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# Herbal fertility treatments used in North America from colonial times to 1900, and their potential for improving the success rate of assisted reproductive technology


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**Abstract** This paper serves to fill a gap in the literature regarding evidence for the use of botanical remedies in the promotion of fertility. It examines the botanical remedies that were used in North America (1492–1900) for all stages of reproduction from preconception to birth, and discusses their potential for future use with present-day infertility treatments. Each medicinal plant discussed in this paper is assessed using an ethnomedicinal methodology that entails examining the published ethnobotanical, phytochemical and pharmacological data. A few clinical trials have shown that there is potential for medicinal plants to improve the success rate of assisted reproductive technology (ART) treatment if used in an integrated manner, similar to the integrated use of traditional Chinese medicine with ART treatment. For example, research has shown that older women who become pregnant have a high miscarriage rate, and this is one area that complementary and alternative medicines can address. 

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## Introduction

In pre-20th century America, women relied on midwives, neighbours and homemade botanical remedies to support

their reproductive health (Drinker, 1991; England and Kramer, 1922; Leavitt, 1986; Tannenbaum, 2002). (Allopathic medical knowledge of the time was suspect and expensive, and only used when traditional medicines failed (Frader and Stage, 1982; Ray,

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2009). Dangerous substances like mercury were used, and doctors believed in harmful practices, such as bleeding, vomiting, blistering, purging, anodynes and so forth (Abrams, 2013; Douglass, 1854; Duffy, 1993; Haller, 1981; Ray, 2009).

There are several medicinal plants that could be used in combination with assisted reproductive technology (ART) to lower the cost and increase the success rate of infertility treatment (Kooreman and Baars, 2012). Using herbs in this way is not a new idea. As infertility treatment is expensive and has a low success rate – approaching 49% with cumulative attempts (Vrtacnik et al., 2014) – some women use medicinal plants to try to improve their odds of success without telling their doctor (Broussard et al., 2010). Vitex was used by one woman who was undergoing in-vitro fertilization (IVF) treatment, and she showed signs of mild ovarian hyperstimulation (Cahill et al., 1994). Pregnant women use medicinal plants to give them greater control over their experience, and this control improves birth satisfaction (Clark et al., 2013; Hall et al., 2012; Shannon et al., 2010; Smith et al., 2010; Westfall, 2001; Zeyneloglu and Onalan, 2014). There are case reports of women who have become pregnant following alternative treatments. A 38-year-old Caucasian woman gave birth after being treated with Ayurvedic medicine in a German clinic. The treatment included some of the plants discussed later in this paper. The patient had secondary infertility of unknown cause, and had previously had 18 conventional fertility treatments in five different fertility centres in three different countries (Kessler et al., 2015). However, most fertility specialists do not know or ask what plants their patients are using (Shannon et al., 2010; Zeyneloglu and Onalan, 2014), and the testing of plant therapies in controlled trials is rare. However, there are some initial steps being taken towards an integrated approach in some clinics and in clinical trials. For example, Shahin et al. used black cohosh in combination with clomiphene citrate, and reported an increased clinical pregnancy rate for women under 35 years of age (Shahin and Mohammed, 2014; Shahin et al., 2008, 2009). These clinical trials are discussed later in the paper.

The argument put forward in this paper is two-pronged: (i) women are already using traditional botanical remedies, with or without the consent or knowledge of their doctors (Hall et al., 2012; Shannon et al., 2010; Smith et al., 2010) – this paper examines the published phytochemical and pharmacological data on the plants that are being used to assess their safety and efficacy; and (ii) there are potential benefits to examining plants that have been used for centuries by Native Americans, or that came to America through European immigration, or that have a basis in historical Greek or Arabic medical treatises, such as opopanax (*Opopanax chironium*), asafoetida (*Ferula assa-foetida*) and others. There is anecdotal and other evidence that at least some of the biochemically active compounds in the plants that have been used traditionally could serve as adjuncts to fertility treatments, potentially reducing costs by raising efficacy and offering hope and help to women barred from accessing ART treatment due to variable age and cost limits in different countries.

The most promising areas for the use of botanicals in improving livebirth rates are: (i) age-related decreased ovarian reserve ( $\geq 40$  years of age), (ii) stress associated with subfertility (oxidative stress or linked to increased prolactin levels), (iii) luteal-phase defects, and (iv) increased rate of

miscarriage for older women receiving ART because fertility declines with age and the demand for IVF typically increases with age. If herbs can increase the success rate of ART by preventing miscarriages and improving implantation rates, for example, this would lower the cost of ART.

This paper identifies the sources of herbal remedies in North America up to 1900, describes evidence for their effectiveness and any side effects, and examines how the use of plants may help ART.

## Materials and methods

An ethnomedicinal validation technique is used in this paper to identify traditional medicines with contemporary value. Validation includes examining the published phytochemical and pharmacological data to establish whether or not the reported folk use of plants is safe and effective (Lans et al., 2003). As this is a search for potential plant compounds to be used in future clinical trials and a historical study, exclusion criteria were not used in the validation process for the literature reviewed in this paper. Many of the books and journals used from 1492 to 1900 have been digitized, and these were searched online for terms related to reproductive problems; the plants used to treat patients with the noted condition were recorded. In most cases, these documents were patient reports, discussions of newly analysed plant compounds, or discussions of new patent medicines based on newly discovered North American plants. The databases used for the validation of the plants were ScienceDirect, PubMed and Scopus. The databases JSTOR and ProjectMUSE were also searched, but yielded little information.

The dates for the time periods relevant to this paper are listed by the Gilder Lehrman Institute of American History (<https://www.gilderlehrman.org/history-by-era/early-republic/essays/early-republic>), as follows:

- Colonial Period, 1585–1763: colonists brought their herbals to America, *Poor Richard's Almanac* first printed.
- Revolutionary Era, 1764–1783: the first home health books were printed, and the first sales of Lydia Pinkham's formula took place.
- Early Republic, 1783–1815: midwives like Martha Ballard kept diaries, the Bartrams' work entered the botanical literature.
- National Expansion and Reform, 1815–1860: scientific publications on American plants increase.
- Civil War and Reconstruction, 1861–1877: *The Lancet* published a discussion of Lydia Pinkham's formula (see below).
- Rise of Industrial America, 1877–1900: more plant uses based on Native American traditions enter the *United States Pharmacopoeia*.

A key to apothecary measurements used in dosages is given in Supplementary Material Item 32.

## Women's use of herbal medicine in colonial America and their sources of information

The knowledge of colonial Americans has been documented for well-known colonists and by women whose diaries have

been preserved. Tannenbaum (2012) discusses the diaries kept by colonists such as Elizabeth Drinker, which include family sicknesses and treatment, the names of physicians such as William Shippen, and some public health matters. Abigail Adams (1744–1818) developed her own knowledge on herbal medicine and on disease transmission (Diomi, 2014). Adams read Buchan's *Domestic Medicine* while travelling to England in the mid-1780s. She recommended the book to her sister, and recalled that political writer Mercy Otis Warren owned a copy (Hayes, 1996). Liquorice was used and preserved by Abigail Adams (Richards, 1917). William Buchan's *Domestic Medicine* was one of the most popular home health references in America from 1769 until the 20th century, and was among the first works written in English for the lay public (Dunn, 2000; Tannenbaum, 2012). Buchan was trained in medicine at Edinburgh University and worked at the Foundling Hospital in Yorkshire, then at a practice in Sheffield and later returned to Edinburgh (Dunn, 2000). Plants or related species discussed in this paper that are found in Buchan's book are myrrh, Asarum, gentian, logwood, juniper berries, sarsaparilla, liquorice, pennyroyal, hemlock, and black and white hellebore (Buchan et al., 1772).

Nicholas Culpeper took advantage of civil unrest and the resulting relaxation of professional control of medicine in England to publish the *Complete Herbal & English Physician* as a guide for lay people (Culpeper, 1795). It was very popular. Culpeper's *Pharmacopoeia Londinensis* or the *London Dispensatory* was the second book printed in British North America, and his *English Physician* also had many American editions (Tannenbaum, 2012). After the *Complete Herbal & English Physician*, the *Directory for Midwives: or a Guide for Women, in their Conception, Bearing and Suckling their Children, etc.* was Culpeper's second most popular book; it was reprinted 17 times, the last edition in 1777 (Thulesius et al., 1994). Culpeper democratized medicine by translating the physicians' *Pharmacopoeia Londinensis* from Latin into English. Culpeper's *London Dispensatory* was affordable and widely available to the common man (Farthing, 2015).

