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Medicinal plants used for menstrual disorders in Latin America, the Caribbean, sub-Saharan Africa, South and Southeast Asia and their uterine properties: A review

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Review

Medicinal plants used for menstrual disorders in Latin America, the Caribbean, sub-Saharan Africa, South and Southeast Asia and their uterine properties: A review



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ABSTRACT

Ethnopharmacological relevance: Menstrual disorders are generally not perceived as major health concerns by global health organizations, despite being disruptive to women's daily activities, particularly when access to sanitary facilities or analgesics is limited. Improving menstrual health requires access to safe and effective medication, but many women in Latin America, Africa or Asia prefer traditional medicine above modern remedies (such as contraceptives), as they can cause physical symptoms associated with fertility loss. Many medicinal plants are used for menstrual disorders, but few have been examined for their pharmacological activities related to traditional uses. Plants that have a smooth muscle-relaxant effect could ease menstrual cramps, but there are indications that dysmenorrhea in low-income countries is commonly treated with emmenagogues. This review aims to assess the most salient plants used to treat menstrual morbidity in Latin America and the Caribbean, sub-Saharan Africa, South and Southeast Asia, their uterine properties and adverse effects. To test whether plants used for painful menstruation could have uterine contracting properties, we recorded whether these species were also used to ease birth, induce menstruation, abortion or expel the afterbirth, as these suggest spasmogenic activities.

Materials and methods: We reviewed the literature documenting traditional plant use in the study area for dysmenorrhea, regulating or inducing menstruation, uterine cleansing, uterine fibroids, expelling the placenta and lochia and for easing childbirth. Thirty genera (59 species) used in at least two continents or frequently throughout one continent, where shortlisted from the 90 most salient plant species emerging from our literature review. Using Medline, we searched for pharmacological properties and/or mechanisms of action relevant to their traditional uses of the shortlisted species. We searched VigiBase™, the WHO global individual case safety report database, on reported adverse drug reactions associated with these species.

Results: More than 2000 plant species are used for menstrual disorders in the study area. The most salient uses are to treat painful menstruation, induce or regulate menses, and induce abortion. Around half (29) of the 59 most salient species have been tested for their pharmacological effects, of which 48% act as uterine spasmolytics and 31% as uterine spasmogenics. Several frequently used species contain toxic constituents, which may put women and their unborn children at serious risk. VigiBase™ listed adverse drug reactions for 18 of these species, but few reports came from the study area.

Conclusions: Research into the risks and benefits of medicinal plants for menstrual complaints should be given a higher priority in reproductive health programs that respect traditional knowledge and practices.

Abbreviations: WHO, World Health Organization; UMC, Uppsala Monitoring Centre; ICSR, the WHO global individual case safety report database (VigiBase™); ADR, adverse drug reactions; SOC, system-organ-class; MedDRA, Medical Dictionary for Regulatory Activities

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Increased data collection is needed on adverse drug reactions among women using herbal medicines for reproductive health, especially in countries with limited reproductive health facilities.

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1. Introduction

Complications related to reproductive health remain the leading cause of morbidity and mortality for women of childbearing age worldwide (United Nations, 2012). Nonetheless, menstrual disorders are generally not perceived as major health concerns, and therefore not considered in global reproductive health programs (Harlow and Campbell, 2000), despite the fact that research in various low-income countries reveals that menstrual morbidity has a huge impact on women's health status, quality of life, social integration and access to education (Caldwell and Caldwell, 1987; Daar and Merali, 2002; Harlow and Campbell, 2004; Tjon A Ten, 2007). Moreover, menstrual disorders are a risk marker for other reproductive morbidities. Abnormal or irregular uterine bleeding may be a symptom of cervical tumors, uterine fibroids, genital tuberculosis or hemorrhagic dengue fever, while excessive or prolonged bleeding can cause anemia and may eventually be life-threatening if left untreated (Harlow and Campbell, 2000). Infrequent (oligomenorrhea) or absent (amenorrhea) menses may reflect underlying endocrine disorders, malnutrition, endometrial tuberculosis, AIDS or cancer (Harlow and Campbell, 2000). Although not always life-threatening, menstrual disorders can be particularly disruptive to daily activity patterns, particularly in the absence of appropriate sanitary facilities, or analgesics in the case of painful menstruation (Harlow and Campbell, 2000; Tjon A Ten, 2007). Improving reproductive health of women requires access to safe and effective medication and methods of fertility control (Siedlecky, 2001). In Western countries, menstrual disorders are often treated with hormonal therapy (including contraceptives) or nonsteroidal, anti-inflammatory medications. For many women in low-income countries, these treatments are unavailable or unaffordable. Moreover, modern oral contraceptives can cause symptoms that are perceived to be similar to fertility loss, such as

