fibrosis is the only histological feature associated with long-term outcomes of patients with NAFLD.

The study provides interesting in vivo and in vitro evidence to support silymarin as a potential therapeutic candidate for NAFLD and NASH. Lifestyle interventions can significantly revert changes induced by an HFHC diet, which was supported by the findings of this study; however, adopting these changes successfully can be challenging for many. Further research is required to further assess silymarin and its bioavailability, efficacy and safety in NASH and NAFLD in humans.

Bacopa monnieri on hippocampal synaptic potentiation in rats

Promsuban C, Limsuvan S, Akaraseereenont P, Tiloskulchai K, Tapechum S, Pakaprot N. 2017. *Bacopa monnieri* extract enhances learning-dependent hippocampal long-term synaptic potentiation. *NeuroReport* 28:1031–1035.

Bacopa monnieri, commonly known as Brahmi, has been used in Ayurvedic medicine as a memory enhancer for many years; however, its effect on brain and synaptic plasticity has not been well investigated. Long-term potentiation facilitates synaptic strength and may play important roles in hippocampal-dependent spatial learning and memory processes. Whilst many studies have researched molecular effects of Brahmi, the synaptic effect of the compound is less well understood

and accordingly, the current study aimed to examine this based on the hypothesis that Brahmi would enhance learning-dependent hippocampal synaptic response.

Twenty-four male wistar rats were divided randomly into four groups. The rats were orally administered either sterile water or the ethanolic extract of *B. monnieri* for 60 days, at doses of 80, 160 or 240 mg/kg. Acute hippocampal slices were prepared after the 8 weeks of administration of Brahmi or control, after the rats were euthanised. Extracellular recordings were then performed to measure the field excitatory postsynaptic potential in the hippocampal slices.

Basal synaptic transmission was examined in the hippocampal slices by measuring post synaptic stimulus response curves induced by gradual increases of stimulus intensity. No interaction was observed with no significant differences between groups, suggesting Brahmi does not affect the basal synaptic transmission of hippocampal synapses. When looking at the long-term potentiation magnitudes, all Brahmi-treated groups were significantly higher than that of the control group. The authors suggested these results support the memory-enhancing effect of Brahmi extract by demonstrating the extract can significantly enhance the learning-dependent synaptic response of the hippocampal synapses, which plays a critical role in learning and memory formation.

Understanding the mechanisms of traditionally used herbal medicines may lead to better understanding of best and appropriate uses of these compounds. Further research to demonstrate the effectiveness of Brahmi on learning and memory formation in humans is required for optimising its therapeutic potential and use.

Ashwagandha in patients with subclinical hypothyroidism

Sharma AK, Basu I, Singh S. 2017. Efficacy and safety of Ashwagandha root extract in subclinical hypothyroid patients: A double-blind, randomized placebo-controlled trial. *J Altern Complement Med* 2017. In print. doi: 10.1089/acm.2017.0183

Subclinical hypothyroidism (SCH) is estimated to occur in 3–8% of the total population, affecting females more than males. Biochemical markers may reveal elevation of serum thyroid stimulating hormone (TSH) despite normal serum thyroxine (T4), possibly with presence of antithyroid antibodies. Treatment for SCH is usually limited to levothyroxine and often only recommended with TSH levels exceeds 10μIU/L as the utility of levothyroxine for TSH levels below this remains controversial when considering risks versus benefits. *Withania somnifera* (ashwagandha) is a herbal adaptogen commonly recommended by traditional Ayurvedic healers for a variety of hormonal conditions including thyroid imbalances. Previous research has demonstrated effect on thyroid hormone profiles in animal and human studies. The current study is a prospective, randomised, double-blind, placebo-controlled pilot study designed to evaluate the safety and efficacy of ashwagandha root extract in a subclinical hypothyroid patient population.

The study was conducted at an Indian hospital with participants recruited from attendees of general health camps conducted at the study centre. Participants were aged between 18 and 50 years, were without significant medical history, and had serum TSH levels between 4.5–10μIU/L, and serum T3 and T4 within normal ranges. Exclusion criteria included smoking history within the past year, known hypersensitivity to ashwagandha or related herbal product, diagnosis of heart disease, diabetes, stroke, depression or neurologic/psychiatric disorders, and recent use or under-treatment of thyroid medication, nutritional/energy supplements, hypotensives, beta-blockers, inhaled beta agonists, hormonal contraceptives, corticosteroids, or pyschotropics. Participants were randomly allocated to receive either 300mg of ashwagandha root aqueous extract capsule (Ixoreal Biomed, California) twice daily or matching placebo for eight weeks. General health, physical, vital, haematological and biochemical markers including serum TSH, T4 and T3, were obtained at baseline and follow-up visits in week 4 and week 8 (end of study).