Colonial women passed Culpeper's books down through the generations. Hayes (1996) describes how the 1667 London edition of Culpeper's *London Dispensatory* in the Boston Medical Library collection was owned by apothecary Elizabeth Greenleaf, the wife of the parson-physician Daniel Greenleaf. Elizabeth Greenleaf passed her copy to her daughter Grace who, in turn, gave it to her sister. The 1720 copy of Culpeper's *London Dispensatory* in the Boston Medical Library contains an inscription that the book was given to Rachel Martin by her mother 5 days before she died on 13 March 1765, with the wish that Rachel would become the family's healer (Hayes, 1996). This meant that the herbal knowledge remained unchanged through different generations. Nathaniel Brook's *The Queen's Closet Opened* (1655) was also handed down in New England families, especially in those whose ancestors were physicians (Earle, 2008). Juniper is mentioned in Brook's work. Plants discussed in this paper that are the same or similar to those found in Culpeper's works are: myrrh, angelica, *Artemisia abrotanum*, *Asarum europium*, *Chelidonium majus*, *Origanum dictamnus* (sometimes compared with dittany of this paper), *Sambucus nigra*, *Sambucus humilis*, *Matricaria parthenium*, *Acorus adulterinus*, various *Erigeron* spp. including *E. canadense*, various *Senecio* spp., *Hellebrous niger*, *Actaea spicata*,

*Juniperus communis*, *Glycyrrhiza glabra*, various *Mentha* spp. including *M. pulegium*, *Leonurus cardiaca*, *Artemisia vulgaris*, *Prunus domestica*, *Populus nigrum*, *Ruta graveolens*, *Populus alba*, *Juniperus sabina*, *Asclepias syriaca* and *Hypericum androseum* (Culpeper, 1955).

Schiebinger (2004) describes an abortifacient provided in a medieval midwifery manuscript, and notes that midwives began writing more books in the 17th century but they were mainly polemics about male midwives. The pseudo-Aristotelian works such as *Aristotle's Masterpiece* contained useful gynaecological information and practical advice on pregnancy, conception and childbirth, but these were mainly read by men as pornography and aids to seduction (Hayes, 1996).

Dr. Thomas Williams was born in Newton, Massachusetts in 1718 and died in Deerfield in 1775. Dr. Williams' collection of papers contains a 28-page, personally copied book by William Salmon, MD, entitled *The English Herbal: of History of Plants* (Pollock, 2009; Salmon et al., 1710). The text is an alphabetical listing of medicinals in addition to definitions, qualities, applications and formulation recipes. Salmon (1644–1713) was an untrained English doctor practising near the gates of St Bartholomew's Hospital in London. A New Jersey physician with a large practice, and therefore some available wealth, paid the cost of a messenger to England to obtain the volume, which he then used from 1758 to 1777 (Stackhouse, 1908). This is one example of how books arrived in the USA and how one doctor copied and adapted available literature for his own practice. John Josselyn of Essex published *New England's Rarities Discovered* in 1672. Josselyn carried with him the 1633 edition of Gerard's *Herball or Generall Historie of Plantes* that he used to help identify plants (Vogel, 1970), providing another example of a book being taken to the USA.

The medicinal botanical guides by John Bartram and his son, William Bartram were another source of information. These guides included Native American remedies learned during plant-collecting trips across the eastern colonies of America and Ontario. These guides, including *True Indian Physic, or Ipecacuanha*, were published in the 1741 *American Almanac* in Philadelphia by John German and in Benjamin Franklin's 1741 *Poor Richard's Almanack* (Ray, 2009). *Poor Richard's Almanack* and other almanacks also conveyed information from African-Americans (for poison and snakebite cures) (Hayes, 1996). One-third of colonial families bought an almanack annually (Tannenbaum, 2012). John Bartram and Benjamin Franklin were founding members of the American Philosophical Society (1743–1746), which merged with other groups, including a medical society, but excluded women (Burns, 2005). Bartram's *Description Virtues and Uses of Sundry Plants of these Northern Parts of America, and Particularly of the Newly Discovered Indian Cure for the Venereal Disease* was bound with Thomas Short's popular *Medicina Britannica* in 1751. Franklin and David Hall reprinted the *Medicina Britannica* in an American edition, with Bartram's work in a preface showing where the plants described could be found in the USA (Bartram and Squier, 1853; Bell, 1975; Klepp, 2001; Murphy, 1991; Ray, 2009; Rosenberg and Helfand, 1998; Rothstein, 1985). William Bartram also travelled across the USA collecting information and botanical samples, including Native American use of botanical medicines. Benjamin Smith Barton based his 1798 edition of *Collections for an Essay*

*Towards a Materia Medica of the United States* on William Bartram's unpublished manuscript called *Pharmacopoeia*. Barton based his *New Views of the Origin of the Tribes and Nations of America* on Bartram's unpublished manuscript *Answers to Queries about Indians* and Bartram's *Observations on the Creek and Cherokee Indians* (which was "lost" from 1789 to 1853) without always crediting Bartram, and Barton's students published Bartram's drawings in their own works (Ray, 2009). John and William Bartram added 184 flora species, including *Polygala senega* and *Sanguinaria canadensis*, to the knowledge of the European colonists. In his works, John Bartram also listed many of the plants discussed in this paper, including *Aralia nudicaulis*, *Erigeron philadelphicus*, *Erigeron canadensis*, *Sanguinaria canadensis*, *Chmaelirium luteum*, *Aletris farinosa* and *Asclepias tuberosa* (Hobbs, n.d.)

The standard English herbals all obtained their information from Greek and Latin herbals (Schiebinger, 2004; Touwaide et al., 2005). The early Roman–Greek compilations were translated into German by Hieronymus Bock (1498–1554), whose herbal published in 1546 was called *Kreuterbuch*. A Dutch translation, *Cruydeboeck*, by Rembert Dodoens (1517–1585) was translated into French by Charles de L'Écluse (Carolus Clusius, 1526–1609) and called *Histoire des Plantes*. The Latin translation was called *Stirpium historiae pemptades*. The book was translated into English by Henry Lyte in 1578 as *A Nievve Herball*. Lyte's book became John Gerard's (1545–1612) *Herball or General Hiftorie of Plantes* (Blunt and Raphael, 1994; Kay, 1996). Owing to these translations and compilations, we now know that some of the plants used in pre-20th century America have been used since ancient times (Ambrosini et al., 2013).

Medical almanacs of two female authors of 17th century England, Sarah Jinner of London and Mary Holden of Sudbury, transmitted classically-based medical cures for women. Jinner's almanac informed women about abortifacient and emmenagogic drugs from Galen and Hippocrates (Weber, 2003). Of more than 200 plants in his works, Hippocrates lists 44 plants with gynaecological uses; more than any other category and more devoted to treatment than the non-gynaecological uses, which are more theoretical (Touwaide and Appetiti, 2015).

Avicenna's *Canon of Medicine* was used in medical studies across Europe and Asia from the 12th century until the beginning of the 18th century (Modanlou, 2008). Avicenna wrote the Canon because "The ancient Hippocratic corpus was enigmatic, Galen prolix, Rāzī confusing... neither the Greeks nor the Arabs had any book that could teach the art of medicine as an integrated subject" (Shoja et al., 2011). Avicenna had rules for testing drugs that suggest clinical experience and experimentation (Shoja et al., 2011). A brief history of herbals and other texts (see Supplementary Material Item 1) indicates that the latest editions of Culpeper and Avicenna should be sufficient for researchers who want to investigate which botanical remedies could be used in combination with ART in an integrated way. It also indicates that many plant uses are common across Europe, America and parts of the Arab world, and would be culturally acceptable to patients in those areas.

*The Arthur and Elizabeth Schlesinger Library on the History of Women in America* at Harvard University houses the records of 19th century entrepreneur Mrs. Lydia Pinkham (1819–1883). As a young woman, she worked as a midwife, nurse and schoolteacher. In 1873, Pinkham founded the

*Lydia E. Pinkham Medicine Company* in order to market the herbal medicine, *Lydia E. Pinkham's Vegetable Compound* that her husband had received as payment for a debt (Conrad and Leiter, 2008). After using it for the health problems of her immediate circle of family, friends and neighbours, her son convinced her to advertise and sales increased. Her vegetable compound and emmenagogues were sold to women with various ailments, including delayed menstruation, fallen womb and inflammation of the uterus (Frader and Stage, 1982; Young, 1980). The compound contained 20% alcohol, 8 oz. unicorn root (*Aletris farinosa*), 6 oz. of liferoot (*Senecio aureus*), 6 oz. of black cohosh (*Actaea racemosa*), 6 oz. of pleurisy root (*Asclepias tuberosa*) and 12 oz. of fenugreek seeds (*Trigonella foenum-graceum*), all macerated (Stage, 1979). Other compounds included liquorice root (*Glycyrrhiza glabra*), dandelion root (*Taraxacum officinale*), gentian (*Gentiana catesbaei*), helonias/false unicorn root (*Helonias dioica*), matricaria/chamomile flowers (*Matricaria chamomilla*) and thiamine hydrochloride (vitamin B1). The formula also contained Jamaica dogwood [*Piscidia piscipula* (L.) Sarg.] at one point (Records of the Lydia E. Pinkham Medicine Company, 1776–ca.1985; item description, dates. MC 181, folder #. Schlesinger Library, Radcliffe Institute, Harvard University, Cambridge, MA, USA).

