Scoping the Evidence for the Effectiveness of Herbal Medicines

A Selective Review on behalf of the European Herbal and Traditional Medicine Practitioners Association (EHTPA)

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Introduction

A recent systematic review of surveys into the use of complementary medicine estimated that in the first decade of this century more than a third of UK citizens used herbal medication.[1]

Herbal medicines are frequently used in the treatment of long-term conditions which are inadequately managed by conventional biomedicine. These have been termed 'effectiveness gaps' and include many of the chronic degenerative diseases that are now making the most pressing demands on healthcare systems in the developed world.[2] Herbal medicine may be used autonomously in these contexts or to support biomedical treatment and counteract the side-effects of conventional drug therapy.

Until recently the evidence base for herbal medicines comprised a recorded history of traditional use stretching back hundreds, and in some instances, thousands of years.[3,4] In the last few decades biomedicine has been revolutionised by the application of the principles of Evidence Based Medicine (EBM) as a way of establishing the effectiveness and safety of modern medical interventions.[5] The same requirement for rigorous, transparent, and consistent evidence is now being demanded of herbal medicines.[6-8] Whilst this scrutiny is to be welcomed, herbal medicine is distinct from biomedicine in several important respects that need to be taken into account when developing and analysing a herbal evidence base.[9]

Firstly, herbal medicine practice routinely uses combination herbal formulations, termed polypharmacy, designed to enhance the effectiveness and minimise any potential side-effects of treatment. Synergy between active ingredients is a characteristic aspect of herbal treatments and occurs at both a pharmacodynamic level (whereby plural constituent components target the same physiological system simultaneously) and at a pharmacokinetic level (whereby processes of drug absorption, distribution, biotransformation/metabolism,

or elimination are enhanced by the simultaneous presence of plural active ingredients).[10,11] In both cases, active ingredients demonstrate potentiated effects – in other words, the therapeutic effect of herbal medicines is greater than the sum of its constituent parts (see Appendix page 40).[12] In recent times, systems-based approaches have been found useful in understanding and working with this inherent complexity.[13-15] The potential of herbs to operate synergistically can also be exploited to enhance the effects of conventional drugs such as antibiotics.[16,17] This is timely as antimicrobial resistance to antibiotics is increasing to a critical degree.[18] Moreover, research has demonstrated the ability of herbal medicine to act synergistically with other therapies such as acupuncture.[19,20]

Secondly, in herbal medicine practice herbal prescriptions are typically individualised according to the unique requirements of each patient at initial presentation and are reconfigured in response to clinical developments over the course of treatment. Whilst much herbal medicine usage in the UK involves over-the-counter herbal products usually comprising single herbs, it is important that herbal medicine research takes into account the traditional methods of prescribing herbs by practitioners employing the principles of polypharmacy, widely regarded as best practice. Such individualised treatment is not easily evaluated by the relatively simple investigative models used for drug research wherein single active compounds are standardised and tested by randomised, double-blind, placebo-controlled trial.

Thirdly, limitations in funding present a further significant obstacle to herbal medicine research, particularly when it comes to researching professional practice where there are difficulties in assessing complex prescriptions that do not readily yield a marketable commercial product. Whilst most research into pharmaceutical drugs is funded by the pharmaceutical industry, there is no equivalent corporate structure or financial incentive to investigate herbal medicine since, as naturally occurring plants, these cannot be exclusively patented and are thus unlikely to provide the necessary financial returns to make investment in research a viable commercial proposition.

Given these unique characteristics and limitations, it is hardly surprising that research into herbal medicines has proceeded at a slower rate than its biomedical counterpart. However, there is now considerable progress being made and there are a growing number of rigorous and well-designed clinical trials being conducted and reported within high-quality, peer-reviewed journals that can be reviewed systematically and subjected to meta-analysis.[21]

Rationale

Statutory regulation for herbal practitioners in the UK has seen much discussion in recent years. The Secretary of State for Health issued a Ministerial Statement on 16 February 2011 recommending statutory regulation for practitioners of herbal medicine and mandating the Health and Care Professions Council (HCPC) to establish a statutory register of practitioners supplying unlicensed herbal medicines.[22] This register has not yet been established and the Government has announced a further working group to carry forward this initiative.[23]

Against this backdrop and a recent Department of Health report [24] on the need to evaluate the evidence for alternative treatments, a scoping review of the evidence base for the effectiveness of herbal medicine is timely. A more comprehensive review is planned in the next few years under the auspices of the EHTPA's Research Committee.

Methodology

This presentation is a selective review of the effectiveness of herbal medicine for a number of common diseases. It has been formulated to illustrate some of the areas where herbal medicine could make a useful contribution to mainstream healthcare. It is not intended as a comprehensive and systematic evaluation of the evidence.

Searches were performed between January and November 2013 in databases including AltHealthWatch, AMED, Embase, Estar, Cinahl, the Cochrane Library and PubMed, using broad search terms to capture as many studies as possible from across different herbal traditions.

In order to provide a practical and transparent evaluation of the evidence presented in this review we have employed an adapted version of the widely used and well-respected GRADE approach (Grades of Recommendation, Assessment, Development and Evaluation) as used by the Cochrane Collaboration.[25] This allows for 4 levels of rating of the research evidence - High, Moderate, Low and Very Low. For the purposes of this review we have amalgamated Low and Very Low grades into a single category of Preliminary evidence. This selective review is an accurate reflection of the quality of the evidence; it highlights potentially fruitful areas for future research that need to be investigated in more rigorous trials. The system was applied independently by two reviewers and any discrepancies resolved through discussion.

In the GRADE system, randomised controlled trials (RCTs) are generally considered to give a higher quality of evidence than non-randomised studies. The same approach applies to systematic reviews with, for example, several well-conducted RCTs achieving a High rating. The quality of all individual studies and systematic reviews have been considered and scored according to their risk of bias, their consistency with other similar studies, the relevance of the trial design to real world populations, the precision of their results and the extent to which they are subject to publication bias which may be particularly important when it comes to assessing herbal medicines.[26]

Methodological shortcomings in the historical evidence base for herbal medicine are well documented.[27-30] Much ongoing work concerns the development of appropriate models for examining the efficacy and effectiveness of herbal medicine treatments which are methodologically rigorous whilst simultaneously capturing the complexity of the herbal medicine approach.[9,31-34] These innovative ways of assessing herbal medicine are also contributing to the evidence base for the safety and quality of herbal medicine.[35-40] The present review demonstrates that there is ample evidence of at least Preliminary strength supporting the use of herbal medicines for some of the most important current health problems in the UK today.

Herbal medicine for the treatment of cardiovascular conditions

In 2009, around a third of all deaths in the UK were caused by cardiovascular diseases, including 82,000 deaths caused by coronary heart disease and 49,000 by stroke.[41]

Grant et al. have recently found that, in 16 studies reporting on the prevalence of CAM use by cardiovascular patients, between 2 and 46% of respondents made use of herbal remedies[42] Many herbal medicines traditionally held to promote cardiovascular health, have now been shown to operate via biologically plausible pathways.[43-44] A selection of these are listed in the table below.

Table 1: Herbal medicine for the treatment of cardiovascular conditions

Study Design	Publication Details	Main Findings	Possible Mechanisms	Strength of Evidence
Cochrane Review - a meta-analysis of hawthorn (*Crataegus monogyna or laevigata*) extract for chronic heart failure in 14 double-blind, placebo-controlled RCTs involving 1110 subjects.	Pittler et al. (2008) *Cochrane database of systematic reviews (Online)*, (1), CD005312.[45]	Hawthorn extract is superior to placebo as an adjunctive treatment for chronic heart failure. Meta-analysis of 5 included trials where maximal workload was the main outcome measure revealed statistically significant improvements ($p<0.001$).	Hawthorn extract has inotropic effects, blocks repolarising potassium currents in ventricular myocytes, decreases atrio-ventricular conduction time, and increases coronary blood flow. It also increases refractory period and is therefore associated with anti-arrhythmic activity.[45]	**High**
Double-blind, placebo-controlled randomised trial of the efficacy and tolerability of adjunctive treatment with Chinese herbal medicine (CHM) Dan Shen (*Salvia miltiorrhiza*) and Ge Gen (*Pueraria lobata*) to improve vascular function and structure in 100 coronary heart disease patients.	Tam et al. (2009) *Journal of Alternative and Complementary Medicine* **15**(4): 415–21.[46]	Significant improvement in brachial flow-mediated dilation (BFMD) and carotid intima-media thickness (CIMT) was found in the group taking Dan Shen and Ge Gen compared with placebo both during the course of the placebo-controlled trial (BFMD, $p<0.001$: CIMT, $p<0.05$) and after 6 months further open-label treatment. (BFMD, $p<0.0001$: CIMT, $p<0.0001$) Treatment with the herbal mixture was well-tolerated.	The vascular protective effects of the Dan Shen /Ge Gen mixture may derive from anti-atherogenic properties which the authors note in both cell modulation and antioxidant activity.[46]	**Moderate**

Double-blind randomised controlled trial of the tolerability of Chinese red yeast rice (*Monascus purpureus*) compared with pravastatin in 43 subjects with dyslipidemia and myalgia necessitating statin discontinuation.	Halbert et al. (2010) *The American Journal of Cardiology* **105**(2), 198–204.[47]	Red yeast rice was as well tolerated as pravastatin, and achieved comparable reduction in low-density lipoprotein cholesterol, similarly low incidence of muscle weakness (no significant difference between the two measures, p=0.82 at week 12) and treatment discontinuation caused by myalgia (p=0.99).	Red yeast rice has well-studied cholesterol-lowering effects via monacolins which inhibit cholesterol synthesis.[48]	**Moderate**

Herbal medicine for the management of diabetes

4.6% of the UK population suffers from diabetes, in both its type I and type 2 variants, with a total known diagnosed population of 3 million.[49] 2008 statistics from the Yorkshire and Humber Public Health Observatory attributed more than one in ten deaths amongst 20 –79 year olds in England to diabetes.[50] 10% of the total NHS budget in 2012 was spent on managing this condition.[51]

Diabetic patients typically exhibit hyperglycaemia owing to deficiency or suboptimal effectiveness of endogenous insulin production. The hypoglycaemic properties of several medicinal plants enable them to play a crucial role in the management of diabetes, especially in developing countries where access to conventional pharmaceuticals may be unreliable.[52] Herbal treatments with potential to improve glycaemic control appear in the table below.