From 90 individuals identified at the health camps with TSH levels 4.5–10μIU/L and serum T3 and T4 within normal ranges, 50 met the study inclusion criteria and were allocated to treatment. Baseline demographics and health parameters were similar between groups. At baseline, mean TSH levels were not significantly different between ashwagandha and placebo groups being 6.48 and 6.72μIU/L, respectively. There was no significant difference between groups for baseline T4 or T3 levels. For the ashwagandha treated group, significant increases were observed at week 4 and week 8 for T3 and T4 levels from baseline, with a significantly decrease for TSH levels from baseline also observed at weeks 4 and 8. At the end of week 8, mean TSH levels were 5.35 and 7.05 μIU/L for the ashwagandha and placebo groups, respectively. No significant change for TSH, T4 or T3 levels from baseline was observed for the placebo group at week 8.

As a pilot study, limitations include its small sample size and study duration. With the significant increases in thyroid hormones reported in the active intervention, it is important to monitor for ongoing safety and any risk of thyrotoxicosis. Further long-term studies with larger and diverse study populations are required, as well as more studies assessing the clinical outcomes of normalising thyroid indices to better understand optimal treatment strategies.

Saffron and women with mild-to-moderate postpartum depression

Tabeshpour J, Sobhani F, Sadjadi SA, Hosseinzadeh H, Mohajeri SA, Rajabi O *et al.* A double-blind, randomized, placebo-controlled trial of saffron stigma (C*rocus sativus* L.) in mothers suffering from mild-to-moderate postpartum depression. *Phytomedicine* 2017;36:145–152.

Postpartum depression (PPD) occurs in approximately 14.5% of new mothers and can have major health implications for both mother and baby. As PPD can impact on the baby's development and is implicated in risk of infant cognitive disorders and effect on social development, treatment strategies are of great importance.

Antidepressant medications may have a role but are associated with side effects and are known to cross into and are excreted in breast milk. Saffron (*Crocus sativus*) has demonstrated promising results for its antidepressant effects and early clinical research in mild-to-moderate depression. The aim of the current study was to evaluate the antidepressant effect of saffron in PPD breastfeeding mothers and the possible adverse effects of treatment.

The study was a randomised, double-blind, placebo-controlled trial conducted in Iran. Participants included 60 new breastfeeding mothers who had a maximum score of 29 on the Beck Depression Inventory-Second Edition (BDI-II). In the BDI-II scores of 0–13 denoted minimal depression, 14–19 denoted mild depression, 20–28 denoted moderate depression and scores of 29–63 denoted severe depression. Women were to have no present or past history of drug or alcohol abuse or use during pregnancy, no medication use known to affect mood, no previous psychiatric conditions, no significant medical illness, no signs of psychosis, no suicidal thoughts and must have given birth to live and healthy singleton term infants within the previous nine months. Exclusion criteria included pregnancy, taking anticoagulants, and current benefit from psychotropic medications. Women were randomly assigned to receive saffron (15mg/BD) or equivalent placebo for eight weeks. The primary endpoint was change in the BDI-II scores after 8 weeks compared to baseline. Secondary outcomes included the response and remission rates.

In total, 78 women were randomised for treatment with 18 dropping up before the first follow-up visit resulting in 60 women completing the trial. Demographics of the two groups were comparable. There were no statistically significant differences in baseline BDI-II scores between the saffron and placebo groups. Reductions in BDI-II scores from baseline demonstrated significant differences between the two groups by the study's endpoint. By week 8, the mean BDI-II scores had decreased from 20 to 8.4 and from 19.7 to 15.3 for the saffron and placebo groups, respectively. Significant differences in groups were also seen at week 4. The authors considered and analysed for a number of potential confounders including the age of the mother, BMI, the infant's gender, number or pregnancies and the mother's education, after which the results remained significant. The authors reported no serious adverse effects in the saffron group; however, it is unclear whether safety assessment and adverse effects were based on all final participants or intention to treat.

As the sample size of the study is quite small, interpretation of the results is limited. Additionally, whilst no serious adverse events were reported, it should be noted that saffron has not been demonstrated to be safe in breastfeeding women with neither enough evidence to suggest saffron is safe or unsafe for breastfeeding women and their infants. The study provides early clinical support that saffron is more effective than placebo in treating mild to moderate PDD in breastfeeding mothers. More research is required to understand the longer term benefits and ensure safety in breastfeeding mothers.

Reviews of medical journal articles

Jodie Tester

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 naturopathy and herbal medicine. A dominant theme is often present throughout the journals, which will be reflected in the reviews.

Arguments for and against the Mediterranean diet in patients with chronic kidney disease

Chauveau P, Aparicio M, Bellizzi V, Campbell K, Hong X, Johansson L *et al.* 2017. Mediterranean diet as the diet of choice for patients with chronic kidney disease. *Nephrol Dial Transplant* 2017. In print. doi:10.1093/ndt/gfx085

The Mediterranean diet (MD) is a well-researched dietary approach that has demonstrated significant benefit in a number of health populations. Emerging evidence has suggested a potential role for fruit and vegetable-rich diets such as the MD in patients with chronic kidney disease (CKD). CKD dietary guidance has traditionally focused on the quantity of macronutrient intake of energy and protein, with restriction of single micronutrients. Reluctance to advise these diets may arise because of conflict of some of the typical components of the MD diet with traditional dietary restrictions of CKD. The current study reviewed the evidence and arguments for and against adopting the MD for the CKD patient population.