The label of Lydia Pinkham's compound described female weaknesses as leucorrhoea, irregular and painful menstruation, inflammation and ulceration of the womb. Her business expanded to reap profits of \$300,000 annually, and the production of the compound switched from her kitchen and cellar to a laboratory. Part of the reason for her success was that doctors advocated removal of the ovaries for vaginal cramps, and this surgery had a mortality rate of 40% (<http://ocp.hul.harvard.edu//ww/pinkham.html>). The plants in Pinkham's formulation and their properties were discussed in *The Lancet* (Anon, 1863). Unicorn root (*Aletris farinosa*) was described as a tonic in small doses and an emetic in large doses. Aletridin, a precipitate of the plant, was said to be a uterine tonic. Senecionin, a tincture made from the leaves and roots of various liferoot (*Senecio*) species including *Senecio aureus*, was sold as an emmenagogue, and it was reported to tone the uterus and restore menstruation (Anon, 1863). Bethroot (*Trillium pendulum*) was used to promote parturition, and was recommended for haemorrhage, menorrhagia and leucorrhoea. Pharmacists Bradley and Bourdas wrote in a letter to the editor of *The Lancet* that they had *Trillium pendulum* for sale as a "remedial agent" for "uterine diseases"... "any gentleman who may wish to try its effects can be supplied with it" (Notices to Correspondents, *The Lancet* London, 18 July 1863, p. 87). This letter was written in response to the discussion of the plants listed in Pinkham's formulation in *The Lancet* (see Anon, 1863). One of the plants listed as understudied in this paper, *Piscidia piscipula*, was used only in Pinkham's formulation. *Asclepias tuberosa* and *Helonias dioica* were not often found in the literature associated with reproductive problems. One can only speculate that Pinkham's 1876 patent made further investigations of these plants uninteresting.

## Botanical remedies used for reproductive health before 1900

The following section examines the botanical remedies that were used to support the reproductive health of American

women before 1900. Emmenagogues, contraceptives and abortifacients are most commonly found in the historical documentation that is available today. Also common are herbs used as uterine tonics and herbs used to induce labour. Less common are herbs that specifically enhance fertility. All the various categories will be discussed as it is unknown at this time which plants will prove useful for combined therapy with ART.

### Women's gynaecological practices in North America pre-1900

Uterine tonics used early in the Colonial Period were either ancient herbal remedies or toxic chemicals. These uterine tonics included various salts of iron (possible adverse effects), bromide of potassium (an anticonvulsant), bi-tartrate of potass (increased potassium in the body can cause heart or kidney problems) and various phosphates (toxic) (*The Lancet*, 1863). The ancient herbal tonics were myrrh (*Commiphora myrrha*), savin (*Juniperus sabina*) and ergot (*Claviceps purpurea*) (*The Lancet*, 1863). The newly introduced American uterine herbal tonics were blue cohosh (*Caulophyllum thalictroides*), black cohosh (*Actaea racemosa*), unicorn root (*Aletris farinosa*), butterfly weed (*Asclepias tuberosa*), squaw weed (*Senecio gracilis*) and bethroot (*Trillium pendulum*), most of which were non-toxic. These tonics will be discussed later in the paper.

Women took care of the health of their households by relying on several books, including the many editions of William Buchan's *Domestic Medicine* printed in the UK and the USA (Buchan et al., 1772). Some of these books are listed in Supplementary Material Item 1).

### Botanical remedies used historically in women's reproductive health

American scientists and medical practitioners working before 1900 were open to blending indigenous medicinal plants into a pharmacopoeia that relied heavily on the herbals described above and on more informal ones (see Supplementary Material Item 2). Medical practitioners in Britain and America shared the knowledge of the newly discovered Native American plants such as black cohosh (*Actaea racemosa*) and black haw (*Viburnum prunifolium*) for dysmenorrhoea (pain during menstruation) at medical meetings and in journals (Royal Academy of Medicine in Ireland, 1900).

Household slaves served as informal medical practitioners in some homes (Tannenbaum, 2012). Granny midwives attended childbirths on some slave plantations as a cost-saving measure for the owners, but sometimes acted as abortionists (Vaughan, 1997). Vaughan (1997) records the plants or plant-based products used by slaves to abort, and several are discussed in this paper: tansy, catnip, thyme, horse mint, rue, pennyroyal, cedar berries, *Origanum vulgare*, *Thuja occidentalis*, oil of savin, leaves of *Juniperus virginiana*, fruit of *Juniperus communis*, *Cimicifuga racemosa*, *Caulophyllum thalictroides*, *Actea rubra*, *Helleborus viridis*, *Leonotis leonurus*, *Trillium undulatum*, *Trillium sessile*, *Trillium erectum* and *Cunila organoides*. Scudder (1870) was told by several parties that planters forced their slaves to drink an infusion of viburnum

tonic daily whilst pregnant. This tonic maintained their pregnancies even though they used cotton root (*Gossypium herbaceum*) to try to abort their pregnancies. A physician from Texas reported that he had observed this anti-abortive use of the plant for 15 years, and that he had prescribed it in many cases without a failure (Scudder, 1870).

Blue cohosh (*Caulophyllum thalictroides*) was listed in the *United States Pharmacopoeia* between 1882 and 1905 as a labour inducer (Dugoua et al., 2008), copying Native Americans who used it to relieve menstrual cramps and ease childbirth pains. "Cohosh" is said to mean "pregnancy" in the Algonquian language (Johnson and Fahey, 2012). Indian uses of the plant became known to botanists through an irregular publication entitled *The Indian Doctor's Dispensatory* issued in Cincinnati in 1812 by Peter Smith (Lloyd, 1898). Peter Smith was born in Wales, educated at Princeton and, as an adult, collected information from physicians whom he met in New Jersey, Pennsylvania, Virginia, North and South Carolina, Georgia, Kentucky and Ohio while he travelled with his young family as a preacher (Lloyd, 1898). Disapproving of slavery, he left the slave states of the South and moved to Ohio. In Smith's words: "... I have incidentally obtained a knowledge of many of the simples used by the Indians...". Native Americans explained plant medicine to Smith as "This thing is good for that thing; this medicine will cure that complaint" (Smith, 1812).

Black haw (*Viburnum prunifolium*) was discussed in *The Lancet* of 1888 as being valuable because there was no known substitute for the American plant. *The Lancet* noted that *Viburnum prunifolium* had a "reputation as an ovarian and uterine anodyne", and stated that it was "used in amenorrhoea and menorrhagia" and "gave excellent results in the treatment of dysmenorrhoea, after-pains and ovarian irritation and disposition to miscarriage", although others disputed this. *Viburnum* was used for pregnancy pains. For this indication, it was recommended to be taken regularly for a long time. There was also discussion of a case in which viburnum was believed to have held a fetus, which was not known to be dead, in the uterus for months until it was aborted (*Pharmacology and Therapeutics*, 1888). Other plant uses are listed below.

### Validation of plants used for fertility enhancement

This section considers the safety and effectiveness of herbal remedies used for fertility enhancement by examining the phytochemical and pharmacological data for any scientific basis for the potential use of plant-derived compounds to prevent miscarriage and to delay the decrease in ovarian follicles in women aged 40 years or older.

Predisposing factors for infertility in women include amenorrhoea (absence of menstrual period), oligomenorrhoea (irregular menstruation) and pelvic inflammatory disease (infection of the reproductive organs). Dysmenorrhoea linked to endometriosis is the cause of infertility in 30–50% of women with the condition (Bulletti et al., 2010). Secondary dysmenorrhoea (linked to endometriosis, uterine fibroids and ovarian cysts) can lead to infertility or ectopic pregnancies (Bulletti et al., 2010). The colonial term "delayed menses" typically means amenorrhoea due to stress, poor nutrition, overwork

or early pregnancy. Hippocrates believed that untreated amenorrhoea was fatal (Warren and Fried, 2001). Stress, poor diet and overexercising are some of the factors that can result in amenorrhoea (Meldrum, 2013; Wu et al., 2015). Amenorrhoea and oligomenorrhoea make it difficult to detect ovulation, if it takes place at all, leading to infertility. Emmenagogues have traditionally been used to stimulate menstruation; in some cases, they may be used to cause an abortion surreptitiously (Riddle, 1992).

Fertility for both sexes declines slowly after 30 years of age and more rapidly after 40 years of age, and age is considered to be the main limiting factor in treating infertility. Normally, 75% of women trying to conceive at 30 years of age will give birth within 1 year, compared with 66% at 35 years of age and 44% at 40 years of age. The conception rates over a 4-year timespan are 91%, 84% and 64%, respectively (Baird et al., 2005). The most important reason for decreased fecundity is the decrease in the population of ovarian follicles, and a decline in ovarian hormone production beginning before 40 years of age. Also, insulin-sensitive patients have a greater decline of follicle-stimulating-hormone-sensitive antral follicles as diabetes creates oxidative stress (Bentov and Casper, 2013). The ageing of the reproductive organs does not occur until 50 years of age, brought on by reduced uterine blood flow, progesterone-related effects or an increase in the number of fibroids (Ng and Ho, 2007). This is why donor oocytes from young women are often recommended to older women (Baird et al., 2005; Bentov and Casper, 2013), and why donor-egg pregnancy rates decline after 50 years of age.

### Botanical remedies that can potentially reduce or reverse genetic damage

The fertility-boosting potential of some plants can be linked to their antioxidant properties. Oxidative stress linked to aging results in the decreased production of glutathione and a negative impact on the granulosa cells that nourish the oocyte (Meldrum, 2013; Wu et al., 2015). In older women, there are increases in cortisol level, and changes in luteinizing hormone and growth hormone (Ben-Meir et al., 2015; Ng and Ho, 2007). Some of these processes can be reversed with antioxidants, including those found in medicinal plants (Table 1).