amenorrhea or mid-cycle breakthrough bleeding. For this reasons many women in Latin America, Asia and Africa continue to prefer traditional medicine for menstrual disorders or family planning (Bearinger et al., 2007; Castle, 2003; Levin, 2001; Williamson et al., 2009). Some researchers argue that in countries where access to modern healthcare facilities is limited or where traditional therapies are generally considered more culturally appropriate, research on the efficacy and safety of indigenous therapies for menstrual disorders should be encouraged to promote their use as an acceptable alternative to synthetic pharmaceuticals (Gwekwe and Monera, 2012; Harlow and Campbell, 2004; Lindsey et al., 1998; Michel et al., 2007). Others advocate culturally sensitive integration of traditional and modern practices to reduce infant and maternal mortality without replacing significant cultural heritage (De Boer and Lamxay, 2009; De Boer et al., 2011; Lamxay et al., 2011; van Andel et al., 2008).

Many plant species are used worldwide in traditional herbal remedies for reproductive health issues, but very few species have been examined for their pharmacological activities related to menstrual disorders. Plants used traditionally for female reproductive health, in particular those used for abortion, have received little attention from researchers, as for a long time these were considered as used for sinful or illegal objectives (Schiebinger, 2004). In recent decennia, however, a growing number of ethnobotanical studies have been published on plants used for reproductive health in the tropics (e.g., De Boer and Cotingting, 2014; Kamatenesi-Mugisha and Oryem-Origa, 2007; Michel et al., 2006, 2007; Ososki et al., 2002). Some authors are still struggling with prejudices regarding women's choices over their own sexuality. In a paper on abortifacients in southern Cameroon, for example, the authors state that practices in which plants are used to produce sterility, death, and low population growth should be prohibited (Noumi and Tchakonang, 2001). Similarly, several African societies

are said to perceive abortion, murder, sorcery and witchcraft as equally serious crimes (Iwu, 1993).

Several ethnobotanical studies have overlooked the significance of traditional plant use for women's health, and either omit plants used for women's health (Mohamad et al., 1991; Westermayer, 1988) or group all uses under single generic terms, such as 'reproductive disorders' (Caniago and Siebert, 1998), 'gynecological diseases' (Zheng and Xing, 2009), or 'postpartum remedy' (Roosita et al., 2008). Others avoid the topic of abortion (e.g., Bourdy and Walter, 1992), but whether the lack of abortifacients is due to (deliberate) avoidance by researchers or because of cultural taboos is not always easy to interpret (Schiebinger, 2004). To avoid mentioning abortion, both researchers and informants may use terms like 'emmenagogues' and plants that treat 'amenorrhea', 'bring on the menses' or 'cleanse the uterus' (Schiebinger, 2004; Sobo, 1996; van Andel and Ruysschaert, 2011). Painful menstruation (dysmenorrhea) results partly from an excess production of prostaglandins that stimulate or increase uterine contractions. Research on the effectiveness of plants used for dysmenorrhea has focused on compounds that regulate prostaglandins. Inhibition of key enzymes in the prostaglandin biosynthetic pathway may relieve menstruation pain by preventing contraction of the uterus or by relaxing its smooth muscles (Lindsey et al., 1998). Plant compounds that work as muscle relaxants (spasmolytics) could therefore be effective in the treatment of menstrual cramps (Ortiz de Montellano and Browner, 1985). There are, however, indications that dysmenorrhea in low-income countries is commonly treated with emmenagogues (Harlow and Campbell, 2004; Levin, 2001). During an analysis of potential spasmolytic activities of plants popularly used to treat dysmenorrhea, it was found that extracts of *Gossypium barbadense* L (a red-leaved cultivar of cotton) increased rather than reduced the contraction of smooth muscle tissue under laboratory settings (Mans et al., 2004). This effect was confirmed by Surinamese women who drank a tea of red cotton leaves to treat pain during menstruation and to expel blood clots, dirty blood and bad smell (van Andel and Ruysschaert, 2011). Ghanaian women mentioned that shortly after taking an extract of cotton leaves in palm wine, a big blood clot would come out directly and the menstruation would start, which in turn would relieve pain (Van Onselen, 2011).