The traditional MD promotes high consumption of fruit, vegetables, bread and wholegrain cereals, beans, nuts, seed, and extra virgin olive oil, moderate consumption of dairy, fish, poultry and eggs, low consumption of red meat and sweets, and low-to-moderate consumption of wine with meals. The MD diet has been associated with cardiovascular (CV) benefits and risk reduction of CV disease. It has also been recognised for prevention of obesity or type II diabetes, and reductions in blood pressure, inflammation and oxidative stress, and improved lipid profiles.

The authors report a number of arguments to support the MD recommendation in patients with CKD to include that: the MD provides a healthy protein and fat intake profile, noting that the protein recommendations are similar to traditional recommendations; the MD provides a low glycaemic index and low glycaemic load, which may have a relevance for dialysis patients; the MD allows for a moderate consumption of wine, which may also benefit patients with CKD; the persistent inflammation and oxidative stress of CKD may benefit from the increased olive oil consumption; the MD favours natural versus processed foods, which may impact on CKD progression and has demonstrated benefit in end-stage renal disease patients; and the MD promotes increased dietary fibre intake, which may complement research that a high fibre intake relative to protein may reduce CV risk in individuals with mild CKD.

There are two key arguments against prescribing MDs to patients with CKD that are put forward by the authors. Firstly, concerns that high consumption of fruit and vegetable leads to increased consumption of potassium and subsequent risk of hyperkalaemia. The authors agree that the issue warrants further study, but suggest the recommendation of fruit and vegetables with low potassium content in addition to close potassium monitoring. A second argument is that dietary acid load misbalance may favour low acid load; however, the authors suggest that an overall decrease in net endogenous acid production may lead to better control of metabolic acidosis.

The authors do well in balancing the arguments for and against the recommendation of MDs to patients with CKD. Concerns are legitimate when prescribing an increased intake of fruit and vegetables, particularly those high in potassium due to the potential to contribute to hyperkalaemia, electrolyte balance and serum acidity which lead to serious adverse outcomes for these patients. The authors also note the cardioprotective effects of the vitamins, fibre and antioxidants of such a diet and benefits in both CV and kidney disease prevention. The article provides a good summary piece in considering dietary recommendations for patients with CKD.

Psychiatric disorders in children and maternal antidepressant use during pregnancy

Liu X, Agerbo E, Ingstrup KG, Musliner K, Meltzer-Brody A, Bergink V, Munk-Oslen T. 2017. Antidepressant use during pregnancy and psychiatric disorders in offspring: Danish nationwide register based cohort study. *BMJ* 2017;358:j3668. Available from: http://dx.doi.org/10.1136/bmj.j3668

Antidepressants have been increasing used during pregnancy, with approximately 2–8% pregnant women receiving antidepressant treatment. Selective serotonin reuptake inhibitors (SSRIs) are the most commonly prescribed antidepressants. Recent studies have linked SSRI use during pregnancy to autism spectrum disorder in offspring; however, results have been conflicting. One potential explanation for the association is that SSRIs cross the placenta barrier and affect foetal brain development. If this is the case, it stands that in utero SSRI exposure may increase the risk for various psychiatric disorders. Accordingly, the authors of the present study aimed to investigate the association between in utero exposure to antidepressants and risk of psychiatric disorders using data from a population-based cohort study.

The study used data from the Danish Medical Birth Registry, identifying all liveborn singletons during 1998–2012. Children with missing or errors in gestational age, with chromosomal abnormalities, and/or with missing links to their fathers were excluded. Antidepressant use during pregnancy came from the Danish National Prescription Registry which covers all prescriptions dispensed in Denmark since 1995. Dispensing date was used to indicate the start of antidepressant use. Antidepressant use during pregnancy was defined as a prescription dispensed on any date from one month before pregnancy until delivery. Recent maternal use of antidepressant was defined by including antidepressant prescriptions from two years before pregnancy to delivery. Children were divided into four groups depending on maternal antidepressant prescribing for analysis: the unexposed group with no maternal antidepressant use before or during pregnancy; the discontinuation group had use before but not during pregnancy; the continuation group had antidepressant use before and during pregnancy; and the new user group had use only during pregnancy. The primary outcome was first diagnosis of psychiatric disorders. Secondary outcomes included the subcategories autism spectrum disorder, mood disorder, behavioural and emotional disorder, and mental retardation amongst others. A number of potential confounders were identified and considered including parental psychiatric history at delivery, other prescription medications during pregnancy including antiepileptic drugs and other psychotropic drugs, smoking, education, income status and year of delivery.