*Asarum canadense* contains quercetin glucosides (Iwashina and Kitajima, 2000; Schaneberg and Khan, 2004). *Helleborus niger* contains a quercetin glycoside (Vitalini et al., 2011). Chinese liquorice (*Glycyrrhiza uralensis*) has quercetin in its leaves (Duke et al., 1994). Quercetin is an antioxidant that improved the in-vitro development of porcine oocytes by reducing the levels of reactive oxygen species (ROS) (Kang et al., 2013). Quercetin also reduced the ROS in chilled stored rabbit sperm (Johinke et al., 2014). Quercetin has an anti-abortion effect in mice, and acts by reducing the overproduction of tumour necrosis factor-alpha and nitric oxide, and by maintaining the balance of CD4+/CD8+ T lymphocytes and the cytokine interferon- $\gamma$ /interleukin-4 balance in the uterus (Wang et al., 2011). *Leonurus cardiaca* contains chlorogenic, caffeic and ferulic acid and phenylethanoids that scavenge ROS (Flemmig et al., 2015). A few of the plants contain vitamins (*Aralia nudicaulis*, *Juniperus communis*). Taking multivitamins was associated with decreased pregnancy loss in a prospective cohort study in the USA with preconception enrolment (Buck et al., 2016).

A more systematic approach to tackling the aging oocyte and diminishing ovarian reserve may lie in the practice of Chinese medicine that prepares the whole body for pregnancy. This would be useful for all ART patients. Patients could continue to be treated with this whole-body traditional Chinese medicine (TCM) that appears to reset the body organs to normal functioning. Endometriosis associated with infertility has been diagnosed in TCM as kidney deficiency and blood stasis, and the TCM treatment is designed to address those underlying conditions first rather than sending the patient straight for ART treatment (Ding and Lian, 2015). Other Chinese medicine diagnoses are called "tonification of the kidney system and of the spleen, qi tonification of the liver blood and heart blood, and harmonization of the liver..." which "roughly corresponds to anovulation patterns, thin endometrial lining and poor ovarian quality due to age" (Sela et al., 2011).

A detailed review of TCM diagnosis of syndromes associated with diminished ovarian reserve (DOR) is provided in Zhang and Xu (2016). The blood, liver, heart, kidneys, spleen and lungs are all checked and treated if necessary to ensure that the entire body is ready for implantation. *Artemisia argyi* was one of the plants used in a multicomponent formula for DOR. *Angelica sinensis* was used in another treatment for DOR during the luteal phase. Cao et al. (2013) point out that

**Table 1** Validation of natural compounds as potential fertility enhancers – coenzyme Q10.

Medical condition or study	Biochemistry confirming traditional use	Reference
Stress decreases sperm membrane integrity, sperm DNA damage and decreased sperm mobility	Coenzyme Q10 concentration is correlated with sperm count and motility, and supplementation can improve motility from 4.5% to 6%	Ko and Sabanegh, 2014
Chromosome abnormalities in the aging oocyte. Age-related functional declines in granulosa cells, consistent with premature luteinization	Coenzyme Q10 may correct abnormalities. Follicle-stimulating hormone levels need to be optimal in older patients	Ben-Meir et al., 2015; Bentov and Casper, 2013; Wu et al., 2015
Prospective randomized controlled trial – ovulation induction in clomiphene-citrate-resistant polycystic ovary syndrome	Combined oral coenzyme Q10 and clomiphene citrate. More follicles, greater endometrial thickness, more ovulation, and higher clinical pregnancy rate with combination. Coenzyme Q10 intake is diet-related, so this study bolsters the Mediterranean diet study	El Refaey et al., 2014

**Table 2** Validation of natural compounds as potential fertility enhancers – medicinal plants.

Medical condition or study	Clinical trials	Biochemistry confirming traditional use	Reference
Sperm quality – review paper. Antioxidant activity	<i>Juniperus virginiana</i> leaves/twigs, <i>Gaultheria procumbens</i> leaves, <i>Asarum canadense</i> roots, <i>Populus tremuloides</i> bark, <i>Aralia racemosa</i> roots, <i>Senecio aureus</i> , <i>vitex</i>	Nutraceuticals: coenzyme Q10, glutathione, omega-3 s, selenium, vitamins A, C and E, zinc	Ko and Sabanegh, 2014; Maltas et al., 2010; Meldrum, 2013; Saglam et al., 2007
Oocyte quality, ovarian blood flow and improved embryo implantation; a positive impact on granulosa cells; gonadotrophin stimulation produces a negative effect on the oxidant–antioxidant balance	<i>Juniperus virginiana</i> leaves/twigs, <i>Gaultheria procumbens</i> leaves, <i>Asarum canadense</i> roots, <i>Populus tremuloides</i> bark, <i>Aralia racemosa</i> roots, <i>Senecio aureus</i>	Fish consumption resulting in omega-3 s consumption	Bentov and Casper, 2013; Hansen and Knudsen, 2013; Meldrum, 2013; Oszkiel et al., 2014; Palini et al., 2014
Stress associated with subfertility (oxidative or linked to increased prolactin levels). Observational prospective study	<i>Juniperus virginiana</i> leaves/twigs, <i>Gaultheria procumbens</i> leaves, <i>Asarum canadense</i> roots, <i>Populus tremuloides</i> bark, <i>Aralia racemosa</i> roots <i>Acorus calamus</i> <i>Senecio</i> , <i>Polygala senega</i> , all have antioxidant properties	A preconception “Mediterranean” diet by couples undergoing IVF/ICSI treatment improved pregnancy rate; consumption of cereals, vegetables and fruits positively influenced the embryo quality at the cleavage stage; high plasma vitamin E was associated with high numbers of total and mature oocytes retrieved per patient, which leads to higher pregnancy rates	Amarowicz et al., 2004; Braga et al., 2015; Kessler et al., 2015 McCune and Johns, 2002; Michel et al., 2014; Palini et al., 2014; Vujkovic et al., 2010

IVF, in-vitro fertilization; ICSI, intracytoplasmic sperm injection.

*Angelica sinensis* was used in 15 of the 20 trials that they evaluated. The 20 trials investigated whether Chinese herbal medicine (including decoctions and granules) could improve the clinical (or laboratory) outcomes of IVF compared with IVF alone (see Supplementary Material Item 31).

This paper has focused on specific uses of plants for infertility treatment, and does not recommend their long-term use. Some plants could be used together with IVF or intrauterine insemination treatment; others would be used to support any resulting pregnancy according to the needs of the individual patient. Tailoring treatment to individual needs is the practice in Chinese medicine (Sela et al., 2011). For clinical trials of plants, it may be necessary to group

patients into infertility groups with similar causes, such as luteal-phase defect or polycystic ovary syndrome (PCOS), to test specific plants. This is especially necessary to ensure that there are no adverse effects (Boivin and Schmidt, 2009), or null effects for older women (Jo et al., 2016).

### Plants for further investigation

The validation process established that all the plants used historically for reproductive problems could be used in an integrated way with ART, and merit further study. Below is an evaluation of the most-studied plants. These plants may

**Table 3** Sweet flag (*Acorus calamus* L.) (Acoraceae): (a) traditional use and (b) validation.

(a)				
Person	Use	Latin name	Dosage/ administration	Reference
Oklahoma Delaware	Suppressed menses	<i>Acorus calamus</i> L. (Acoraceae). Plant is native to Asia. Sweet flag	Root eaten or boiled with milk, pimento or ginger	Cook's Physiomedical Dispensatory, 1869; Moerman, 1998; Tantaquidgeon and Tantaquidgeon, 1972
(b)				
Medical condition or study	Clinical trials	Biochemistry confirming traditional use	Reference	
Review	Anti-inflammatory activity; anticonvulsant and antispasmodic activity	Alpha and beta asarone. Overdoses of a pill form resulted in health problems similar to an amphetamine overdose	Rajput et al., 2014; Zuba and Byrska, 2012	

**Table 4** Black cohosh (*Actaea racemosa* L.) synonym *Cimicifuga racemosa* (L.) Nutt., (Ranunculaceae): (a) traditional use and (b) validation.