Table 2: Herbal medicine for the management of diabetes

Study Design	Publication Details	Main Findings	Possible Mechanisms	Strength of Evidence
Randomised double-blind controlled trial of Xiaoke (diabetes) Pill, a combination of the allopathic drug Glibenclamide and Chinese herbal ingredients, compared with Glibenclamide alone for diabetes in 800 subjects	Ji et al. (2013) *PloS one* **8**(2), e56703. doi:10.1371/journal.pone.0056703.[53]	Mean reduction in glycosylated haemoglobin A1c (HbA1c) from baseline was 20.70% and 20.66% for Xiaoke Pill and Glibenclamide respectively. In the drug naïve group, the total hypoglycaemia rate and incidence of mild hypoglycaemic episodes in the Xiaoke Pill arm were 38% (p=0.024) and	Xiaoke Pill produces significant reduction in hypoglycaemia and simultaneous improvements in glycaemic control. One of its CHM ingredients, astralagus root (*Astragalus membranaceus)*, has been shown to amplify the glucose counter-regulatory response to insulin-induced hypoglycaemia in rats and is active in two	**High**

divided into two study groups, one drug naïve and one previously treated with Metformin.		41% (p=0.002) lower than in the Glibenclamide arm; in the Metformin group, the average annual rate of hypoglycaemia was 62% lower in the Xiaoke Pill arm (p=0.003).	brain regions, the paraventricular hypothalamus and nucleus tractus solitaries, which are involved in glucose-sensing during hypoglycaemia.[53]	
Meta-analysis of the effect of a range of single herbal supplements on glycaemic control in type 2 diabetes in 9 RCTs involving 487 subjects.	Suksomboon et al. (2011) *Journal of Ethnopharmacology*, **137**(3), 1328 – 33.[54]	Supplementation with sweet potato (*Ipomoea batatas*), milk thistle (*Silybum marianum*) and fenugreek (*Trigonella foenum-graecum*) significantly improved glycaemic control in type 2 diabetes. The pooled mean differences (MD) in HbA1c were −0.30% (95% CI −0.04% to −0.57%; p=0.02) for sweet potato, −1.92% (95% CI −0.51% to −3.32%; p=0.008) for milk thistle and −1.13% (95% CI −0.11% to −2.14%; p=0.03) for fenugreek. Fasting blood glucose was significantly reduced by sweet potato -10.20mg/dL (95% CI −5.32 mg/dL to −15.08 mg/dL; p<0.0001) and milk thistle -38.05 mg/dL (95% CI −9.54 mg/dL to −66.57 mg/dL; p=0.009).	Sweet potato enhances glucose uptake but also delays total carbohydrate absorption; sweet potato's ability to improve metabolic control may be linked to increased adiponectin and decreased fibrinogen levels. Milk thistle's active constituent is silymarin, a flavolignan which can improve insulin resistance and improve β-cell restoration. Fenugreek contains various active constituents including 4-hydroxyisoleucine, soluble fibre and saponins which stimulate insulin secretion, reduce glucose absorption and improve peripheral glucose utilization. Fenugreek may also improve glucose metabolism by regulating gluconeogenic, glycolytic and lipogenic enzymes.[54]	**Moderate**
Systematic Review of Asian Ginseng (*Panax ginseng*), for type 2 diabetes amongst a range of other conditions in 65 RCTs involving 3843 subjects	Shergis et al. (2012) *Phytotherapy Research* doi:10.1002/ptr.4832.[56]	Ginseng was rated promising in improving glucose metabolism, but the heterogeneity of included studies prevented meta-analysis. One included trial showed statistically significant decreases in glucose tolerance test indices compared with placebo (p<0.05).[64] Other findings included	Active constituent ginsenoside Rc enhances glucose uptake by inducing the generation of reactive oxygen species which in turn activates protein kinase enzymes, important regulators of cell function.[56-57]	**Preliminary**

		evidence for ginseng's ability to moderate immune response.[63]		
FDiabCochrane Review of Ayurvedic herbal mixtures for type 2 diabetes in 7 RCTs involving 354 subjects.	Sridharan et al. (2011)*Cochrane database of systematic reviews (Online)*, (12), CD008288.[26]	Proprietary herbal mixtures Diabecon, Inolter and Cogent DB significantly lowered glycosylated haemoglobin A1c (HbA1C) levels compared to controls (Diabecon, MD-1% (95% CI, -1.9 to -0.1); Inolter, MD -0.8% (95% CI, -0.9 to -0.7); Cogent DB, MD -2.1(95% CI, -3.3 to -1). Significantly lower fasting blood glucose levels at the end of each study compared with baseline were also found for these three products (Diabecon, -18mg/dl (95% CI, -28 to -8); Inolter -39mg/dl (95% CI, -66 to -12); Cogent DB, -63mg/dl (95% CI, -97 to -29).	A range of pancreatic and extra-pancreatic mechanisms discussed, including inhibition of glucose transport, modulation of insulin secretion and slowing of carbohydrate absorption.[26]	**Preliminary**
Systematic review of the efficacy of a range of herbs and dietary supplements for glycemic control in type2 diabetes in 108 RCTs involving 4565 subjects.	Yeh et al. (2003) *Diabetes Care*, 26(4), pp.1277–94.[58]	Best evidence of efficacy found for ivy gourd (*Coccinia indica*) and American ginseng (*Panax quinquefolius)*, with positive preliminary results indicated for fenugreek (*Trigonella foenum-graecum*), gurmar (*Gymnema sylvestre*, *Aloe vera*, bitter melon (*Momordica charantia*) and nopal cactus AKA prickly pear (*Opuntia ficus-indica*). Heterogeneity precluded meta-analysis.	Mechanisms of action include insulin-mimetic properties (ivy gourd) and hypoglycaemic effects via triterpenoid saponin glycosides (American ginseng).[58]	**Preliminary**

Herbal medicine for the treatment of skin conditions

Skin conditions rank amongst the most intractable of chronic ailments. 5 million children and adults in the UK suffer from eczema (also known as dermatitis).[59] Psoriasis is estimated to affect 2 – 3% of the UK population, up to 1.8 million people.[60]

The National Eczema Society advises that use of topical herbal creams and herbal tablets may offer symptomatic relief for some eczema sufferers.[59] Use of herbal medicines may allow reduction in use of topical steroids which though effective in the short-term may, with prolonged use, give rise to side-effects including thinning of the skin and loss of elasticity.[61]

Table 3: Herbal medicine for the treatment of skin conditions

Study Design	Publication Details	Main Findings	Possible Mechanisms	Strength of Evidence
Randomised double-blind placebo-controlled crossover trial of the efficacy of traditional Chinese herbal product Zemaphyte in adult atopic dermatitis in 40 subjects.	Sheehan et al. (1992) *Lancet* **340**, 13 – 17.[62]	Statistically significant reductions in the extent and severity of erythema and surface damage were found in both active phases of treatment (both $p<0.0005$).	Zemaphyte's composite herbs, including rehmannia (*Rehmannia glutinosa*), liquorice (*Glycyrrhiza glabra*) and Chinese cinquefoil (*Potentilla chinensis*), possess anti-inflammatory, anti-microbial and immunosuppressive properties.[62]	**Moderate**
Randomised double-blind placebo-controlled crossover trial of the efficacy of a traditional Chinese herbal formula in child atopic dermatitis in 47 subjects.	Sheehan & Atherton (1992) *British Journal of Dermatology* **126**, 179 – 184.[63]	Statistically significant reductions in the extent and severity of erythema and surface damage were found in the active treatment phase. Percentage decrease in erythema scores was 51.0% in the active group compared with 6.1% in the placebo group (95% CI for this difference, 13.4 to 89.7) and percentage decrease in surface damage scores was 63.1% in the active group compared with 6.2% in the placebo group (95% CI for this difference, 19.2 to 97.9).		**Moderate**
Randomised double-blind placebo-controlled trial of the efficacy and safety of traditional Kampo medicine Hochu-ekki-to in the adjunctive treatment of atopic	Kobayashi et al. (2010) *Evidence-Based Complementary and Alternative Medicine: eCAM* **7**, 367–73.[64]	Treatment with Hochu-ekki-to allowed significant reduction in the use of topical steroids ($p<0.05$). Aggravated rate (cases where there was >50% increase in use of topical steroids since baseline) was significantly lower in the Hochu-ekki-to group compared with placebo (3% v 18%, $p<0.05$).	Granulated Hochu-ekki-to contains hot water extracts of 11 herbs including ginseng (*Ginseng radix*), astragalus (*Astragalus membranaceus*) and ginger (*Zingiber officinale*).	**Preliminary**