In total, 905,383 liveborn singletons born during the specified period were followed from birth until July 2014, death, emigration or date of first psychiatric disorder, whichever occurred first. Of these, over 21,000 (2.3%) were born to mothers who used antidepressants during pregnancy. In total, approximately 1.8% mothers used SSRI monotherapy, 0.4% used non-antidepressant therapy, and 0.2% used combined SSRI and non-SSRI antidepressants. Children were followed for a maximum of 16.5 years. Overall, 32,400 children were diagnosed with having psychiatric disorders with the mean age at first diagnosis being 8.5 years. An increased risk of psychiatric disorders was observed in all three groups of antidepressant users (discontinuation, continuation, and new user group) compared with the unexposed group. The cumulative incidence of psychiatric disorders was 8.0% in the unexposed group, 11.5% in the discontinuation group, 13.6% in the continuation group, and 14.5% in the new user group. The risk for psychiatric disorders among offspring was higher in the continuation group than that in the discontinuation group which remained after adjusting for potential confounders. Timing of antidepressant exposure also influenced associated risk, with exposure during the first trimester only having a lower risk of psychiatric disorders compared to children exposed in the second or third trimester or exposed during more than one trimester. No significant differences in hazard ratios were observed between commonly prescribed SSRIs. A higher risk was also associated for antidepressant use greater than 180 days. Increased risks in the continuation group compared with the discontinuation group was also observed for autism spectrum disorder, mood disorder, somatoform disorder, and behavioural disorder, but not mental retardation.

Limitations of the study include using prescription data to define antidepressant exposure in utero, which may be influenced by a number of factors including compliance and misclassification. Strengths of the study include the population-based study, which provides large numbers of participants and the range of disorders it followed for long-term outcomes. Antidepressant use during pregnancy was associated with an increased risk of psychiatric disorders in offspring. The clinical challenge remains in deciding whether to discontinue, maintain or change antidepressant treatment during pregnancy as these actions too can have long-lasting effects on both the child and mother.

Weight loss interventions in adults with obesity and all cause mortality

Ma C, Avenell A, Bolland M, Hudson J, Stewart F, Robertson C *et al.* Effects of weight loss interventions for adults who are obese on mortality, cardiovascular disease, and cancer: systematic review and meta-analysis. *BMJ* 2017;359:j4849. Available from: http://dx.doi.org/10.1136/bmj.j4849

Obesity is global health burden, with adult obesity associated with increased risk of premature mortality, cardiovascular disease, some cancers, and type 2 diabetes, amongst other diseases. Whilst these associations are evident, limited evidence is available from randomised controlled trials (RCTs) to demonstrate whether weight loss interventions can prevent serious harm for people with obesity. Some studies have indeed reported adverse consequences of deliberate weight loss in some obese populations. The present study aimed to assess whether weight loss interventions for adults with obesity affect all-cause, cardiovascular, and cancer mortality, cardiovascular disease, cancer, and body weight.

The study was a systematic review and meta-analysis of RCTs conducted in adults with a mean BMI >30 at baseline and a minimum follow-up period of one year. Trials were required to be clearly focused on weight loss with a weight reduction diet, with or without physical activity advice or programmes. Trials in pregnant or postpartum women were excluded. Three primary outcomes were assessed for: all-cause mortality, cardiovascular mortality, and cancer mortality. Secondary outcomes included new cardiovascular events, new cancers, and weight change.

In total, 54 RCTs were included in the final review, involving 30,206 adults with obesity. The populations of the studies were diverse, including Asian, North American, European, Australian and Brazilian populations. A variety of weight loss diets were employed including low-fat, Mediterranean, reduced

carbohydrate, low glycaemic index, and the DASH diets. Regarding the primary outcomes, weight loss interventions were associated with a decrease in all-cause mortality from high-quality evidence. This equated to an 18% relative reduction in premature mortality. Moderate-quality evidence supported a decrease of cardiovascular mortality and low-quality evidence showed an effect on cancer mortality with weight reduction. Weight change reported was a mean reduction of 3.42 kg after one year, and a 2.51 kg reduction after two years; however, a wide diversity of effect on weight loss from the different interventions was noted. The study was unable to demonstrate effect of weight loss on new cardiovascular events or new cancers.

The study provides evidence to support mortality benefits for weight reduction in adults with obesity, in addition to the already proven benefits such as type 2 diabetes prevention. With many different approaches to weight loss, it remains important to assess the strategies through clinical evidence frameworks to enable comparison of weight reduction strategies and to better understand their effects on mortality and morbidity beyond weight change.

B-vitamin intake in younger adulthood and association with middle-age cognitive function

Qin B, Xun P, Jacobs DR Zhu N, Daviglus ML *et al.* Intake of niacin, folate, vitamin B-6, and vitamin B-12 through young adulthood and cognitive function in midlife: the Coronary Artery Risk Development in Young Adults (CARDIA) study. *Am J Clin Nutr* 2017;106;1032–40.