(a)			
Person	Use	Dosage/ administration	Reference
Dr Lawrence Bohun, a 17th century Virginia physician, and Philadelphia pharmacist Elias Durand Native Americans, colonists	Amenorrhoea		Blanton, 1972; England and Kramer, 1922; Gill, 1972; Hughes, 1957. King et al., 1898
J. King, eclectics	Leucorrhoea and excoriation of the cervix uteri Tone the reproductive tract, restore suppressed menses, treat dysmenorrhoea, relieve sickness and heartburn in pregnancy, extreme postpartum depression, sedative	"Equal parts of alum-root and black cohosh-root in decoction" <a href="http://www.henriettes-herb.com/articles/cohosh.html">http://www.henriettes-herb.com/articles/cohosh.html</a>	Johnson and Fahey, 2012; King et al., 1898
Botanist Alfred Hall	Promote menstruation	2 oz. sliced or pulverized if dry, steeped 2 days in one pint of gin. 4 oz. green to 1.5 pints gin, sweetened with honey and diluted with water, one wineglass full every 3 h	Hall, 1843
(b)			
Medical condition or study	Clinical trials	Biochemistry confirming traditional use	Reference
Overcome anti-oestrogenic activity of clomid on cervical mucus and endometrium	Phytoestrogen group fewer days for follicular maturation, thicker endometrium, higher oestradiol concentration, higher luteal-phase serum progesterone but 14% clinical pregnancy rate versus 21% rate for ethinyl oestradiol	Group I received additional oral phytoestrogen ( <i>Cimicifuga racemosa</i> ) 120 mg/day from days 1 to 12	Shahin et al., 2009
Randomized, double-blind, parallel-controlled study	Sopropanolic black cohosh extract (iCR) compared with tibolone provided relief from menopausal symptoms and inhibited the growth of fibroids	Agonist and competitive ligand for the $\mu$ -opoid receptor – analgesic effect	Johnson and Fahey, 2012; Xi et al., 2014
Randomized trial of a dry extract of black cohosh used with clomiphene citrate on days 1–12	Improved clinical pregnancy rates, endometrial thickness and serum progesterone		Shahin et al., 2008
Randomized trial of black cohosh and clomid versus clomid alone	Days until hCG injection, endometrial thickness, serum levels of mid-luteal and mid-cycle oestradiol, LH as well as mid-luteal progesterone. Higher clinical pregnancies per cycle		Shahin and Mohammed, 2014
Various studies and reviews	Mimics endogenous hormones. Dopaminergic and serotonergic systems may be affected by black cohosh. Receptor agonists	The triterpene glycosides (acteïn, 23-epi-26-deoxyacteïn, 27-deoxyacteïn and cimicifugoside), alkaloids (cysteine and N-methyl cytosine), phenolic acids (ferulic acid, iferulic acids, soferulic acid, fukinolic acid, piscidic esters) and $N_{\omega}$ -methylserotonin act as 5-HT1A and 5-HT7 serotonin receptor agonists at the thermoregulatory centre in the hypothalamus. Standardized extracts are typically based on the content of 27-deoxyacteïn	Blumenthal, 2000; Bolle et al., 2007; Liske and Wustenberg, 1998; Murray, 1997; Seidlova-Wuttke et al., 2003; Shahin and Mohammed, 2014; Tanmahasamut et al., 2015; Toh et al., 2012; Ulbricht and Windsor, 2014; Wuttke et al., 2014

(continued on next page)



Table 4 (continued)

(b) Medical condition or study	Clinical trials	Biochemistry confirming traditional use	Reference
Various studies and reviews	Recent research suggests inhibition of serotonin receptors. Selective oestrogen-modulating effect on some tissues such as bone, serotonin-binding properties in the brain. Tissue-selective oestrogen receptor modulatory activity accompanied by centrally acting dopaminergic, serotonergic and GABAergic effects. No consistent pattern of influence on serum hormone levels (oestradiol, FSH, LH), endometrial tissue or vaginal tissue		Fritz et al., 2014; Merchant and Stebbing, 2015; Mohammad-Alizadeh-Charandabi et al., 2013; Rostock et al., 2011; Schellenberg et al., 2012
Safety study	No effect on circulating LH, FSH, prolactin or oestradiol		Raus et al., 2006; Taylor, 2015
Double-blind human study with electroencephalography and the concentrations of salivary chromogranin-A and cortisol to assess stress	Can reduce stress associated with subfertility		Nadaoka et al., 2012
Inhibition of methylglyoxal-induced protein glycation and DNA damage by isoferulic acid from <i>Cimicifuga dahurica</i>		Free radical scavenging by cinnamic acid derivatives (ferulic acid, isoferulic acid, piscidic and fukiic esters also found in <i>Actaea racemosa</i> )	Meeprom et al., 2015

FSH, follicle-stimulating hormone; hCG, human chorionic gonadotropin; LH, luteinizing hormone.

be easiest to justify investigating first. Understudied plants are listed in Supplementary Material Items 3–30.

### Sweet flag (*Acorus calamus*)

*Acorus gramineus* Soland (“shi chang pu”) (same plant family as *Acorus calamus*) and glycyrrhiza (“gan cao”) (part of Deborah Read’s formula in the Supplementary Material) are used in multicomponent remedies in TCM to treat both sexes (Ding and Lian, 2015; Tempest et al., 2008).

### Black cohosh (*Cimicifuga racemosa* (L.) Nutt./*Actaea racemosa* L.)

Black cohosh is widely used to treat symptoms of menopause, and a number of clinical investigations have verified its effectiveness as a supplement to or substitute for hormone replacement therapy (Blumenthal, 2000; Kessel and Kronenberg, 2004). Black cohosh is currently used in allopathic medicine, but it is only indicated for menopause-related neurovegetative and emotional symptoms (Schellenberg et al., 2012). The German Commission E approved black cohosh treatments for premenstrual syndrome, dysmenorrhoea and menopausal symptoms (Fritz et al., 2014). Dog et al. (2010) list the herb–drug interactions for black cohosh and the current regulatory requirements for its active compounds.

Black cohosh may cause gastrointestinal problems if used long term (Elvin-Lewis, 2001); however, this adverse effect needs to be evaluated against the claims that black cohosh prevented bone loss and bone marrow fat accumulation in ovariectomized rats (Schilling et al., 2014; Soni et al., 2011). Midwives have reported adverse effects from black cohosh. Wuttke et al. (2014) claim that many commercial preparations have Asian varieties of black cohosh (*Cimicifuga racemosa*, “sheng ma”) which contain different chemical constituents from North American varieties, and the Asian varieties have been less studied, but adverse reactions to black cohosh in Canada were claimed to be due to the use of the Asian species (*Actaea cimicifuga*; Dog et al., 2010). Sheng ma is indicated for headache and digestive distress, and is not typically used to treat infertility in TCM.

### Angelica (*Angelica archangelica*)

*Angelica gigas* Nakai and *Angelica sinensis* (Oliv.) Diels (“dang gui”) (in the same plant family as *Angelica archangelica*) are used in multicomponent Chinese medicine remedies to treat infertility (Ding and Lian, 2015; Jo and Kang, 2016; Zhang and Xu, 2016). Dang gui is commonly known as “the women’s herb” and is indicated for many different kinds of gynaecologic disorders in TCM. However, its use is not limited to women’s concerns, as dang gui is used in many multicomponent Chinese

herbal formulas to treat male factor infertility, including improving sperm motility, morphology and count (Jo and Kang, 2016). The possibility of adulturation has to be taken into account when reading reports of liver toxicity for *Angelica archangelica* (Teschke et al., 2014). *Angelica glauca* was part of the multiplant treatment used by Kessler et al. (2015). *Archangelica officinalis* is a synonym of *Angelica archangelica* L. (Apiaceae).

### Blue cohosh (*Caulophyllum thalictroides*)

Midwives have reported adverse effects from blue cohosh such as nausea, increased meconium-stained fluid and transient fetal tachycardia. Case reports of health problems in newborns associated with maternal use of blue cohosh are possibly due to caulosaponin and caulophyllosaponin, constituents of blue cohosh that cause coronary blood vessel constriction, a toxic effect on cardiac muscles and myocardial toxicity (Gunn and Wright, 1996; Jones and Lawson, 1998). The mother in the adverse case report had been advised by the midwife to take one blue cohosh tablet per day for 1 month

prior to delivery to help induce uterine contractions. The mother elected to take three times the dose for 5 weeks. She had increased contractions and a decrease in fetal activity. The delivery took 1 h. The infant required intubation after 20 min and had cardiogenic shock caused by myocardial ischaemia, was critically ill for several weeks, but survived (Elvin-Lewis, 2001; Jones and Lawson, 1998).

### *Chelidonium majus*

*Chelidonium majus* is used in TCM ("bai qu cai") to treat PCOS. In a single-arm pilot study, 0.4 g berberine was given three times per day for 4 months to 102 anovulatory Chinese women with PCOS, and 14 women restarted regular menses (Li et al., 2015). [Berberine is found in *Chelidonium majus*; see multiplant formula listed for *Populus tremuloides* in the dosage listed below (Supplementary Material Item 24)]. Ten women taking *Chelidonium majus* for 3 months (which we are not recommending) showed liver injury (elevated serum alanine aminotransferase and alkaline phosphatase, but no liver failure) (Bunchorntavakul and Reddy, 2013). A

**Table 5** *Angelica* (*Angelica archangelica* L.) (Apiaceae): (a) traditional use and (b) validation.

(a)			
Person	Use	Dosage/ administration	Reference
Colonists	Emmenagogue	Cordial	Gray, 1821; Milne-Edwards and Vavasseur, 1831
(b)			
Medical condition or study	Clinical trials	Biochemistry confirming traditional use	Reference
Correlate the follicular levels of IL-1 alpha, IL-2, tumour necrosis factor-alpha and LTB <sub>4</sub> with oocyte maturity, fertilization, becoming pregnant	LTs are compounds that cause contractions by stimulating receptors in arteries and increase vascular permeability. LTD <sub>4</sub> was found in follicular fluids of stimulated women undergoing in-vitro fertilization. This compound is also released by human granulosa cells and may act on follicular maturation	Isoquercitrin, a flavonoid that inhibits the activity of leukotriene LTD <sub>4</sub>	Bili et al., 1998; Schneider and Bucar, 2005; Sigurdsson et al., 2013
Medical condition or study	Biochemistry confirming traditional use	Reference	
Calcium antagonistic activity; chemical analysis	Secondary metabolites, beta-phellandrene (74.7%) in angelica seed oil. The root oil contained a larger amount of macrocyclic lactones (1.3%) such as muscolide in comparison with the seed oil (0.4%). Contains adenosine, coniferin and glycosides. Seeds contain six coumarins	Härmälä et al., 1992; Kumar et al., 2013; Lemmich et al., 1983; Lopes et al., 2004; Muller et al., 2004	
Anxiolytic effects of coumarins – animal models	Volatile oil, valeric acid, angelic acid, sugar, a resin called angelicin, selimone, archangelin, oxypeucedanin and a glycoside	Kumar et al., 2013	
Staged therapy of infertile women with endometriosis, <i>Angelica sinensis</i> used with other compounds including <i>Artemisia argyi</i> and <i>liquorice</i>	The pregnancy rate within 12 months of follow-up was 45.0% (36/80): 21 in Group A (traditional Chinese medicine) (52.5%, 21/40), and 15 in Group B (12.5 mg mifepristone orally daily) (37.5%, 15/40)	Ding and Lian, 2015	

IL, interleukin; LT, leukotriene.

study on the swine uterus (*Sus scrofa domestica*) compared butylscopolamine (hyoscine butylbromide, Buscopan, derived from *Atropa belladonna*), atropine (Belladonnysat Bürger, derived from *Atropa belladonna*, *Hyoscyamus niger* and *Datura stramonium*), denaverine (Spasmalgan), celandine (Chelidonium, Paverysat), pethidine (Dolantin, Demerol), morphine (Paveriwern, derived from *Papaver somniferum*) and metamizole (Novaminsulfon-ratiopharm). Celandine (found in *Chelidonium majus*) caused contractions in uterine muscle and may promote rapid sperm transport (Kuenzel et al., 2013).