dermatitis in 77 *Kikyo* (delicate constitution) subjects.			Relevant actions of these might include immunomodulatory activity of cycloartane-type saponins found in astragalus[65] and anti-inflammatory properties of ginsenosides found in ginseng.[66]	
Randomised single-blind placebo-controlled trial of Unani formulations Majoon Ushba (oral) and Roghane Hindi (topical) for psoriasis in 30 subjects.	Lone et al. (2011) *Journal of Ayurveda and Integrative Medicine* **2**, 26 – 31.[67]	Psoriasis Area and Severity Index shows significant reduction in symptoms in the experimental group compared with placebo ($p<0.01$).	Both formulations are multi-ingredient, with Majoon Ushba containing 15 herbs and Roghane Hindi 5. Relevant actions of these might include anti-inflammatory and detergent effects of Chob chini (*Smilax china*), Ushba (*Smilax officinalis*), Gaozuban (*Borage officinalis*), Darchini (*Cinnamomum zeylanicum*) Sana makki (*Cassia angustifolia*) and Kabab chini (*Piper cubeba*).[67]	**Preliminary**
Preliminary study of the effects, safety and acceptibility of zimade mohasa, a polyherbal Unani formulation, for acne vulgaris in 25 subjects.	Lone et al. (2011) *Journal of Ayurveda and Integrative Medicine* **3**, 180–3.[68]	Cook's Acne Grading Scale shows significant reduction in symptoms ($p<0.01$). No adverse effects were reported.	Zimade mohasa, which contains irsa (*Iris florentina*), barghe neem leaves (*Azadirachta indica*), poste saras bark (*Acacia speciosa*) and ghungchi safaid (*Abrus precatorious*) has astringent, detergent, anti-inflammatory and antibacterial properties.[68]	**Preliminary**

Herbal medicine for the treatment of irritable bowel syndrome (IBS)

IBS is the most common functional gastrointestinal disorder amongst UK adults with a prevalence of 10.5%.[69] It is associated with psychological distress and quality of life impairment as well as pain.[70,71]

Capello et al. found that peppermint oil capsules caused a statistically significant reduction in total IBS symptom scores after a four-week course of treatment and importantly this effect was sustained for four weeks after the end of that course of treatment.[72] A further study of peppermint oil capsules has since additionally shown significant improvements in quality of life scores measured on a Visual Assessment Scale (VAS) compared to placebo after just one week of treatment (P = 0.007).[73]

Bensoussan et al's 1998 study of a combination herbal formulation for IBS was the first trial of Chinese herbal medicine (CHM) to employ the diagnostic criteria and treatment processes of traditional Chinese medicine (TCM) whilst simultaneously operating within rigorous methodological parameters.[74] This is work that is currently being extended as Bensoussan and colleagues have recently tested a standard CHM formulation for constipation-predominant IBS which offers similar levels of improvement in all relevant criteria over placebo.[75]

The synergistic interactivity of the many herbal ingredients in the Tibetan formula Padma Lax constitutes a comprehensive poly-pharmaceutical approach to the disease.[76] The details of these and other studies can be found in the table below.

Table 4: Herbal medicine for the treatment of irritable bowel syndrome (IBS)

Study Design	Publication Details	Main Findings	Possible Mechanisms	Strength of Evidence
Review and meta analysis of peppermint oil in the treatment of irritable bowel syndrome.	Ford AC et al. (Nov 2008) BMJ: 13;337:a2313.[77]	Four studies on 392 people peppermint oil to placebo. (26% patients randomised to peppermint oil had persistent symptoms compared 65% receiving placebo (relative risk 0.43, 95%C.I. 0.32-0.59). The number needed to treat with peppermint oil to prevent one patient having persistent symptoms was 2.5 (95%C.I. 2-3)	Peppermint oil has anti-spasmodic properties and relaxes gastrointestinal smooth muscle by reducing calcium influx.[78]	**High**
Randomised double-blind placebo-controlled 3-arm trial of individualised	Bensoussan et al. (1998) *JAMA: The Journal of the American Medical Association* **280**, 1585–1589.[74]	Patients in the active treatment groups receiving either individualised CHM or a standardised CHM Formulation containing 20 separate herbal ingredients experienced significant improvement in bowel symptom scores	Many different active components are involved. As an example: Yin Chen Hao *(Artemesia capillaris)*, a Chinese	**Moderate**

CHM Formulations, a standardised CHM formulation and placebo for IBS in 116 subjects.		compared with placebo as rated by both the patients themselves (p=0.03) and by gastroenterologists (p=0.001) and significant global improvement, again as rated by the patients (p=0.007) and by gastroenterologists (p=0.002).	herb which made up 13% of Bensoussan's original 20-herb formula, has been shown to possess anti-inflammatory properties.[79]	
Randomised double-blind placebo-controlled trial of CHM for constipation-predominant IBS In 127 subjects.	Bensoussan et al. (2012) *Proceedings from the International Scientific Acupuncture and Meridian Symposium, Oct 5 -7 2012, Sydney, Australia.*[75]	Initial results suggest that a standardised CHM formulation offers improvement in symptom relief (p<0.015), bowel satisfaction (p<0.001) and stool consistency (p<0.001) in constipation-predominant IBS compared with placebo.		**Moderate**
Randomised double-blind placebo-controlled trial of Peppermint (*Mentha piperita*) oil capsules in 57 patients diagnosed with IBS according to Rome II criteria.	Cappello et al. (2007) *Digestive and Liver disease: official journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver* **39**, 530–6.[72]	After a 4-week course of treatment with peppermint oil capsules, 75% of the patients in the peppermint oil group showed a >50% reduction of basal total IBS symptoms score compared with 38% in the placebo group (p<0.009). Both immediately after the course of treatment and in follow up 4 weeks later, the peppermint oil group showed a statistically significant reduction of the total irritable bowel syndrome symptoms score (p<0.01), while no change was found with the placebo.	Menthol present in the peppermint oil relaxes gastro-intestinal smooth muscle by blocking Ca2+ channels in the gut.[72]	**Moderate**
Cochrane Review of herbal medicines for IBS in 75 RCTs involving 7597 subjects.	Liu et al. (2011) *Cochrane database of systematic reviews (Online)* **CD004116**.[80]	This review looked at a total of 71 different herbal medicines in a variety of RCT designs, including herbal preparations compared with placebo, herbal preparations compared with conventional pharmacologic therapy, and herbal preparations combined with conventional therapy compared with conventional therapy alone. Several different herbal medicines were found to significantly improve global symptoms compared with placebo, including Tibetan Padma Lax, TCM (TXYF), individualised TCM treatment and an Ayurvedic	A wide range of mechanisms are involved. As an example, Tong Xie Yao Fang's (TXFY) active ingredients include monoterpene glycosides, flavonoids including the antioxidant and inhibitory naringin and hesperidin, and chromones. Paeoniflorin has also been shown to play a key role in the anti-inflammatory effect of TXYF.[81]	**Moderate**

		preparation containing *Marmelos correa* (bilva) powder and *Bacopa monnieri* (brahmi). A total of 22 herbal medicines demonstrated statistically significant symptom improvement compared with conventional therapy, and 6 herbal preparations of 9 tested in combination with conventional therapy showed greater improvement than the monotherapy alone. Three trials rated high quality in terms of generation of allocation sequence, concealment of allocation, double-blinding and inclusion of Intention-To-Treat (ITT) analysis.[80,82.83]		
Randomised double-blind placebo-controlled trial of the safety and effectiveness of commercially available herbal preparation STW 5, research herbal preparation STW 5-II and single herb extract of bitter candytuft (*Iberis amara*) in 203 subjects.	Madisch et al. (2004) *Alimentary Pharmacology and Therapeutics* **19**, 271–279.[82]	This 4-arm trial found that both the combination herbal preparations, STW 5 which consisted of 9 plant extracts including bitter candytuft and STW 5-II which consisted of 6 plant extracts including bitter candytuft, were significantly better than placebo at reducing total abdominal pain score (STW 5: p=0.0009, STW 5-II: p=0.0005) and IBS symptom score (STW 5: p=0.001, STW 5-II: p=0.0003) after 4 weeks of treatment based on ITT analysis. A single herb extract of bitter candytuft did not outperform placebo.	Pharmacological work supports the synergistic effects of the constituent ingredients of STW 5 and STW 5-II, where action on smooth muscle tone is supported by motility stimulation and a spasmolytic effect. Anti-inflammatory and anti-bacterial qualities are also present.[82]	**Moderate**
Randomised double-blind placebo-controlled pilot study of the safety and effectiveness of Tibetan herbal formula Padma Lax in treating constipation-predominant IBS in	Sallon et al. (2002) *Digestion* **65**, 161 – 171.[76]	After 3 months of treatment, patients in the Padma Lax group had increased their mean stool frequency compared with the placebo group (p=0.002). A gastroenterologist's assessment of constipation severity was significantly improved in the Padma Lax group compared with the placebo group (p=0.0001). Abdominal pain scores were significantly lower in the	Padma Lax, sold as a herbal laxative in Switzerland, comprises several herbal ingredients with known laxative properties, including aloe (*Aloe ferox* and/or *Aloe barbadensis*), frangula (*Frangula alnus*), cascara (*Rhamnus purshiana)*, and Chinese rhubarb root	**Moderate**