In an ageing population, the global burden of cognitive impairment and dementia is significant and identifying potentially preventative lifestyle and dietary behaviours is of great interest. Evidence suggests that cognitive decline may already be evident by middle age, indicating a possibility that the critical period for preventative strategies against dementia may be earlier than predicted. Few studies have evaluated the association of B-vitamin intake in young adulthood with cognitive function in later life. Accordingly, the authors of the present study aimed to assess associations of niacin, folate, vitamin B-6, and vitamin B-12 intake in younger adulthood with cognitive function in midlife.

The CARDIA (Coronary Artery Risk Development in Young Adults) study was a community-based, multicentre, longitudinal study of 5115 men and women from across the United States of America, aged 18–30 years that commenced in 1985–86 (baseline year 0). Participants were re-examined during 7 follow-ups at years 2, 5, 7, 10,15, 20, and 25. For the present study, the authors used data for participants who had undergone cognitive measurements at year 25 and who had at least one measurement of B-vitamin intake at either baseline, year 7, or year 20. Dietary intake, including dietary and supplemental B-vitamins, was assessed though an interviewer-administered dietary questionnaire with nutritional intake assessed based on the Nutrition Data System for Research database. In participants who had multiple dietary assessments, mean total intake was used to reflect long-term intake. Cognitive function was assessed at the 25-year follow-up through the use of the Rey Auditory Verbal Learning Test (RAVLT) for verbal memory, the Digit Symbol Substitution Test (DSST) for psychomotor speed, and a modified Stroop interference test for Stroop interference test for executive function.

From the 5115 participants recruited in the CARDIA study, dietary data and cognitive function assessments were available for 3136 participants. Of these participants, 55% were white, 56% were female, and had a mean age of 25.1 years at baseline. Participants with a higher intake of niacin, folate, B-6 or B-12 were older, more likely to be female and white, exercised more, and had a higher education level. The study found when comparing the highest intake with the lowest quintiles, cumulative total intake of niacin was significantly associated with improved DSST and Stroop tests. Total folate was associated with improvement on the DSST scores. Higher intakes of vitamin B-6 and B-12 were both associated with improved psychomotor speed as measured by the DSST scores when comparing the highest and lowest intake quintiles.

Strengths of the study include the long term follow up periods and dietary assessments across a number of time points. The authors identified and adjusted for potential modifiers in analysing the results. The study is limited by cognitive function being assessed only once, thus not providing a baseline level to assess and evaluate changes in cognitive function and decline from. Estimated dietary and supplemental intake through recall questionnaires remains a challenge to accurately capture intake. Furthermore, identifying an association between individual vitamins remains difficult due to the high correlation between B-vitamins.

The study provides some interesting results and points for consideration. As previously highlighted, if early stages of cognitive decline are evident in middle age, then potentially the time to employ preventative strategies against cognitive decline and dementia is prior to this. The study provides an evaluation of this time course finding that higher intakes of B-vitamins from both food and supplemental sources may be associated with better cognitive performance in middle age, especially for psychosocial speed. Further studies are required to better understand this better as are longer term CARDIA follow ups to identify and assess the ongoing effects of B vitamin intake and cognitive function.

The DASH diet, Western diet and risk of gout

Rai SK, Fung TT, Lu N, Keller SF, Curhan GC, Choi HK. The Dietary Approaches to Stop Hypertension (DASH) diet, Western diet, and risk of gout in men: prospective cohort study. *BMJ* 2017;357:j1794. Available from: http://dx.doi.org/10.1136/bmj.j1794

Gout is the most common inflammatory arthritis with increasing prevalence over recent decades in some Western countries including the UK and USA. Gout is associated with hyperuricemia, and is complicated by a high level of cardiovascular co-morbidities. The conventional dietary approach for gout includes low dietary purine intake which provides limited efficacy, palatability and sustainability.

The Dietary Approaches to Stop Hypertension (DASH) diet has been studied extensively, has demonstrated effectiveness in reducing blood pressure and is recommended to prevent cardiovascular disease. The DASH diet promotes a dietary emphasis on dietary intake of fruit, vegetables, low-fat dairy foods, and reduced intake of saturated and total fats. A recent analysis found that the DASH diet lowers levels of serum uric acid among people with hyperuricemia. The present study aimed to further evaluate the relation between the DASH and Western diets and risk of gout in a large prospective cohort.

The Health Professionals Follow-Up Study is an ongoing longitudinal study established in 1986 with participants providing a baseline questionnaire providing data for diet, medical history and medication use, with follow-ups occurring at a two-year assessment cycle. Dietary intake is assessed every four years using a validated food frequency questionnaire. In the current study, a total of 44,444 men were included with no history of gout at baseline and for whom complete information on dietary patterns were available. Men with a history of gout prior to 1986 were excluded. To represent the DASH and Western diets, each participant was assigned a DASH dietary pattern score and a Western dietary pattern score. The DASH score was based on intake of fruit, vegetable, nuts, legumes, low fat dairy products, and wholegrain and a low intake of sodium, sweetened beverages, and red and processed meats. The Western dietary scores were based on a high intake of red and processed meats, French fries, refined grains, sweets, and desserts. Incident cases of gout were ascertained using the American College of Rheumatology survey criteria for gout. Potential confounders were adjusted for including age, body mass index, hypertension, diuretic use, and alcohol intake.