### Skullcap (*Scutellaria baicalensis*) (Lamiaceae)

Skullcap was part of the Dioivburnia cordial made by Dios Chemical Co., of St. Louis, Missouri (Shrady, 1891). Skullcap ("huang qin") is one of the top 40 herbs in TCM herbology, and is used in herbal combinations for a wide variety of gynaecologic and obstetric conditions. It is also used in herbal formulas to prevent miscarriage and to stop metrorrhagia. The main chemical constituents of huang qin are baicalein, baicalin, wogonin, wogonoside, neobaicalein, acetophenone,

**Table 6** Blue cohosh (*Caulophyllum thalictroides* (L.) Michx) (Berberidaceae), squaw root: (a) traditional use and (b) validation.

(a)			
Person	Use	Dosage/ administration	Reference
Eclectic and homeopathic practitioners	Native Americans used a decoction of the root for 2 or 3 weeks prior to labour to facilitate <i>childbirth</i>	Dose of the infusion (root 3j to aqua Oj), from 1 to 3 oz., every 3 or 4 h	Ferguson and Edwards, 1954; King et al., 1898; Smith, 1812
Patent formula	Induce childbirth	Caulophyllin, asclepin, helonin and scutalaria	Newton et al., 1856
Prof. B.L. Hill, Professor of Surgery in the Eclectic Medical Institute, of Cincinnati, Ohio	Emmenagogue, for uterine leucorrhoea (white or yellow discharge), amenorrhoea, dysmenorrhoea, to facilitate parturition in combination with <i>Mitchella repens</i> , and for menstrual pain	Dose of the infusion (root 3j to aqua Oj), from 1 to 3 oz., every 3 or 4 h	King et al., 1898
(b)			
Medical condition or study	Clinical trials	Biochemistry confirming traditional use	Reference
Review; anti-inflammatory effects determined by Western blotting and in adrenal glands of mice	Enhances oestradiol binding to oestrogen receptors	Alkaloid methylcysteine and the glycoside caulosaponin (steroidal saponin) account for the physiological activity. Blue cohosh's oxytocic (hastening childbirth) effects are linked to the glycoside caulosaponin, a derivative of the triterpenoid saponin hederagenin. These substances are considered to be phytoestrogens because of their steroid backbone. Their chemical structure is similar to that of anti-inflammatory glucocorticoids	Dugoua et al., 2008; Lee et al., 2012;
Review	Demonstrated oestrogenic activity, decreased luteinizing hormone levels and increased serum ceruloplasmin oxidase activity		Dugoua et al., 2008
Blue cohosh ( <i>Caulophyllum thalictroides</i> ) enhances oestradiol binding to oestrogen receptors		An active oxytocic compound that is responsible for increasing uterine tone; it contains quinolizidine alkaloids (anagryne (teratogenic), baptifoline, n-methylcystisine) (nictotinic), aporphine alkaloids (magnoflorine, taspine, boldine), norlupanine alkaloids (sparteine, cytisine, lupanine), piperidine alkaloids (thalictroidine, caulophyllumines A and B), steroidal glycosides and several triterpene glycosides	Matsuo et al., 2009; Rader and Pawar, 2013
Adverse effects from overdose – nausea, increased meconium-stained fluid and transient fetal tachycardia		Caulosaponin and caulophyllosaponin, constituents of blue cohosh that cause coronary blood vessel constriction, toxic effect on cardiac muscles and myocardial toxicity	Elvin-Lewis, 2001; Gunn and Wright, 1996; Jones and Lawson, 1998

**Table 7** Greater celandine (*Chelidonium majus* L.) *Papaveraceae*: (a) traditional use and (b) validation.

(a) Person	Use	Dosage/ administration	Reference
Component of homeopathic preparation Phyto Hypophyson L with main ingredient being vitex	Causes limpness and tone reduction in smooth muscle. <i>Chelidonium majus</i> is an official drug in the <i>European Pharmacopoeia</i> and has anti-inflammatory, analgesic and hepatoprotective effects	Donine, berberine, chelerythrine, stylosine, seven isoquinoline alkaloids, sangunarine and benzyloisoquinoline alkaloid which changes to coptisine after plant harvesting. Other compounds are listed in <a href="#">Park et al., 2011</a>	<a href="#">Li et al., 2015</a> ; <a href="#">Orvos et al., 2015</a> ; <a href="#">Park et al., 2011</a> ; <a href="#">Paulsen et al., 2015</a>
(b) Medical condition or study	Clinical trials	Biochemistry confirming traditional use	Reference
Anti-inflammatory activity		Compounds with hydroxy methine constituents such as norchelidonine, chelidonine and 8-hydroxydihydrosanguinarine reduced nitric oxide production and showed anti-inflammatory activity	<a href="#">Park et al., 2011</a>

palmitic acid, oleic acid, proline, benzoic acid, radix scutellariae enzyme and  $\beta$ -sitosterol. Its decoction *in vitro* has various degrees of inhibition on various bacteria. It also reduces fever, lowers blood pressure, protects the liver and gallbladder, inhibits intestinal motility, lowers lipids, resists oxidation, regulates cAMP levels and fights tumours. The possibility of adulteration has to be taken into account when reading reports of liver toxicity for *Scutellaria baicalensis* ([Teschke et al., 2014](#)).

### Liquorice (*Glycyrrhiza uralensis*) (Fabaceae)

Liquorice (*Glycyrrhiza uralensis*) (Fabaceae) was part of Deborah Read Franklin's formula (see Supplementary Material) and Lydia Pinkham's formula discussed above. IVF success in mice improved with the addition of a water extract of *Glycyrrhiza uralensis* to the artificial insemination culture medium. Adding glycyrrhizic acid was not successful ([Tung et al., 2015](#)). The relevant compounds are isoliquiritigenin and formononetin. Isoliquiritigenin may be metabolized to form liquiritigenin, which is an active flavonoid. Isoflavones such as formononetin can improve impaired oestrous cycling, ovarian function, and functions of the hypothalamus and pituitary gland ([Tung et al., 2015](#)). Adverse effects are seen with doses

of liquorice above 600 mg/day and it is not recommended for long-term use ([Tovar and Petzel, 2009](#)). An ovarian counterpart of glycyrrhiza acts as an inhibitor of glucocorticoid metabolism (in common with liquorice) by  $11\beta$ HSD, and has a positive effect on the ability of an embryo to develop and implant by affecting the cortisol:cortisone ratio ([Michael, 2003](#)).  $11\beta$ HSD in the placenta reduces fetal exposure to maternal glucocorticoids ([van Uum et al., 1998](#)).

### Rue (*Ruta graveolens*) Rutaceae

Slaves used rue (*Ruta graveolens*) to abort and it was used for suppressed menses either alone or in combination with tansy (*Tanacetum parthenium*), savin (*Juniperus sabina*) and pennyroyal (*Mentha pulegium*) ([Riddle, 1992](#); [Vaughan and Clark Atlanta University, 1997](#)). Some reports of *Ruta graveolens* (and pennyroyal) being used for abortions fall into the category: 'her bereaved relatives rued the day she ever used that plant' ([Ciganda and Laborde, 2003](#)). The mouse trial conducted by [de Freitas et al. \(2005\)](#) suggests that *Ruta graveolens* had little or no negative effects in early pregnancy, but there were negative effects in the later stages of pregnancy.