61 subjects.		Padma Lax group compared with the placebo group (p=0.002).	(*Rheum palmatum)* as well as ingredients with anti-diarrhoeal properties, such as elecampane (*Inula helenium*) and gentian (*Gentiana lutea).* The ginger (*Zingiber officinale*) present may enhance gastrointestinal mobility, while calumba (*Jateorhiza palmata*) contains the isoquinoline alkaloid jatrorrhizine, which is associated with anxiolytic and sedative effects.[76]	
Systematic Review of *27* in vitro, in vivo and human studies of single herbs and compound herbal preparations for IBS.	Rahimi & Abdollahi (2012) *World Journal of Gastroenterology* **18**, 589–600.[83]	This review visits the evidence for the effectiveness of peppermint, CHM STW 5 and Padma Lax as presented above.[78-80,82,83] The wide range of this review additionally allows it to present a range of herbal medicines which warrant further clinical investigation, including traditional Iranian medicines.	A range of mechanisms are explored. As an example: black cumin's (*Nigella sativa)* anti-inflammatory, immunomodulatory and anti-microbial properties. [81]	**Preliminary**

The potential of antibacterial herbs to help combat growing antimicrobial resistance

An urgent need to find agents that might support failing antibiotics against common but deadly bacteria has resulted in significant exploration of the use of medicinal herbs[84] to re-activate common antibiotics that have lost their efficacy. Most of this research has been in the lab rather than on human populations. A recent review provided evidence of 34 different herbs containing constituents known to inhibit the bacterial efflux pumps.[85] For example *E. coli,* a bacterium commonly implicated in both hospital and community acquired infection, is currently resistant to several common antibiotics but when combined with extracts of *Sophora alopecuroides* isolates of the bacteria were found to be susceptible to ciprofloxacin.[86] Similarly, Klančnik et al. (2013) found that extracts of *Rosmarinus officinalis* inhibited *Campylobacter,* a common food-borne bacterium that now exhibits drug-resistant strains.[87] Extracts from several other plants in this study, have shown similar inhibitory effects on *Campylobacter,* as have extracts of green tea (*Camellia sinensis).* [88]

Another major concern is the drug-resistant bacterium, Methicillin-resistant *Staphylococcus aureus* (MRSA). Exposure to berberine, a compound found in many medicinal plants (e.g. *Coptis chinensis* and *Phellodendron amurens)* together with antibiotics such as levofloxacin and azithromycin[89] (which have recently proved ineffective against MRSA), resulted in the reactivation of the efficacy of the antibiotic drugs. Similar results were found employing *Scutellaria baicalensis* against *Staphylococcus aureus* to restore the antibacterial actions of ciprofloxacin via similar mechanisms of efflux pump inhibition. [90] Indirubin, extracted from the leaves of *Wrightia tinctoria,* used in Ayurvedic medicine, has also been found to have an inhibitory effect on *Staphylococcus aureus.*[91] Nineteen herbs commonly used in Chinese medicine plants have inhibitory effects of which *Dendrobenthamia capitata*, *Elsholtzia rugulosa, Elsholtzia blanda, Geranium strictipes, Polygonum multiflorum* offer promising anti-MRSA possibilities.[92] Zuo et al. investigated the antimicrobial effects of 30 plants traditionally used to treat skin infection focusing on their potential to inhibit *Staphylococcus aureus.* Of these, 21 extracts were found to have anti-MRSA effects with *M. yunnanensis* and *S. arborescens* being the most active.[86]

The following table identifies some promising studies where herbal medicines have demonstrated anti-bacterial actions in common infections affecting the upper respiratory tract, the urinary tract, and the stomach. There is increasing worldwide alarm that antibiotic drugs are losing their effectiveness against these and other infections and there is now a pressing need to investigate the role that herbal medicines can play in helping to combat the threat of antimicrobial resistance. Herbal medicines have been used as antibiotics for thousands of years, yet remain effective, suggesting that bacteria have reduced ability to adapt to a plant derived antibacterial regime.

Table 5: Antibacterial herbs

Study Design	Publication Details	Main Findings	Possible Mechanisms	Strength of Evidence
An evidence-based systematic review of umckaloabo (*Pelargonium sidoides*) by the US Natural Standard Research Collaboration.	Ulbricht C et al. (2010) *Journal of Dietary Supplements* ;7(3):283-302.[93]	This comprehensive systematic review concluded that there was strong scientific evidence (Grade A) - including 4 good quality RCTs involving 933 participants - to support the use of pelargonium for acute bronchitis and good scientific evidence (Grade B) for its use in acute pharyngitis and the common cold. No serious toxic effects have been observed in any trial relating to Pelargonium.	Pelargonium has exhibited a marked antibacterial action against a wide range of pathogenic bacteria.	**High**

Efficacy and safety of a combination herbal medicinal product containing nasturtium (*Tropaeoli majoris herba*) and Horseradish (*Armoracia rusticana)* for the prophylactic treatment of patients with respiratory tract diseases: a randomised, prospective, double-blind, placebo-controlled phase III trial.	Fintelmann V et al. (2012). *Current Medical Research Opinion*; 28(11):1799-807.[94]	351 participants were randomly allocated to either active treatment (Group 1), a lower dose of active herbs + placebo (Group 2), or just placebo (Group 3). The maximum duration of treatment was 84 days. In the intention to treat (ITT) population excluding early infections (n = 344) the infection rates were 13.3% for Group 1, 18.4% for Group 2 and 25.6% for placebo Group 3. The statistical trend test showed significant results (p = 0.0171). The herbal combination appears to offer a prophylactic advantage which could help reduce antibiotic prescription.	These herbs contain several isothiocyanates which have a marked in vitro broad spectrum anti-bacterial action.[96]	**Moderate**
A double blind randomised control trial where 107 participants were randomised to receive either liquorice root (*Glycyrrhiza glabra*) - trade name *gutgard* - or placebo for 60 days.	Puram et al. (2013) *Evidence-Based Complementary and Alternative Medicine*; Article ID 263805.[95]	The results showed that 56% (n=28) were *Helicobacter pylori* negative compared to 4% (n=2) in the placebo group. In other work by the same team, the herb extract reduced symptoms of dyspepsia and there were no adverse events reported.	*Glycyrrhiza glabra* showed antimicrobial activity in vitro and anti-adhesive properties against *H. pylori*.[95]	**Moderate**
A randomised, double-blind, placebo-controlled trial of a herbal medicinal product Angocin Anti-Infekt N containing nasturtium (*Tropaeolum majus)* and horseradish *(Armoracia rusticana)* for the prophylactic treatment of patients with chronically recurrent lower urinary tract infections (RUTIs).	Albrecht U et al. (2007). *Current Medical Research Opinion*;23(10):2415-22.[96]	129 patients with RUTIs were randomised to active herbal or placebo treatment for 90 days. The primary outcome was the number of laboratory confirmed urinary tract infections. The per protocol mean number of recurrent UTIs in the study period was 0.43 versus 0.77 for the placebo group. This result is statistically significant (p = 0.035). A total of 36 patients in the test group and 37 patients in the placebo group reported adverse events. Two serious adverse events were reported in the placebo group and one serious adverse event in the treatment group (not associated with the study medication). This herbal product appears to be effective and safe as a prophylaxis for RUTIs.	Mustard oils (including glucosinolates) found in these two herbs have been shown to have a broad spectrum antibacterial action.[96]	**Preliminary**
A randomised control trial of a complex Chinese herbal	Huang MJ. (2007). *Hubei Journal of Traditional*	300 women were randomised in a 2:1 ratio to the Chinese herbal remedy or an antibiotic regime. The treatment was	Several of the included herbs,	**Preliminary**