It is essential to know more about the pharmacological properties, possible benefits and adverse effects of traditional remedies before they can be safely and appropriately integrated into conventional medicine. Plants that are used worldwide for the same purposes are more likely to be effective and have putative pharmacological properties (Farnsworth, 1990). The aim of this review paper is to make an inventory of the most salient plants used to treat menstrual disorders in Latin America, the Caribbean, sub-Saharan Africa, South and Southeast Asia and to identify their known pharmacological properties, mechanisms of action and adverse effects. Our hypothesis was that the plants most frequently used for dysmenorrhea by women in the study area possess both spasmolytic and spasmogenic properties. Therefore, we also recorded whether plants used for painful menstruation were also used to ease birth, induce menstruation, abortion or expel the afterbirth, as these suggest spasmogenic activities. The main questions that we sought to answer included: 1) What are the most frequently used plant species in the study area for menstrual disorders?; 2) How common is it that species used for dysmenorrhea are also used to cleanse the uterus or to provoke abortion?; 3) How many of these plants have been tested for their pharmacological properties linked to menstrual disorders?; 4) Are adverse drug reactions commonly reported for these species, and, if so, their type and frequency?; 5) How should health workers and scientists in the field interpret the frequent use of such plants?

In our opinion, this review was needed because: a) Many women in low-income countries face severe challenges regarding reproductive health, including menstruation problems; b) Many

plant species are used to treat menstrual complaints, but no comprehensive overview exists of the most salient species worldwide; c) Little is known about the pharmacological properties of plants used for women's healthcare, and of their possible benefits and adverse effects related to traditional use; d) In traditional treatments, both species with uterine relaxant and uterine contractant properties are commonly used, but the underlying motives and objectives of their uses are poorly understood; and e) A more thorough understanding of the safety and efficacy of traditional uterine modulators is essential for a culturally sensitive integration of traditional and conventional medicine.

2. Material and methods

2.1. Literature search on medicinal plants for menstrual morbidity

In order to test our hypothesis, we searched for peer-reviewed scientific articles that documented traditional plant use in the study area related to menstrual disorders. We followed the categories of menstrual morbidity defined by Harlow and Campbell (2004) and listed medicinal plant use for: 1) painful menstruation (dysmenorrhea); 2) irregular cycles, including a long duration of menstrual flow and excessive, heavy bleeding, (menorrhagia / polymenorrhea); 3) inducing delayed, infrequent or absent menses (oligomenorrhea / amenorrhea). To analyze whether these plants had spasmogenic properties, we added the categories: 4) cleansing the uterus after childbirth, miscarriage, abortion or menstruation; 5) uterine fibroids; 6) expelling the afterbirth; 7) abortion; and 8) to ease birth. Literature reviews were performed during March–April 2013, using Google Scholar, PubMed, Medline and the keywords 'reproductive health', 'menstruation', 'abortion', 'abortifacient', 'uterus', 'emmenagogue', 'fibroids', 'afterbirth', 'amenorrhea', 'dysmenorrhea' and 'menorrhagia' in combination with 'herbs', '(medicinal) plants' and 'Africa', 'Asia', 'Latin America', 'Caribbean', or specific countries in these geographical areas. Additional literature was found in reference lists of collected publications (snowball method). To limit the data to accessible digitized literature, we focused mostly on English literature published from 1980 onwards, although some key references in French and Dutch were included, as well as papers published in Asia and Africa. Data for South and Southeast Asia were taken from a database, maintained by one of the authors (HJdB) on literature on medicinal plant species used for women's health care (De Boer and Cointing, 2014). Plant use information without a clear definition of the use, i.e. broad descriptions like 'menstrual problems' or 'women's health', was not included in our review. Our geographical scope was restricted to Latin America and the Caribbean, South and Southeast Asia and sub-Saharan Africa. Our geographical review aimed to spread geographical coverage as much as possible over the continent, and used only one paper per country (preferably one published in a peer-reviewed journal and citing substantial ethnobotanical practises regarding our subject), unless it was clear that the two papers covered ethnobotanical information from different ethnic groups and/or localities. Since the efficacy of genital steam baths, ointments, and vaginal inserts is harder to justify pharmacologically, we have limited this review to orally administered herbal remedies (decoctions, infusions, extracts, and juices).