**Table 8** Liquorice (*Glycyrrhiza glabra* L) (Fabaceae): (a) traditional use and (b) validation.

(a) Person	Use	Dosage/ administration	Reference
Plinius the Elder	Combat sterility		<a href="#">Fiore et al., 2005</a>
(b) Medical condition or study	Latin name	Biochemistry confirming traditional use	Reference
Antisterility	<i>Glycyrrhiza glabra</i>	Triterpene saponins (glycyrrhizin) and flavonoids with oestrogenic effects	<a href="#">Fiore et al., 2005</a> ; <a href="#">Kessler et al., 2015</a> ; <a href="#">Pliny and Mayhoff, 1967</a>
Toxicology review	<i>Glycyrrhiza glabra</i>	Blocks metabolism of prostaglandins E and F <sub>2</sub> alpha	<a href="#">Tovar and Petzel, 2009</a>

**Table 9** Motherwort (*Leonurus cardiaca* L.) (Lamiaceae): (a) traditional use and (b) validation.

(a) Person	Use	Latin name	Dosage/ administration	Reference
Female patients told authors of <i>The Physicians and Surgeons' Investigator</i>	Tonic	<i>Leonurus cardiaca</i> , motherwort	Infusion at puberty, avoid uterine disorders in later life	Anon, 1889
King's American Dispensatory, Delaware, Micmac, Modheman, Shinnecock, Mohegan, Eclectic physicians, early Greek remedy	Amenorrhoea, suppressed lochia, dysmenorrhoea, a superior antispasmodic, nervine, and emmenagogue. As a fomentation to the bowels in suppressed and painful menstruation, etc., anxiety in pregnancy	<i>Leonurus cardiac</i> <i>Ictodes foetidus</i> is <i>Symplocarpus foetidus</i> (L.) Salisb. ex W.P.C. Barton (Araceae)	'Combined with ictodes and resin of black cohosh as emmenagogue. Dose of decoction, from 2 to 4 fluid ounces, every 1, 2 or 3 h; of the extract, from 3 to 6 grains, every 2 to 4 h'	Brenyo and Aktas, 2014; King et al., 1898; Moerman, 1998; Tantaquidgeon and Tantaquidgeon, 1972
(b) Medical condition or study	Clinical trials	Biochemistry confirming traditional use	Reference	
Isolated rat heart – animal model	Leonurine alkaloid uterine stimulant effects <i>in vitro</i> . Lavandulifolioside decreases blood pressure	The alkaloid stacydrine may stimulate oxytocin release, the alkaloid leonurine has shown uterine stimulant effects <i>in vitro</i> . The alkaloid stachydrine may stimulate oxytocin release	Blumenthal, 2000; Kuchta et al., 2012; Mitkowska-Leyck et al., 2002	
Lactoperoxidase activity		Flavonoids (rutin, quercetin), flavones (apigenin, genkwanin), phenylethanoids (lavandulifolioside, verbascoside), p-hydroxycinnamic acid derivatives) caffeic, ferulic, chlorogenic, cichoric acids), diterpenes, iridoids, terpenes, betains (stachydrin, betonicin, turicin)	Flemmig et al., 2015	
Review		Commercial preparations sold in Europe must have 0.2% flavonoids, expressed as hyperoside. Alkaloids, leonurine and stachydrine have sedative effects and lower blood pressure	Wojtyniak et al., 2013	
Mice uteruses – increased strength and frequency of contractions	Relaxation of rat portal vein	Uterus shrinking justifies traditional use to expel placenta and shrink uterus. Vasodilating activity may justify traditional use for dysmenorrhoea	Wojtyniak et al., 2013	

**Table 10** Rue (*Ruta graveolens* L.) (Rutaceae): (a) traditional use and (b) validation.

(a) Person	Use	Dosage/ administration	Reference
George Capron and David Slack	Delayed menses	Infusion – “steeping an ounce in a pint of boiling water, from a wine-glassful to a gill [0.25 pint] is the usual dose. It may be taken several times a day”	Capron et al., 1853
Dr William Shippen, Philadelphia, al-Razi's <i>trochisci e myrrha</i>	Obstructed menses	<i>See Commiphora abyssinica</i>	Fee, 2015, Klepp, 2009; Royal College of Physicians of London, 1716
Botanist Alfred Hall	Suppressed menses	Tea, bathe feet for all remedies	Hall, 1843
(b) Medical condition or study	Clinical trials	Biochemistry confirming traditional use	Reference
Animal model	Aqueous extract can interfere with pre-implantation development and embryo transport		Gutiérrez-Pajares et al., 2003
Human sperm immobilization Antifertility activity		Coumarin <i>n</i> -butanol-soluble fraction and rutin had uterotonic activity	Naghbi et al., 2015 Salib et al., 2014

**Table 11** Squaw bush *Viburnum opulus* (L.) and *Viburnum prunifolium* (Adoxaceae): (a) traditional use and (b) validation.

(a) Person	Use	Latin name	Dosage/ administration	Reference
Native Americans, colonists, Dr. Elisha Smith of New York, Dr. Hulbert	Regulate menstrual cycle, procure abortions, <i>dysmenorrhoea</i>	<i>Viburnum opulus</i>	Decoction 'Viburnum – Bark, Siii j Water, Oiii. Reduce by boiling to two pints, and strain. Dose – a wine-glass three to four times daily. Add loaf sugar if desirable.  Tincture Viburnum Compositum – Bark, coarsely powdered, lb. i: Lobelia Leaves, powdered, 5iv; Sweet Flag-root, coarsely powdered, 5ii; boiling Water, Oii. Digest 24 h and bottle. Add Alcohol, Oii, and digest 5 days. Add Port or Sherry Wine, Oiv, and digest 5 days. Dose – floi to iv, three to five times daily'	Leonard, 1884; Hollembaek and Foote, 1865; Klepp, 2001
Hayden's Viburnum Compound (London, UK)		<i>Viburnum opulus</i> dioscorea and <i>Scutellaria lateriflora</i>	'Black Haw ( <i>Viburnum prunifolium</i> ) 6 parts, Cramp Bark ( <i>Viburnum opulus</i> ) 4 parts, Beth root ( <i>Trillium erectum</i> ) 4 parts, Clove ( <i>Eugenia caryophyllus</i> ) 4 parts, Cinnamon bark ( <i>Cinnamomum cassia</i> ) 3 parts, Orange peel ( <i>Citrus reticulata</i> ) 2 parts, Wild Yam ( <i>Dioscorea villosa</i> ) 2 parts, Skullcap ( <i>Scutellaria lateriflora</i> ) 1 part.  Coarsely grind herbs together, moisten with alcohol and let sit overnight. Add enough alcohol to make a 1:4 tincture, macerating for 2 weeks, or by making a percolation. Add 1 part simple syrup to the strained tincture to bring the strength to 1:5. Dosage is 5–15 ml, taken 3–4 times daily for severe cramping'	Reports and Analytical Records of August 13, 1910; <a href="http://www.geocities.ws/noshrift/hayden/hayden.html">http://www.geocities.ws/noshrift/hayden/hayden.html</a>
Oklahoma Delaware	To strengthen the reproductive tract, to relax the uterus and thus reduce menstrual pain and to bring the fetus to full term	<i>Viburnum prunifolium</i> L. (Adoxaceae) Black haw		Moerman, 1998
Eclectics	Sterility in men	<i>Viburnum prunifolium</i>	<a href="http://www.henriettes-herb.com/eclectic/kings/viburnum-prun.html">http://www.henriettes-herb.com/eclectic/kings/viburnum-prun.html</a>	King et al., 1898
Prof. A. Jackson Howe; case studies in the <i>British Medical Journal</i> in the late 1800s, as a remedy for miscarriage, Dr. Hulbert	Uterine tonic for menstrual pain, hemorrhage, deficient menses, uterine colic, uterine congestion and inflammation, <i>dysmenorrhoea</i>	<i>Viburnum prunifolium</i>	<a href="http://www.henriettes-herb.com/eclectic/kings/viburnum-prun.html">http://www.henriettes-herb.com/eclectic/kings/viburnum-prun.html</a>	Leonard, 1884; Campbell, 1886; Green, 1886; General Medical Council, & Royal College of Physicians of London, 1990; King et al., (continued on next page)

Table 11 (continued)

(a) Person	Use	Latin name	Dosage/ administration	Reference
Dr D.L. Phares, of Mississippi, Oklahoma Delaware, Dr. Green, Dr. Wilson, Dr. E. Nelson	Threatened miscarriage, repeated miscarriage at the same stage of development, to strengthen the reproductive tract, to relax the uterus and thus reduce menstrual pain and to bring the fetus to full term	<i>Viburnum prunifolium</i>	<a href="http://www.henriettes-herb.com/eclectic/kings/viburnum-prun.html">http://www.henriettes-herb.com/eclectic/kings/viburnum-prun.html</a>	1898; Owen, 1890; Wilson, 1886 Leonard, 1884; Green, 1886; King et al., 1898; Marsden, 1879; Moerman, 1998; Tantaquidgeon and Tantaquidgeon, 1972; Wilson, 1886

(b) Medical condition or study	Latin name	Clinical trials	Biochemistry confirming traditional use	Reference
Pharmacological assay on rabbit jejunum	<i>Viburnum prunifolium</i>	Relaxed isolated rabbit jejunum and guinea pig trachea through an interaction with the beta-adrenergic system and may also act through Ca <sup>2+</sup> channel interactions	Four iridoid glucosides	Cometa et al., 2009

## Discussion

This ethnomedicinal examination has documented a scientific basis for the folk use of some herbs, while clinical evidence is lacking in other cases. This is typically due to the fact that many of the herbs have not been studied at all in a clinical setting, rather than their effectiveness having been disproved. Anything that helps treat the infertile more effectively is needed. The global provision of ART corresponds to only 20% of the demand in developed countries and 1% of the estimated demand in developing countries (Collins, 2002). IVF costs are 50% higher than the gross national income per capita of most developing countries (Vayena et al., 2009), and greater than 50% of the average annual disposable income in the USA (Quinn and Fujimoto, 2016). The cost in India for one IVF cycle is US\$ 1300 or 6 months' salary (WHO, 2010). In the USA, statistics from the National Survey of Family Growth show that access to infertility services declined from 20% of 10,845 women in 1995 to 17% of women aged 25–44 years surveyed from 2006 to 2010 (Quinn and Fujimoto, 2016). In 1982, 56% of women accessed fertility care, compared with 38% of nulliparous women aged 25–44 years surveyed from 2006 to 2010. Of the women who did use infertility services between 2006 and 2010, 16% were non-Hispanic white women with higher levels of education and household income (\$60,256) than the 7.6% of Hispanic white women (\$42,491) and the 8% of non-Hispanic black women (\$35,398). The ability to build a family using infertility services in the USA has been described as a “function of economic prowess” (Adashi and Dean, 2016).