medicine (San Ling Jie Du Tang) in the treatment of women with recurrent lower urinary tract infections (RUTIs)	*Chinese Medicine*;29:38-9.[97]	administered for 7 days with a 6 month follow up. 79.5% of the herbal group reported no infection in the follow up period compared with 49% in the antibiotic group. This was statistically significant ($p<0.05$).	such as tree peony bark (*Paeonia suffroticosa),* have been shown to have a broad spectrum. anti-bacterial action.[97]	
A randomised double blind placebo controlled trial of 57 women with 3 prior episodes of UTI within the previous year. The goal was to study the prophylactic effect of bearberry (*Arctostaphylos uva-ursi)*	Larsson, B., Jonasson, A., & Fianu, S. (1993*). Current Therapeutic Research*, 53(4), 441-443. [98]	The treatment group were give 9 pills of *Arctostaphylos uva-ursi* each day for a month and followed up 6 and 12 months later. 23% (5) of the placebo group had a confirmed UTI in the six months follow-up and none of the treatment group did.	*Arctostaphylos uva-ursi* has been shown to have a bacteriostatic effect. [99] The active ingredient has been identified as arbutin. [100]	**Preliminary**
A Cochrane systematic review of Chinese herbs for sore throat.	Huang Y et al. (2012). *Cochrane Database Systematic Review*. 14;3:CD004877.[101]	12 studies involving 1954 participants were included in this systematic review. 6/12 studies were shown to be more effective than the control with 3 herbal remedies appearing more effective than antibiotics. The remaining 6 studies showed equivalent effectiveness to the controls.	Several of the included herbs such as Japanese Honeysuckle (*Lonicera japonica)*, have been shown to have a broad spectrum anti-bacterial action.[101]	**Preliminary**
Comparative study *of* black cumin *(Nigella sativa)* and triple therapy in eradication of *H. pylori* in patients with non-ulcer dyspepsia. 88 adults with dyspeptic symptoms and positive *H. pylori* test were randomised to four groups: receiving (i) triple	Salem et al. (2010). *Saudi Journal of Gastroenterology*. 16(3):207-14.[102]	*H. pylori* eradication was 82.6% in the antibiotic triple therapy group, 47.6 with 1g of *Nigella sativa,* 66.7% with 2g and 47.8% with 3 g *Nigella sativa.* Eradication rates with 2 g *Nigella sativa* and antibiotics were statistically similar. *Nigella sativa* seeds possess clinically useful anti-*H. pylori* activity, comparable to antibiotic triple therapy. Further clinical studies combining *Nigella sativa* with antibiotics are	*In vitro* study showed that *Nigella sativa* inhibited growth in all strains of *H. pylori* within 60 minutes of exposure. [102]	**Preliminary**

therapy (TT) comprising of clarithromycin, amoxicillin, omeprazole [n= 23], (ii) 1 g *Nigella sativa* + 40 mg omeprazole (OM) [n= 21],(iii) 2 g NS + OM [n= 21] or (iv) 3 g NS + OM [n= 23]. Main outcome was eradication of *H. pylori.*		suggested by the authors.		

Herbal medicine for the treatment of respiratory conditions including asthma

Department of Health statistics for 2012 noted that the prevalence of asthma in England was amongst the highest in the developed world, affecting 5.4 million people. Asthma-related deaths remained at around 1,000 a year between 2000 and 2012, 50% higher than in the rest of Europe and emergency hospital admissions for asthma in the UK were found to number in the tens of thousands.[103]

Allergic rhinitis (seasonal and perennial) affects 20% of the UK population and was found by NICE in 2012 to be increasing in incidence.[104]

Herbal medicine is popular amongst respiratory patients, increasing the need to provide high-quality evidence to support its use.[105] There are cautious pointers to commonly-available herbal treatments for asthma – including *Gingko biloba* and *Tylophora indica*, for which recent systematic review work shows potential to improve lung function.[106] Promising research demonstrates comparable effectiveness of an extract of 3 herbs- *Ganoderma lucidum, Sophora flavescens, Glycyrrhiza uralensis* (via different mechanisms) compared to conventional treatments such as prednisone yet apparently without global immune suppression.[107]

Allergic Rhinitis (and its) Impact on Asthma (ARIA)'s guidelines as revised in 2010 suggest that patients can safely try butterbur-based products certified free of toxic pyrrolizidine alkaloids.*[108] Studies demonstrate the ability of herbal medicines such as butterbur to equate with pharmaceutical drugs in terms of efficacy for respiratory conditions, with the added benefit of avoiding common side-effects such as the drowsiness that can result from the ingestion of anti-histamines and the potentially serious systemic adverse effects that can result from prolonged use of corticosteroids.[109,110]

* In the UK, the Medicines and Healthcare products Regulatory Agency (MHRA) has withdrawn butterbur products due to the current lack of controls to ensure that only pyrrolizidine alkaloid free butterbur products are available.

Table 6: Herbal medicine for the treatment of respiratory conditions including asthma

Study Design	Publication Details	Main Findings	Possible Mechanisms	Strength of Evidence
Randomised double-blind placebo-controlled parallel group trial comparing butterbur (*Petasites hybridus*) and cetirizine for seasonal allergic rhinitis (hay fever) in 125 subjects.	Schapowal (2002) *BMJ (Clinical research ed.)* **324**, 144–6. [109]	Butterbur and cetirizine were similarly efficacious treatments for seasonal allergic rhinitis across a range of outcome measures such as physical function (p=0.75 for comparison between medians) and pain (p=0.44 for comparison between medians), with fewer sedating side-effects reported for butterbur.	Butterbur has been shown to decrease nasal levels of histamine and cysteinyl leukotrienes in vivo.[111] Butterbur has been found to confer complementary anti-inflammatory benefits as an adjunctive treatment to inhaled corticosteroids for asthma patients.[112]	**Moderate**
Randomised double-blind placebo-controlled trial of the efficacy and tolerability of a novel Chinese herbal formula, anti-asthma herbal medicine intervention (ASHMI), compared with prednisone for moderate-severe asthma in 91 subjects	Wen et al. (2005) *The Journal of Allergy and Clinical Immunology* **116**, 517–24.[110]	ASHMI performed as well as prednisone in terms of Clinical symptom scores and use of b2-bronchodilators, and serum IgE levels were significantly reduced to a similar degree in both groups (p<0.001). Moreover, the group taking the herbal mixture had fewer side-effects – their adrenal function was not adversely effected, with cortisol levels significantly increased in the ASHMI group (p<0.001) compared with a significant decrease in cortisol levels the prednisone group (p<0.001).	ASHMI is a mixture of three Chinese herbs – Ling Zhi (*Ganoderma lucidum*), Ku Shen (*Sophora flavescens*) and Gan Cao/liquorice (*Glycyrrhiza uralensis*). The combination has been shown to modulate airway smooth muscle contraction and down-regulate TH2 cytokine responses.[110]	**Moderate**
Randomised open trial of the efficacy of liquorice (*Glycyrrhiza glabra*) compared with frankincense - AKA olibanum - (*Boswellia carterii)* compared with prednisolone for chronic bronchial asthma in 54 subjects	Al-Jawad et al. (2012) *Indian Journal of Allergy, Asthma and Immunology* **26**, 6 – 8.[113]	All three treatments improved pulmonary function parameters (p<0.05) and increased serum electrolyte levels (p<0.05) with liquorice out-performing both olibanum and prednisolone across all measures.	Prednisolone acts as a bronchorelaxant by inhibiting the release of leukotrienes and reversing mucosal oedema. Olibanum's pentacyclic triterpenic acids inhibit inflammatory polymorphonuclear leukocyte infiltration and inhibit the leukocyte elastase, which is involved in the pathogenesis of a range of respiratory conditions. Acetyl-11-keto-β-boswellic acid in olibanum also prevents the release of B4 leukotrienes which induce broncho-	**Preliminary**

			constriction. Glycyrrhizin, the active ingredient of liquorice, has corticosteroid-like activity and antispasmodic effect related to the flavonoids present.[113]	
Systematic review and meta-analysis of oral CHM for improvement of quality of life in patients with stable chronic obstructive pulmonary disease in 27 RCTs involving 1966 subjects.	An et al. (2012) *Journal of Alternative and Complementary Medicine* 18(8).[114]	Statistically significant improvements in Health-Related Quality of life measures were found when oral CHM was used as both adjunctive with a meta-analysed reduction in St. George Respiratory Questionnaire (SGRQ) - scores of -5.15 [95% CI, -7.26, -3.05] and in Cai's Quality of life Questionnaire (Cai's QoLQ) of -0.25 [95% CI, -0.37, -0.13]) and stand-alone treatments (SGRQ score reduction of -6.07 [95%CI, -9.21, -2.93] and -0.20 [95% CI -32, -0.07] in Cai's QoLQ).	A range of active constituents discussed. As an example, ginsenosides found in ginseng (*Panax ginseng*) increase plasma concentrations of some antioxidants which help to combat damage caused by free radicals associated with smoking which contribute to the development of COPD.[115]	**Preliminary**
Systematic Review of herbal treatments other than TCM-based herbal treatments for asthma in 37 RCTs and Quasi-experimental designs (QEDs) involving 1979 subjects	Singh et al. (2007) *The Journal of Asthma: official journal of the Association for the Care of Asthma*, 44(9), 685–98.[116]	Preliminary evidence for many different herbs as primary and/or adjunctive treatments for asthma, including Indian frankincense (*Boswellia serrata*), Indian ipecacuanha (*Tylophora indica*), butterbur *(Petasites hybridus)*, eucalyptus *(Eucalyptus sp.)* and cannabis (*Cannabis sativa*) was found. Heterogeneity precluded meta-analysis.	The herbs investigated have many different mechanisms of action. For instance, eucalyptus oil suppressed arachidonic acid metabolism and cytokine production in human monocytes and further research explored its prednisolone equivalent potency leading to a reduction in the treatment group of steroid use in a small test group (P-0.012). The alkaloid tylophorine found in Indian ipecacuanha *(Tylophora indica)* has an anti-inflammatory action.[117]	**Preliminary**

Herbal medicine for the treatment of depression

The use of St. John's wort (*Hypericum perforatum*) as a treatment for mild, moderate and major depression is well established and based on robust evidence.[118,119] 10.8% of the NHS annual secondary healthcare budget for 2008/9 was spent on mental health services, a total of £10.4 billion; a wider figure, which includes the cost of lost working days, is currently estimated at £105.2 billion per annum.[120] Recent assessment finds St. John's wort as a treatment for depression to be a cost-effective alternative to generic antidepressant drugs.[121] Moreover, St. John's wort has fewer side-effects than commonly prescribed antidepressants.[122]