In the 26 years of follow-up, 1731 new gouts cases were diagnosed. Men in the highest quintile of DASH score tended to be older, have a lower BMI, and lower intakes of alcohol and coffee than participants in the lowest quintile. Men in the highest quintile of Western pattern score tended to be younger, have a higher BMI, and higher intakes of coffee and alcohol. A high DASH dietary pattern score was associated with a lower risk of gout incidence in both age adjusted and multivariable regression models. After adjusting for potential confounders, the relative risk of men in the highest DASH scores compared to the lowest DASH scores was 0.68. In comparison, a higher Western dietary pattern score was associated with a higher risk of gout incidence in both age adjusted and multivariate regression models. After adjusting for confounders, the relative risk for men with the highest compared to lowest Western pattern scores was 1.42. Further analyses found that the Western dietary pattern was independently associated with increased risk of gout.

The study provides the first prospective evidence that the DASH diet is associated with a lower risk of incident gout and could potentially be a preventative dietary approach for the risk of gout. The findings are strengthened by its prospective nature, the size of the study and the many years of follow-up with minimal loss to follow-up. Self-reported dietary consumption is a known limitation of food frequency questionnaires as is potential for misclassification. Further studies which examine the effect of the DASH diet on serum uric acid levels and in management of patients with risk of gout flare-up are warranted.

Prenatal vitamin D and childhood wheeze in different races

Vereen S, Kocak M, Potukuchi PK, Hartman TJ, Tylavsky F, Carrol KN. The association of maternal prenatal vitamin D levels and child current wheeze. *Ann Allergy Asthma Immunol* 2017. In print doi:10.1016/j.anai.20.17.10.005

Wheeze is a common occurrence in early childhood and has been associated with subsequent asthma and decreased lung function. A role of prenatal vitamin D levels on child wheeze and asthma has been previously hypothesised, with prenatal vitamin D influencing immune system and lung development. Skin pigmentation influences cutaneous vitamin D production and potential racial differences have been reported between maternal 25 (OH)D levels and child outcomes. The authors report the findings of study investigating the association between maternal vitamin 25 (OH)D levels and child current wheeze in the third year of life by maternal race.

Study participants were from a prospective cohort study in Memphis, Tennessee that enrolled women between 2006 and 2001. Participants were dyads (mother and child), including black and white women with at least 1 prenatal 25 (OH)D) level, had a non-low-birthweight child born at least 36 weeks estimated gestational age, and had a 3-year study visit that included respiratory and atopic disease assessment. Enrolment was not based on parental history of atopic disease. Study visits occurred during the second and third trimesters, delivery, and annually during early childhood. Maternal plasma 25 (OH)D levels were assessed at enrolment (16–28 weeks). Current child wheeze in the third year of life was assessed and defined by interviewer administrated questionnaire. Covariates considered and adjusted for included maternal education, age, asthma history, smoking during pregnancy, delivery route, child sex, birth season, and parent report of infant respiratory syncytial virus/bronchiolitis hospitalisation.

In total, 853 women were included in the study of whom 63% were black, 53% had high school education

or less, and 11% reported having asthma. Regarding births, 62% were per vaginal, with 31% occurring in fall (September to November). At enrolment, 96% reported taking prenatal supplementation. Black women were noted to have significantly lower median 25 (OH)D levels than white women at second trimester and delivery. Overall, 21% of children had wheeze in the third year of life. No significant interaction was detected for maternal race between the second trimester or delivery and child current wheeze. In multivariate analyses, children of white women with second trimester levels of 25 (OH) D in the highest tertile had decreased relative odds of child current wheeze compared with children of women in the lowest tertile. Among black dyads, higher maternal levels of 25 (OH)D in second trimester and delivery were not associated with current wheeze.

The authors noted limitations to their study included not having first trimester vitamin D levels, and that there were a limited number of white women with lower 25 (OH)D levels and black women with higher 25 (OH)D levels which could affect reliability of results. Further understanding the role of prenatal 25 (OH)D levels and differences between women of racial diversity is necessary to understand differing needs for optimal child health and development. Future research with large, racially diverse cohorts are required.

Fibre intake during pelvic radiotherapy and associated gastrointestinal toxicity

Wedlake L, Shaw C, McNair H, Lalji A, Mohammed K *et al.* Randomized controlled trial of dietary fiber for the prevention of radiation-induced gastrointestinal toxicity during pelvic radiotherapy. *Am J Clin Nutr* 2017;106: 849–57.