Moreover, women seeking IVF are facing age restrictions everywhere. For example, the Czech Republic is preparing

a new act to regulate ART with an age limit of 45 years for women, but with no limit for Czech men (Kocourkova et al., 2015). Of the 73,406 IVF cycles initiated in the USA in 2000, 6989 (9.5%) were performed in women aged over 40 years, for whom the livebirth rates for 1996, 1997, 1998, 1999 and 2000 were 6.4%, 7.3%, 8.3%, 8.1% and 7.8%, respectively (Ng and Ho, 2007). Quebec publicly funds IVF treatment and proposed a ban on women aged over 42 years from seeking treatment even outside the province (Dyer, 2014); it has kept the ban on public funding for women aged over 42 years but allows them to pay, thus making it unaffordable for poorer people (Weeks, 2015). In France, ART is free of charge in public hospitals for women until 43 years of age (Belaisch-Allart et al., 2015). Singapore has a co-funding scheme for couples, which provides partial financial reimbursement to women under 40 years of age undergoing a maximum of three fresh and three frozen ART cycles in public hospitals. The scheme is based on cost-effectiveness and women over 45 years of age are generally barred from ART (Tan et al., 2014). Sweden and Finland have cut-offs of 42 and 40 years, respectively (Gleicher et al., 2014). One reason for the cost constrictions is the low success rate, leading doctors and policy makers to consider ART for older women “a waste of time and money” (Moolenaar et al., 2014; Ng and Ho, 2007). Part of the reason for the low success rates for older women are cost-cutting measures that have led to the transfer of a single embryo to avoid the higher costs associated with multiple births, when older women actually require three or more embryos to be transferred to achieve reasonable livebirth rates and two or more to avoid futility (Gleicher et al., 2015; Spandorfer et al., 2007). Use of plants to improve these outcomes would thus help overcome these barriers to ART treatment.

**Table 12** *Vitex (Vitex agnus-castus L)* (Verbenaceae): (a) traditional use and (b) validation.

(a) Person	Use	Dosage/ administration	Reference
Hippocrates, <a href="#">Dioscorides</a> and Theophrastus	Anti-inflammatory, amenorrhoea, dysmenorrhoea, easing of menopausal symptoms, womb inflammation, endometriosis, infertility, haemorrhage after childbirth and removal of the afterbirth		<a href="#">Riddle, 1992;</a> <a href="#">Vassiliadis, 2013</a>
(b) Medical condition or study	Clinical trials	Biochemistry confirming traditional use	Reference
Double-blind, placebo-controlled clinical study with 52 women	Lengthens luteal phase and improves luteal progesterone synthesis		<a href="#">Milewicz et al., 1993</a>
Open-label clinical observation; clinical effects of three different doses of <i>Vitex agnus castus</i> on PMS sufferers aged 18–45 years. Multicentre, double-blind, placebo-controlled	Agonist activity on prolactin and progesterone, dopaminergic and opiate systems in addition to producing anti-inflammatory and neuroprotective effects. It has not been established whether vitex acts on dopamine receptors without affecting LH or FSH, or if it stimulates LH and inhibits the release of FSH	Diterpenes rotundifuran, prerotundifuran, flavone vitexicarpin similar to sex hormones; diterpenes–clerodadienols bind to recombinant DA2-receptor protein and suppress prolactin release, which is the same action as dopamine	<a href="#">Ambrosini et al., 2013;</a> <a href="#">Schellenberg et al., 2012;</a> <a href="#">Vassiliadis, 2013;</a> <a href="#">Wuttke et al., 2003;</a> <a href="#">Zamani et al., 2012;</a> <a href="#">Zoorob et al., 2010</a>
37 women with oligomenorrhoea (infrequent menstruation) and 30 women with amenorrhoea (no menstruation)	50 drops of the vitex-containing homeopathic preparation Phyto Hypophyson L; pregnancy was achieved in 38 out of 67 participating women and more often from women in the oligomenorrhoea treatment group (82% versus 45%, $P = 0.021$ )		<a href="#">Bergmann et al., 2000</a>
Systematic reviews; double-blind, placebo-controlled clinical study, cultivated lactotrophs as well as animal experiments	Vitex was equivalent to bromocriptine for cyclic mastalgia and mild hyper-prolactinaemia, but patients on vitex showed better compliance. Vitex had a lower cost and no side effects	Serum prolactin levels were reduced in the patients treated with the extract; diterpenes including clerodadienols with dopaminergic properties bound to recombinant DA2-receptor protein. The dopaminergic activity occurs via binding to dopamine-2 receptors which results in prolactin inhibition. Increased prolactin levels due to stress or PMS might inhibit corpus luteal development, reducing progesterone secretion in the luteal phase of the menstrual cycle. Decreasing prolactin levels may help infertile women	<a href="#">Hu et al., 2007;</a> <a href="#">Kilicdag et al., 2004;</a> <a href="#">Nasri et al., 2007;</a> <a href="#">van Die et al., 2013;</a> <a href="#">Vassiliadis, 2013;</a> <a href="#">Wuttke et al., 2003</a>
Prospective comparative Doppler study	Similar effects to ethinyl oestradiol in changing the uterine artery blood flow and reducing menstrual pain (dysmenorrhoea)	Flavonoids, terpenoids, neolignans, phenolics, diterpenes and a glyceride compound	<a href="#">Aksoy et al., 2013;</a> <a href="#">Chen et al., 2011</a>
Corpus striatum membrane dopamine (dopamine receptor binding assay <i>in vitro</i> )		Diterpenes are active compounds acting as dopamine agonists and inhibiting prolactin release	<a href="#">Hu et al., 2007</a>
Pilot study of a FertilityBlend (Daily Wellness, Honolulu, Hawaii) with 30 women	After 5 months, significantly more women given the fertility blend were pregnant (five of 15 versus none in the placebo group) and four of the five women who conceived had healthy births	Increase in the mean midluteal phase progesterone level (from 8.2 to 12.8 ng/ml, $P = 0.08$ ) and a significant increase in the average number of days in the luteal phase of the cycle with increased basal temperatures	<a href="#">Clark et al., 2013;</a> <a href="#">Westphal et al., 2004</a>

FSH, follicle-stimulating hormone; LH, luteinizing hormone; PMS, premenstrual syndrome.



Several studies have indicated that some of the plants described in this paper are recommended by midwives in the USA and the UK, and these studies can provide individualized dosages to test (Hall et al., 2012). Those herbs with a large consumer market – such as black cohosh and vitex – have been subjected to considerably more rigorous clinical and pharmacological study (see Tables 2–12) than more obscure herbs such as false unicorn and downy rattlesnake plantain (see Supplementary Material Items 3–29). The size of the consumer market for black cohosh is suggested by 2004 data from the UK-based Medicines and Healthcare Products Regulatory Agency which recorded 9 million days-worth of treatments purchased annually in capsule and tablet form (Merchant and Stebbing, 2015).

It should also be noted that TCM has a systematic approach to diagnosis and treatment of women's reproductive health concerns dating back as early as 1237 AD with the publication of the text *The Complete Book of Effective Prescriptions for Diseases of Women*. Modern-day clinicians treat infertility likewise and attention is paid to signs of ovulation (e.g. cervical mucus, rise in basal body temperature) and menstruation. Timing and duration of menses, and the quality of the menstrual flow (whether it contains clots, colour of the blood, heavy or light flow) are noted, as well as associated symptoms such as dysmenorrhoea, changes in bowel habits and breast tenderness. Male factor infertility is also treated with the aim of improving sperm count, morphology and motility. An individualized differential diagnosis and treatment plan is determined and implemented for personalized patient care.

In seeking to integrate medicinal plants into infertility treatment, we are not advocating anything extraordinary as herbs are already used with and without the knowledge of the patient's doctor (Smith et al., 2010). Hall et al. (2012) note that pregnant women already use medicinal plants to complement allopathic medicine as it gives them greater participation and control over their experience, and this control improves birth satisfaction.

The clinical trials and historical evidence discussed in this paper suggest that black cohosh can be used with IVF. Vitex could be considered for IVF patients with luteal-phase defect. Viburnum can possibly be used during critical stages of the pregnancy to prevent miscarriage. Unlike the historical case presented in this paper (*Pharmacology and Therapeutics*, 1888), patients taking viburnum would have the advantage of technological fetal monitoring to ensure that they were still carrying a viable fetus. As part of further study necessary to confirm which plants are best suited to which infertility-related issue within an integrated approach with ART, the case reports of doctors in colonial America, some of which have been presented in this paper, could perhaps be collated and analysed so that they can provide guidance for current and future clinical cases and trials.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.rbms.2018.03.001>.

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