Other herbal medicines, including saffron and rhodiola (*Rhodiola rosea*), have been found to be effective as standalone treatments for depressive disorders, and evidence is growing for CHM in this area.[123,124]

Table 7: Herbal medicine for the treatment of depression

Study Design	Publication Details	Main Findings	Possible Mechanisms	Strength of Evidence
Cochrane Review of St. John's wort (*Hypericum Perforatum*) for major depression in 29 RCTs involving 5489 subjects	Linde et al. (2009) *Cochrane database of systematic reviews (Online)* **CD000448**.[119]	St. John's wort extracts in those reviewed trials with a placebo comparator were superior to placebo, with a combined response rate ratio (RR) of 1.28 (95% confidence interval (CI), 1.10 to 1.49) in 9 larger trials and an RR of 1.87 (95% CI, 1.22 to 2.87) in 9 smaller trials. St. John's wort extracts in those reviewed trials with a standard antidepressants treatment comparator were similarly effective to standard antidepressants; compared with tri- or tetracyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs), respectively, RRs were 1.02 (95% CI, 0.90 to 1.15; 5 trials) and 1.00 (95% CI, 0.90 to 1.11; 12 trials). St. John's wort extracts in those reviewed trials with a standard antidepressants treatment comparator had fewer side effects than standard antidepressants.	The exact mechanism giving rise to the antidepressant effects of St. John's wort is yet to be elucidated and may rely on its several constituents including hypericin, (a unique naphthodianthron), flavonoids (e.g. quercetin), bioflavonoids (e.g. biapigenin), xanthons, and phloroglucinol derivatives (e.g. hyperforin). [119,125]	**High**
Meta-analysis of St. John's wort for mild to moderate	Jou et al. (2005) *Nutritional Sciences Journal* **30**, 166 – 173.[126]	Percentage of responders was significantly higher in the St. John's wort groups compared with placebo groups (pooled odds ratio 2.62, 95% CI 1.53-4.46), with similar		**High**

depression in 10 RCTs involving 1532 subjects.		drop out and adverse event rates. Extracts of St. John's wort had no greater side effects than placebo.		
Systematic Review of herbal treatments other than St. John's wort ((*Hypericum Perforatum*) for depression in 9 RCTs involving 408 subjects.	Dwyer et al. (2011) *Alternative Medicine Review* **16**, 40 – 49.[123]	Saffron stigma (from *Crocus sativus*) is significantly more effective than placebo ($p<0.001$) and as efficacious as commonly-prescribed antidepressants imipramine ($p<0.0001$) and fluoxetine ($p<0.001$); Rhodiola *(Rhodliola rosea*) significantly improves symptoms compared with placebo ($p<0.001$); Lavender *(Lavendula angustifolia)* as an adjunctive treatment significantly increases the effectiveness of imipramine ($p<0.0001$).	Constituent components crocin and safranal may contribute to the anti-depressive effects of saffron.[127] Rhodiola's mechanism of action in depression involves beta-endorphins, tryptophan, and serotonin in the brain.[128] Phenolic compounds and rosmarinic acid found in lavender have antidepressant-like actions.[129]	**Moderate**
Randomised controlled double-blind pilot study of curcumin as an adjunctive to standard antidepressant treatment in major depression in 40 subjects	Bergman et al. (2013) *Clinical Neuropharmacology* **36**, 73–7.[130]	Curcumin (from *Curcuma longa*) plus antidepressants (escitalopram or venlafaxine) compared with placebo plus antidepressants showed similarly significant positive changes in Clinical Global Impression-Severity Scale, Hamilton Depression Rating Scale, and Montgomery-Asberg Depression Rating Scale, with the curcumin group demonstrating a trend towards more rapid relief of depressive symptoms compared to the placebo group. In the placebo group, the MADRS scores decreased by a mean of 5.3 points ($p<0.01$) whereas in the curcumin group, the scores decreased by a mean of 10.4 points ($p<0.001$). The HDRS scores in the placebo group diminished by a mean of 5.1 points ($p<0.01$), and those in the curcumin group diminished by a mean of 8.0 points ($p<0.001$). The CGI-S scores in the placebo group diminished by a mean of 0.6 points ($p<0.01$), and those in the curcumin group diminished by a mean of 0.7 points ($p<0.001$).	Animal models have demonstrated the antidepressant activity of curcumin, and the combination of curcumin with some antidepressants potentiates their effects.[131]	**Preliminary**

Review of 5 Systematic Reviews of CHM for depression	Butler & Pilkington (2013) *Evidence-Based Complementary and Alternative medicine : eCAM* **2013**, 739716.[124]	Although results were too heterogeneous for data to be statistically pooled, the authors found potentially beneficial effects worthy of further clinical investigation, particularly for the classical CHM formula Xiao Yao San. Some herbal medicines were found to have greater effects than medication or placebo, and reduction in adverse event rates was noted when some were used as adjunctive treatments.	As an example: Xiao Yao San can reverse increases in tyroxine hydroxylase and neurotrophin 3 in the frontal cortex and the hippocampal CA subregion.[132]	**Preliminary**

Herbal medicine for the treatment of arthritis

More than 6 million people in the UK have painful osteoarthritis in one or both knees and more than 650,000 have the condition in one or both hips. Around 400,000 adults in the UK have rheumatoid arthritis with 20,000 new cases in the UK every year.[133]

Arthritis UK publishes a guide to currently available alternative treatments for arthritic conditions for patients which includes a range of herbal medicines ranked according to a traffic-light score for efficacy and safety.[134]

Table 8: Herbal medicine for the treatment of arthritis

Study Design	Publication Details	Main Findings	Possible Mechanisms	Strength of Evidence
A meta analysis of RCT's for rosehip powder (*Rosa canina)* for pain reduction in oestoarthritis	Christensen et al *Osteoarthritis and Cartilage* (2008) 16, 965-972.[135]	*Rosa canina* appeared to reduce pain with an effect size of 0.37 (95% confidence interval (CI): 0.13-0.60), P=0.002	*Rosa canina* has been shown to have anti-inflammatory properties.[136]	**High**
A review of 15 systematic reviews for several herbs including devil's claw (*Harpagophytum procumbens)*	Chrubasik JE et al. Phytotherapy Research. 2007 (7):675-83. [137]	*Harpagophytum procumbens* was found to be effective at specific doses for low back pain and osteoarthritis	*Harpagophytum procumbens* has anti-inflammatory properties[138] and suppressed the inflammatory response[139], plus a dose dependent weak elastase inhibition[140]	**Moderate**
Randomised Controlled Trial of	Goldbach-Mansky et al. (2009) *Annals of Internal Medicine*, 151(4), 229 –	Patients who continued treatment for 24 weeks achieved significantly greater American College of	Immunosuppressive and anti-inflammatory effects caused by	**Moderate**

Thunder God Vine (*Tripterygium wilfordii* Hook F) (TwHF) compared with sulfasalazine for rheumatoid arthritis (RA) in 121 subjects	240 .[141]	Rheumatology criteria 20% improvement scores (ACR20) with TwHF than with sulfasalazine (p=0.001). 65.0% (95% CI, 51.6% to 76.9%) of the TwHF group met the ACR20 response criteria compared with 32.8% (CI, 21.3% to 46.0%) of the sulfasalazine group. Dropouts were accounted for in this analysis.	the plant's abundant diterpenoids. TwHF also induces apoptosis in lymphocytes and synovial fibroblasts and inhibits their proliferation.[142] *	
Cochrane Review of herbal therapy for rheumatoid arthritis in 22 RCTs involving 1020 subjects.	Cameron et al. *(*2011) *Cochrane database of systematic reviews (Online)*, CD002948(2).[143]	Pooled data from 7 studies indicate potential benefits of evening primrose (*Oenothera biennis*), borage seed (*Borago officinalis*), and blackcurrant seed *(Ribes nigrum*) oils, all of which contain gamma linolenic acid (GLA), in reducing pain intensity (MD= -32.83%, 95% CI, -56.25 to -9.42) and improving disability (MD= -15.75%, 95% CI, -27.06 to -4.44%). Thunder God Vine (*Tripterygium wilfordii* Hook F) (TwHF) was shown to relieve RA symptoms compared with placebo and compared with sulfasalazine,[144] but heterogeneity of the 3 relevant included trials precluded meta-analysis.*	Herbal medicinal products may inhibit cyclo-oxygenase-1 or 2, lipoxygenase and enzymes that destroy cartilage, as well as inhibiting the release of pro-inflammatory cytokines and demonstrating a radical scavenging effect.[143]	**Preliminary**
Randomised pilot study of the efficacy and safety of curcumin compared with NSAID diclofenac sodium compared with a combination of the two for RA in 45 subjects	Chandran & Goel (2012) *Phytotherapy Research* 26(11), pp.1719–25.[147]	The highest percentage of change in Disease Activity Score (DAS) and American college of Rheumatology criteria (ACR) was found for the curcumin-only group (from *Curcuma longa*). Changes in C-reactive protein levels were statistically significant only in the curcumin-only group (52%, $p<0.05$). The curcumin-only group showed the highest reduction in VAS scores from baseline (59.9%, $p<0.05$).There were no adverse events associated with curcumin treatment.	Curcumin is a potent anti-inflammatory that inhibits all cytokines, chemokines and several proinflammatory signalling pathways.[145]	**Preliminary**