2.2. Shortlisting the species

Relevant plants from the selected papers were entered in separate excel files for each of the three continents. Columns contained the eight use categories and rows represented the species. Individual cells contained the number of papers in which

a particular use category for a particular species was reported. Scientific and author names were validated by the Plant List (<http://www.theplantlist.org>), and synonyms were merged. The most salient plants were defined as those most frequently cited in the literature (number of papers citing this species) and those mentioned for the most use categories. From each geographical area, 30 species were selected that had at least five citations. From the combined 90 most salient plant species, we chose a top 30 of genera (59 species) that were used in at least two continents or frequently throughout one.

2.3. Literature search on pharmacological properties or mechanisms of action

A plant's characteristic chemical constituents and/or related constituents can occur in other species as well, particular in those of the same genus (Farnsworth, 1990). In this study, we focused not only on the most frequently used species, but also reviewed the pharmacological activity of a few intrageneric species groups used worldwide for menstrual disorders. For each of the shortlisted species, literature searches were conducted between June and November 2013, using Medline (1946 to current) to identify papers describing in vitro or in vivo studies of extracts of these species and, in some cases, specific major constituents, in respect of use as an uterine or smooth muscle contractant or relaxant, abortifacient, menstruation-inducing agent, or other pharmacological properties or mechanisms of action relevant to their traditional use(s). The search for pharmacological activity comprised the following terms combined using the Boolean operator 'OR': Uterine Contraction/de [Drug Effects]; (uter\$ and (contract\$ or relax \$)).mp.; Abortifacient Agents/; Menstruation-Inducing Agents/; Prostaglandins/; Prostaglandins/ or Prostaglandin Antagonists/; Uterus/de [Drug Effects]; Muscle, Smooth/de [Drug Effects]. This subset was then combined using the Boolean operator 'AND' with the binomial names for the species of interest using the Subject Heading for the species (if one existed) or the keyword. Abstracts of papers retrieved from the search were scrutinized for relevant information, and data were extracted from the full text of the paper in most instances or the abstract alone if adequate.

2.4. Searches for reported adverse drug reactions in VigiBase™

To obtain information on reported adverse drug reactions associated with the species of interest, searches were conducted using VigiLyze, the search and analysis tool of VigiBase™, the WHO global individual case safety report (ICSR) database. VigiBase™ contains summary information from spontaneous reports (also known as individual case safety reports, ICSRs) of suspected adverse drug reactions (ADRs) submitted to the WHO-UMC by the national pharmacovigilance centers of 117 countries (as of December 2013) worldwide. Contrary to scientific literature on adverse reactions, VigiBase™ lists patient reports (symptoms of adverse drug reaction to (phyto-) pharmaceuticals) from doctors and pharmacists from around the world. This international drug monitoring program began receiving reports in 1968 (Lindquist, 2008), after the thalidomide tragedy, and now contains over 8.5 million reports. Using VigiLyze, searches were conducted using the binomial names of the shortlisted 59 species (including some frequently used synonyms). For each species, the total number of reports for single-ingredient preparations was retrieved, along with the total number of ADR terms (since each report can list one or more suspected ADRs experienced by the user/patient), and the MedDRA (Medical Dictionary for Regulatory Activities) system-organ-class group (the top level of the hierarchy for ADRs relating to each body organ), e.g. 'Pregnancy, puerperium and perinatal conditions' of those suspected ADRs. The total number of reports and the total number of suspected ADR terms were also retrieved