Therapeutic radiotherapy is a critically important intervention in the treatment of many cancers including pelvic cancers. Despite advances in radiotherapy techniques, radiation-induced gastrointestinal toxicity is common with an estimated 90% of patients experiencing change in bowel habit during treatment. Ongoing gastrointestinal effects are seen in some, with delayed intestinal radiation toxicity being a progressive condition causing substantial long-term morbidity and mortality. Therapeutic strategies for both its prevention and treatment are limited. Anecdotal evidence suggests patients are commonly advised to reduce fibre intake during treatment with pelvic radiotherapy; however, there is little evidence to support this. Contrary to this, the authors of the current study suggest that a high fibre intake may indeed be beneficial. Accordingly, the authors tested the hypothesis that a high-fibre diet would prevent or reduce acute and chronic radiation-induced gastrointestinal toxicity in patients undergoing radiotherapy for pelvic cancers in a randomised controlled trial.

Patients were recruited from sites in the United Kingdom, with eligible patients including those with histologically proven gynaecologic or lower gastrointestinal cancer, due to receive radical (curative) radiotherapy to the pelvis, with or without concomitant chemotherapy, and able to tolerate 100% oral diet. Exclusion criteria included those with established wheat intolerance or coeliac disease, a gastrointestinal stent or stoma, or enrolled in other trials with conflicting toxicity endpoints. Patients were randomly assigned to receive dietary advice for low-fibre (n=55), habitual-fibre (n= 55), or high-fibre (n=56). Patients allocated to low or high-v were given daily targets with counselling on how to achieve the targets. The intervention was based entirely on dietary manipulation with fibre supplements not provided nor recommended. Patients allocated to the habitual diet group (control) were counselled at the enrolment to maintain their normal diet throughout radiotherapy treatment. Gastrointestinal toxicity was assessed as severity of bowel symptoms experienced during the acute period (baseline to 5–7 weeks) and chronic period (1 year after completed of radiotherapy), with use of an Inflammatory Bowel Disease Questionnaire (bowel subset IBDQ-B). Scores were obtained at baseline, immediately before commencing radiotherapy, and thereafter weekly during the 5–7 weeks of radiotherapy, and 1 year after delivery of the last radiotherapy session. Other measures included stool diaries, fecal short chain fatty acid concentrations, and macronutrient intake.

At baseline, no difference was observed in IBDQ-B scores between the three groups. Overall, IBDQ-B scores decreased during treatment indicative of worsening bowel symptoms. The difference between groups in change in IBDQ-B scores between start and nadir was not significant; however, the change in score between start and end of radiotherapy was significantly smaller in the high-fibre group and the habitual-fibre group. There was no difference observed between the low-fibre and habitual-fibre group, nor between the low-fibre and high-fibre groups. The absolute scores at 1 year post-radiotherapy and the change in scores from baseline were significantly different between groups. After 1 year post-radiotherapy, the difference in IBDQ-B scores between the high-fibre group and both habitual-fibre and low-fibre groups were significant. No significant difference was observed at 1 year post-radiotherapy for absolute scores between the low-fibre and habitual-fibre groups. A gradient effect was not observed, with low-fibre group demonstrating higher scores (less severe symptoms) compared to the habitual-fibre group at both time points.

The study is limited by a number of factors including non-specific dietary interventions and potential for recall limitations of participants. Furthermore, variables and confounders may have impacted the results including drop out rates at year 1 and differences in acute symptom severity during initial radiotherapy. Studies with larger numbers may address some of these limitations. The authors concluded that the dietary advice to follow a high-fibre diet during radiotherapy was tolerated and resulted in reduced gastrointestinal toxicity both acutely at the end of radiotherapy and at 1 year post radiotherapy. Whilst the study noted that some benefit was also observed with a low-fibre diet, the authors recommended that advice to reduce fibre intake during radiotherapy is restrictive, burdensome and should be discarded.

CPE points

The AJHNM-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 and Naturopathic 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 calendar year. For further information please see the NHAA CPE Member's Manual on the NHAA website www.nhaa.org.au.

MedPlant

With reference to the study investigating the use of saffron in mothers with post-partum depression, which of the following statements is incorrect?:

- Postpartum depression can have major health implications on the baby's development and is implicated in risk of infant cognitive disorders.
- Reductions in BDI-II scores from baseline demonstrated significant differences between the placebo and saffron by the end of study.
- By week 4, the mean BDI-II scores had decreased from 20 to 8.4 and from 19.7 to 15.3 for the saffron and placebo groups, respectively.
- The safety of saffron use in breastfeeding women is uncertain with neither enough evidence to suggest saffron is safe or unsafe.

With reference to the study investigating ashwagandha in subclinical hypothyroid, which of the following statements is incorrect?:

- There was no significant difference at baseline between ashwagandha and placebo groups for TSH, T4 or T3.
- Significant increases from baseline were observed at weeks 4 and 8 for TSH levels for the ashwagandha group.
- Significant increases from baseline were observed at weeks 4 and 8 for T3 levels for the ashwagandha group.
- Significant increases from baseline were observed at weeks 4 and 8 for T4 levels for the ashwagandha group.