Systematic Review of the efficacy of oral and topical complementary and alternative medicines for the management of osteoarthritis (OA) in 56 RCTs (numbers of subjects not consistently given).	De Silva et al. (2011) *Rheumatology* **50**, 911–20.[146]	Consistent evidence was found in 5 RCTs with a median Jadad score of 4 that capsaicin derived from chilli peppers (*Capsicum minimum*) is efficacious in the management of OA. Zhang & Po (1994) found that capsaicin cream was superior to placebo for pain relief in OA, with an Odds Ratio of 4.36 (95% CI = 2.77, 6.88). The efficacy of Indian frankincense (*Boswellia serrata*) for knee OA was demonstrated across 3 RCTs with a median Jadad score of 4. The efficacy of rose hip (*Rosa canina*) for OA was demonstrated across 3 RCTs with a median Jadad score of 3.	Local application of capsaicin to the peripheral sensory endings in the skin has been associated with the depletion of substance P, a hendecapeptide implicated in the pathogenesis of OA.[147] Boswellic acids present in Indian frankincense have anti-inflammatory properties.[148] Rose hip also has well-documented anti-inflammatory properties.[149]	**Preliminary**
Systematic Review of the effectiveness and safety of CHM for gout in 57 RCTs involving 4527 subjects	Li et al (2013) *Clinical Rheumatology* doi: 007/s10067-013-2274-7.[150]	CHM combined with conventional medicine was found to be more effective than conventional medicine alone (MD= −0.33; 95 % CI, −0.59, −0.07). CHM was also found to be more effective than conventional medicine in those included trials that reported on function limitation relief (MD= −0.23; 95 % CI, −0.32, −0.15).	Diverse herbal treatments may help to counteract the adverse effects caused by anti-inflammatory drugs or steroids prescribed for gout.[147]	**Preliminary**
Open Randomised Controlled Trial of the efficacy, safety and tolerability of Indian frankincense (*Boswellia serrata*) extract compared with non-steroidal anti-inflammatory drug (NSAID) valdecoxib for knee OA in 66 subjects.	Sontakke et al. (2007) *Indian Journal of Pharmacology* **39**, 27 – 29.[151]	Western Ontario and McMaster Universities OA index (WOMAC) scores for pain, stiffness and difficulty in performing daily activities were taken at baseline and at the end of each month until 1 month after the discontinuation of treatment. At this point, The WOMAC scores in the Indian frankincense group were significantly lower ($p<0.001$) than in the valdecoxib group for all three parameters.	As well as having anti-inflammatory properties, Indian frankincense may prevent the degradation of articular cartilage and thereby arrest the progression of OA.[151]	**Preliminary**

*****In 2011 the Medicines and Healthcare products regulatory Agency (MHRA) advised consumers not to use unlicensed herbal products that contain the herbal ingredient Lei Gong Teng (*Tripterygium wilfordii)* due to possible adverse effects.

Herbal medicine for the treatment of other conditions including gynaecological disorders

Herbal medicine is used for a variety of conditions and for the purposes of the present review a selection is presented below.

Obesity represents a global health crisis, with prevalence in England more than doubling in the last 25 years and predictions for 2050 estimating that 60% of adult men, 50% of adult women and 25% of children will be obese.[152]

Gynaecological conditions are a leading cause of recourse to complementary therapies in the UK, with climacteric women recently surveyed choosing herbal medicine above other CAM modalities.[153] 1.5 million UK women suffer from endometriosis, whilst dysmenorrhoea affects an estimated 25% of all women with the figure thought to be much higher amongst adolescent girls.[154-155]

8 million people in the UK suffer from migraine with an estimated 190,000 attacks occurring every day.[156]

For many patients, herbal medicines represent viable alternative treatments for these conditions which avoid the side-effects associated with NSAIDs and other prescription drugs.[157]

Table 9: Herbal medicine for the treatment of other conditions including gynaecological disorders

Study Design	Publication Details	Main Findings	Possible Mechanisms	Strength of Evidence
Randomised double-blind placebo-controlled trial of the efficacy and safety of CHM formula RCM-104 in the management of simple obesity in 117 subjects.	Lenon et al. (2012) *Evidence-Based Complementary and Alternative Medicine: eCAM, 2012*, 435702.[158]	RCM-104 capsules significantly reduced weight and Body Mass Index (BMI) compared with placebo ($p<0.05$). The RCM-104 group also experienced significant improvements in some Quality of Life measures compared with placebo including shortness of breath ($p=0.002$) and were well tolerated.	Green tea extract in the RCM-104 capsules stimulates thermogenesis and fat oxidation, which may influence weight and body composition via increased energy expenditure.[158]	**Moderate**
Randomised double-blind placebo-controlled pilot study of sublingual feverfew and ginger (LipiGesic™ M) for migraine in 208	Cady et al. (2011) *Headache* **51**, 1078–86.[159]	63% of subjects receiving the LipiGesic feverfew/ginger mixture were pain-free or had only a mild headache after 2 hours compared with 39% receiving a peppermint-flavoured placebo ($p=0.002$). Pain level scores on a 4-point scale for subjects receiving LipiGesic decreased by a mean of -0.24 compared with -0.04 for subjects receiving placebo ($p=0.006$).	Ginger (*Zingiber officinale*) may have abortive and prophylactic properties for migraine, particularly when administered in the early, mild stages of an attack.[160]	**Preliminary**

migraine attacks involving 60 subjects.			Feverfew (*Tanacetum parthenium*) is rich in sesquiterpene lactones including parthenolide, the spasmolytic properties of which can render smooth muscle less responsive to endogenous substances such as noradrenaline, acetylcholine, bradykinin, prostaglandins, histamine, and serotonin. This may produce an antimigraine effect by inhibiting influx of extracellular calcium into vascular smooth muscle cells.[161]	
Cochrane Review of CHM for endometriosis in 2 RCTs involving 158 subjects.	Flower et al.(2012) *Cochrane database of systematic reviews (Online)*, CD006568(8).[162]	CHM produced greater symptomatic relief than menopause-mimicking synthetic steroid danazol (RR= 5.06, 95%CI, 1.28 to 20.05 for CHM compared with RR= 5.63, 95%CI, 1.47 to 21.54 for danazol). CHM also produced reduction in average dysmenorrhoea pain scores for a greater proportion of women compared with danazol (MD= -2.90, 95% CI, -4.55 to -1.25). Moreover, CHM has apparently fewer side-effects than danazol.	Included herbs may affect haemorheology, promote microcirculation, and reduce blood viscosity and inflammation as well as having immunomodulatory actions and regulating hormone levels.[162]	**Preliminary**
Cochrane Review of CHM for primary dysmenorrhoea in 39 RCTs involving 3475 subjects.	Zhu et al. (2010) *Cochrane database of systematic reviews (Online)*, CD005288(11).[163]	CHM resulted in significant improvements in pain relief (14 RCTs; RR 1.99, 95%CI, 1.52 to 2.60), overall symptoms (6 RCTs; RR 2.17, 95%CI, 1.73 to 2.73) and use of additional medication (2 RCTs; RR 1.58, 95% CI, 1.30 to 1.93) compared with pharmaceutical drugs such as NSAIDs and oral contraceptive pills, as well as significant improvements in pain relief compared with acupuncture and heat compression. Individualised herbal treatments outperformed patented formulae.	A wide variety of herbs were used in these RCTs, with treatment principles most commonly involving regulation or reinforcement of *'qi' (vital energy)* and blood, warming the interior and fortifying the kidney and liver. Included herbs may influence dysmenorrhoea through their effects on microcirculation haemorheology and hormones.[163]	**Preliminary**

Conclusion

Whilst there is a need for increased scientific rigour in many herbal medicine trials[24,163] the present review demonstrates that some high and moderate quality evidence already supports a possible role for herbal medicines in the management of commonly occurring conditions such as osteoarthritis, depression, coronary heart disease, diabetes and a number of common infectious diseases. In addition there are large numbers of trials providing preliminary evidence for herbal interventions that are pointers to potentially richly rewarding areas for future research. Many of the diseases identified in this review are instances where conventional treatments are far from satisfactory or, as in the case of antibiotics, where the potency of existing drug treatments is starting to wane.

Herbal medicines may be able to make a significant contribution towards addressing these and other 'effectiveness gaps'. In order to investigate this potential and, where appropriate, adopt herbal medicines more widely within our health care system, considerably more research into these treatments will be required. It is important at this juncture to reflect on some of the key elements that should be incorporated into this research.

This review has stressed the importance of the skilful use of herbal polypharmacy to provide individualised treatment that utilises to the full the therapeutic potential of herbal synergies. It is important that these traditional approaches are respected and explored; they should be regarded as hard earned examples of likely best practice. To investigate them adequately there is a pressing need to adopt a practical orientation to research that maintains a valid model of herbal practice whilst at the same time subjecting both the process and individual herbal medicines to rigorous and scientific scrutiny.

In the short-term, novel approaches such as evidence synthesis[165] (the development of techniques to combine multiple sources of evidence) can be used to integrate and interpret existing information drawn from a wide spectrum of data sources that might otherwise be excluded from the standard systematic review. This will help to illustrate areas where herbal medicine can make an immediate contribution to public health care.

In the long-term what is clearly needed is the development of a range of appropriate research methodologies to investigate herbal medicines.[166] These will include pragmatic randomised controlled trials to assess the 'real world' impact of herbal medicines. Other approaches, such as well-conducted observational studies[167], may be utilised to facilitate the accumulation of large amounts of data to contribute to this process. In order to begin this kind of multi-phased research process it is essential that there is a supportive infrastructure in place that can provide funding, research expertise, and access to existing research networks. Work needs to be done to encourage positive collaboration between herbal practitioners and conventional doctors and researchers.[29 168] Regulatory bodies such as Research Ethics Committees (RECs) and the Medicines and Healthcare products Regulatory Agency (MHRA) need to adjust the somewhat restrictive requirements specifically designed to test pharmaceuticals to render them sufficiently flexible to incorporate trials that validate both herbal practice and its plant medicines. If we are rigorously to investigate the potential of herbal medicines to make a significant contribution to public health care, it is imperative to address these matters and provide adequate

resources to fund a well designed, clearly targeted programme of research. This is surely in the public interest.

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Appendix

Synergy – a key herbal strategy

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The notion of synergy is central to herbal medicine. The word derives from the Greek syn- "together" and ergon "work" meaning "increased effectiveness achieved as a result of combined action."

The concept of synergy provides a key rationale for the use of herbal medicines in that a single medicinal plant contains an orchestra of chemicals working together within the body to maintain health and treat disease. For herbalists the often perceived inexactitude of plant medicine is seen as its strength rather than weakness. The therapeutic effect of the whole plant tends to be significantly more effective than the particular action of any of its known constituents at the concentrations found within the plant. In this context, two and two turns out to add up to rather more than four.

In this way many medicinal herbs act like foods to restore disrupted physiological processes. While it is universally accepted that a diet with plenty of fruit and vegetables is vital for health maintenance protecting against many common diseases such as heart disease, cancer and diabetes, the precise way in which such a diet guards against disease is still not fully understood. However, it is clear that these health benefits are conferred by a complex interplay of numerous phytochemicals naturally occurring in fruits, vegetables, whole grains, nuts, legumes and other plant foods. Similarly, many thousands of secondary plant metabolites (such as alkaloids, terpenoids, and phenolics) have been isolated from medicinal herbs many of which effect potent physiological changes in humans triggering complex biological pathways that induce a cascade of positive physiological outcomes.[1]

For example, in assessment of the antidepressant action of *Hypericum perforatum* (St John's wort), one researcher writes, "Hypericum possesses a unique pharmacology in that it displays the pharmacology of many classes of antidepressants and new mechanisms not typical of standard antidepressants."[2] The biochemistry of *Ginkgo biloba* similarly demonstrates the potentials of synergy. Its constituents have been found to increase cerebral blood flow as well as displaying antioxidant, antiinflammatory and antiplatelet effects.[3] The complex mixture of flavone and terpene lactones, particularly the terpene ginkgolides, present in the leaves act in synergy as potent antagonists of the platelet-activating factor receptor (PAFR) reducing both blood clotting and inflammation.[4]

Plant medicines are thus ideal tools to restore health and treat disease because they consist of a multiplicity of chemical components that act synergistically to make active constituents

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bio-available. Conversely, their constituents may combine antagonistically to buffer otherwise potentially potent active principles, thereby preventing adverse effects. Investigation into the scope and mechanisms of synergy has come to the forefront of phytomedical research in recent years.[5] This is being actively pursued through systems biology, a field of study that "focuses on complex interactions within biological systems, using a more holistic perspective …instead of the more traditional reductionist approach of biological and biomedical research."[6] Development of 'omic' technologies (e.g. genomics, proteomics and metabolomics) also offers a range of appropriate scientific tools to assess the complex synergistic interactions and effects of plant constituents.

The notion of synergy is further extended to validate a key traditional therapeutic herbal strategy now often termed *polypharmacy.* Polypharmacy in herbal medicine is the combining together of several medicinal herbs to achieve extra therapeutic effectiveness. This strategy is a fundamental feature of practically every traditional medicine system the world over. Many traditional Chinese, Ayurvedic and Tibetan herbal formulae contain multiple plant medicines and similarly western herbalists (also called phytotherapists) customarily combine several herbs together in individualised prescriptions.

Polypharmacy can have decidedly negative connotations in conventional medicine. All too often, a patient may be prescribed a cocktail of drugs which has led to a plethora of deleterious side effects especially amongst the elderly.[7] Another reason for the negative reaction to the notion of polypharmacy is that it does not fit the medical model for developing conventional drugs. The notion that combinations of herbs may be clinically effective runs contrary to the fundamental tenets of pharmaceutical drug development since drug companies have historically patented specific, isolated chemicals as medicines. As a result most pharmaceutical research is designed to identify and validate a single chemical entity to treat a particular disease ('specific drugs for specific targets').

Whilst it is true that around 120 current licensed drugs were originally derived from plant sources (e.g. aspirin from willow, steroids from the Mexican yam, digoxin from foxglove, theophylline from tea, morphine from the opium poppy etc [8]) nevertheless, the extracted isolated active is perceived as scientifically purified and assayed and is thus considered superior to its plant source. Plants are thus generally only valued by the pharmaceutical industry for their perceived 'actives' and the remaining 'inert' constituents are ignored and discarded.

This process is now being recognised as having significant limitations. The notion of specific drugs for specific targets is now being called into question as unforeseen secondary molecular targets can be a cause of unwanted side effects when the drug is used in

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practice.[9] The editor of the BMJ observed in a recent editorial "Unfortunately in the balance between benefits and risks, it is an uncomfortable truth that most drugs do not work in most patients"[10] and other commentators have noted "there is a marked decline in the number of new drugs introduced into clinical practice over the past decades. One reason for this failure may be due to the fact that the pathogenesis of many diseases is rather multi-factorial in nature and not due to a single cause. Phytotherapy, whose therapeutic efficacy is based on the combined action of a mixture of constituents, offers new treatment opportunities." [11]

Ironically, the sceptical stance adopted by some to the practice of plant polypharmacy is contradicted by the increasingly common practice of combining drugs to treat a wide range of serious diseases like HIV, AIDS, TB, malaria, diabetes, hypertension, cancer, MRSA etc. Pharmacologists now acknowledge that the individual actions of one drug are subject to modification by a second drug and that multi-drug regimens may confer unique and beneficial new actions that do not occur when using each drug on its own.[12] Over the last decade or so, it has thus been established that combination drug therapy can deliver greater therapeutic effect than can be achieved with a single conventional medicine. Moreover, it has become evident that combination therapy can frequently attain the same therapeutic effect as when using a single drug, but with fewer deleterious side effects.[13]

Pharmacologists differentiate between two types of synergy, based on the nature of the interaction, *pharmacodynamic or pharmacokinetic*. **Pharmacodynamic synergy** results from the enhancement of action when two drugs are directed at a similar receptor target or physiological system. A herbal example of this process can be seen in the constituents of senna, sennocide A and sennocide C. Separately these have a similar laxative action but a mixture of these two compounds in the ration 7:3 (which is more or less the naturally occurring ratio found in senna) all but doubles the laxative effect.[14]

Pharmacokinetic synergy results from alteration of the processes of drug absorption, distribution, biotransformation (metabolism), or elimination. A simple example of pharmacokinetic synergy is the discovery that the simultaneous ingestion of vitamin C can improve the body's absorption of iron.[15] For this reason, many herbs rich in iron and vitamin C such as nettles or watercress would seem an ideal way to combat iron-deficiency anaemia.

The positive benefits of synergistic phytotherapy are now being increasingly recognised. Numbers of papers are currently being published investigating potential benefits conferred

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by the synergistic nature of phytochemicals.[16] [17] [18] [19] For example, exciting possibilities are being explored employing the synergistic combination of plant medicines and conventional pharmaceuticals to treat antimicrobial resistance to antibiotics. Researchers have demonstrated that a combination of antibiotics with plant medicines can enhance and improve the action of antibiotics thereby overcoming antimicrobial resistance.[20] This is achieved in three main ways: firstly by means of a combined phytochemical and antibiotic attack on the bacterial cell wall - epigallocatechin gallate (EGCG) as found in green tea is effective in this regard. Secondly, antibiotic resistance can be overcome by inhibition of enzymes that are generated by bacteria for the deactivation of antibiotics (again EGCG is active here) or by thirdly by disabling an efflux pumping system developed by several bacteria in order to prevent potentially destructive compounds such as antibiotics from penetrating into the bacteria or to expel the antibiotics out of the bacteria cell once they have invaded it.[21]

Thymol and carvacrol, two main compounds in the essential oil of thyme (*Thymus vulgaris*) act as so-called 'membrane permeabilizers' and so aid antibiotics to penetrate into Gram-negative bacteria.[22] In addition, the leaves of thyme contain baicalein also present in the Scutellaria (Lamiaceae) species and baicalein has shown significant ability to reverse MRSA resistance to the antibiotic ciprofloxacin, seemingly by inhibiting the bacteria's defensive efflux pump.[23] Given all this, it is conceivable the synergy of herbal medicine may provide answers to the treatment of many intractable long-term diseases as well as to the increasingly serious problem of antibiotic resistance.

"The whole is greater than the sum of its parts."
Aristotle (*Metaphysics,* Book H 1045a 8-10)

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Notes