Regarding the study investigating the effect of cranberry supplementation for prevention of recurrent UTIs in women, which of the following statements is incorrect?:

- A 26% reduction in risk of UTI recurrence for healthy women who received cranberry, compared to those who did not.
- Cranberry significantly reduced the risk of UTI recurrence by 35% in women who were free of UTI at enrolment.
- A review of quality of included studies highlighted the ongoing need for high-quality research in the area.
- Cranberry significantly reduced risk or recurrence for women with an active UTI episode at time of enrolment.

Regarding the study investigating the effect of silymarin in NASH, which of the following statements is incorrect?:

- The HFHC diet supplemented with silymarin resulted in increased ALT, hepatic inflammation, oxidative stress, and apoptosis.
- The HFHC diet supplemented with silymarin resulted in improved glycaemia, visceral fat, lipid profile, and liver fibrosis.
- *Silybum marianum* has been traditionally used in various liver disorders due to potential hepatoprotective effects.
- Findings of the study supported that lifestyle interventions can significantly revert changes induced by a HFHC diet.

Regarding the study investigating ashwagandha in mild cognitive impairment, which of the following statements is correct?:

- Ashwagandha was associated with significantly enhanced scores in the general memory, working and immediate memory subsets at 4 weeks.
- Executive function, attention, and information processing speed were significantly improved with ashwagandha intervention at both 4 weeks and 8 weeks.
- The working memory index produced conclusive results.
- Executive function, attention and visuospatial processing were significantly improved with ashwagandha intervention at both 4 weeks and 8 weeks.

MedJourn

With reference to the study evaluating intake of B-vitamins in young adulthood with cognitive function in midlife, which of the following statements is incorrect?:

- Participants with a higher intake of niacin, folate, B-6 or B-12 were older, more likely to be female and white, exercised more, and had a higher education level.
- When comparing the highest and lowest quintiles, niacin intake was significantly associated with improved DSST and Stroop tests.
- Lower intakes of vitamin B-6 and B-12 during young adulthood were both associated with improved psychomotor speed in midlife.
- Total folate was associated with improvement on the DSST scores

Regarding the study assessing the DASH diet, Western diet and risk of gout in men, which of the following statements is incorrect?:

- Men in the highest quintile of DASH score tended to be older, have a lower BMI, and lower intakes of alcohol and coffee than participants in the lowest quintile.
- A high DASH dietary pattern score was associated with a lower risk of gout incidence.
- A high Western dietary pattern score was associated with a higher risk of gout incidence.
- The relative risk of men in the highest DASH scores compared to the lowest DASH scores was 1.42.

With reference to the study evaluating the role of maternal antidepressant use during pregnancy on psychiatric disorders in offspring, which of the following statements is correct?:

- The risk for psychiatric disorders among offspring was lower in the discontinuation group than that in the continuation group.
- The study findings support discontinuation of antidepressant treatment during all pregnancies.
- A higher risk was also associated for antidepressant use less than 180 days.
- Exposure during the first trimester only was associated with an increased risk of psychiatric disorders, compared to exposure in the second or third trimester.

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Date
Thursday
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Time
6.30pm for a
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Location
ACNT Pyrmont
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Cost
$5 Members &
Students
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Contact
Sydney Chapter
Team

Sonya Servine
0426 733 727

Natalie Symkowiak
0413 226 346

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PRESENTATION TOPIC

Clinical potpourri: the use of herbal teas in clinic and cultural settings; clinical aspects of case management, professional communication and referral.

Presented By

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Herbalist, Naturopath, Homoeopath, Researcher

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- **Prof Yehuda Shoenfeld, MD FRCP (Hon) (Israel)**
  Prof Yehuda Shoenfeld is the founder and head of the Zabludowicz Center for Autoimmune Diseases, at the Sheba Medical Center, which is affiliated to the Sackler Faculty of Medicine in Tel Aviv University, in Israel. He is the Incumbent of the Laura Schwarz-Kipp Chair for Research of Autoimmune Diseases at the Sackler Faculty of Medicine, Tel Aviv University.

- **Dr Elisa Song MD (USA)**
  Dr Elisa Song, MD founded Whole Child Wellness in 2005; her mission was to create a nurturing environment that integrates allopathic and natural medicine customised to each child's unique need to help children thrive to their fullest potential. Dr Song has a particular interest in providing integrative care for children with complex medical issues.

- **Dr Terry Wahls MD (USA)**
  As well as being a clinical professor of medicine at the University of Iowa where she conducts clinical trials, Dr Terry Wahls is also a patient with secondary progressive multiple sclerosis. She was confined her to a tilt-recline wheelchair for four years. Dr Wahls restored her health using a diet and lifestyle program she designed specifically for her brain and now pedals her bike to work each day.

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