for multiple-ingredient preparations containing each of the species of interest. Searches were conducted on November 20, 2013, using the entire database (i.e. all countries) with no date restrictions. Numbers of retrieved reports were also identified for the subsets of countries from the continents of Africa and Asia (as defined in VigiBase™), as well as for a subset 'developing countries', comprising Africa, the Americas (excluding Canada, USA), Asia (excluding Brunei, Cyprus, Israel, Japan, Singapore, and South Korea), and Oceania (excluding Australia and New Zealand).

3. Results

3.1. Most frequently cited species and their specific uses

Our literature review (in total 263 publications) yielded over 2000 plant species documented as being used in traditional medicine to treat menstrual and gynecological issues (Table 1). In all three geographical focal areas, most species were used in remedies to treat painful menstruation, to regulate menses or to induce abortion. More than a hundred species were used in Africa and Latin America to facilitate the birth process, while in Asia this category seemed less important. Asian women used more than 280 species to induce menstruation, a category not that prevalent in the other two areas. Local plant use can be considered as a proxy for the prevalence of disorders or the importance of a certain cultural bound health concept (Vande Broek et al., 2008), which may indicate that dysmenorrhea is a frequent ailment in the entire study area and plant use to induce abortion or ease birth are common practises in some of these areas. Our review also reveals that in Asia more data on this subject has been collected than in Africa and Latin America, and this has resulted in a larger body of literature and a higher number of recorded plant uses (Table 1).

Our final shortlist contained 59 species that were used in at least two continents or frequently throughout one (cited in at least 10 papers). Several genera (e.g. *Caesalpinia*, *Phyllanthus* and *Senna*) were used worldwide for menstrual disorders, even though the specific species belonging to these genera differed among the three continents. Supplementary file 1 lists the most frequently used genera and species in the three continents and the number of literature reports in the categories of menstrual morbidity and reproductive health. Many of these species are probably used in

Table 1

Number of medicinal plant species encountered in literature for the categories of menstrual morbidity and reproductive health.

| Health issue | Sub-Saharan Africa | South and Southeast Asia | Latin America and the Caribbean |
|--|--------------------|--------------------------|---------------------------------|
| Painful menstruation | 175 | 128 | 152 |
| Irregular cycles | 201 | 252 | 157 |
| Induce menstruation | 72 | 284 | 87 |
| Cleansing uterus | 23 | 31 | 47 |
| Uterine fibroids | 49 | 11 | 28 |
| Expel afterbirth | 37 | 79 | 56 |
| Abortion | 123 | 272 | 160 |
| Ease birth | 121 | 60 | 108 |
| Total nr. of species listed ^a | 448 | 1875 | 420 |
| Total nr. of families listed | 104 | 211 | 111 |
| Total nr. of papers reviewed | 23 | 200 | 40 |

^a This figure does not represent the sum of the figures above, since many species are used to treat more than one menstrual complaint.

mixtures, which complicates verification of their mode of action and efficacy (Vandebroek et al., 2008; van Andel et al., 2012), although our references seldom provided the exact composition of these mixtures but rather listed the botanical ingredients separately.

Several widely domesticated crops dominate the list of frequently used species, such as lime and bitter orange (*Citrus* spp.), cotton (*Gossypium barbadense*), avocado (*Persea americana* Mill.), ginger (*Zingiber officinale* Roscoe), pineapple (*Ananas comosus* (L.) Merr.) and sesame (*Sesamum indicum* L.). Some common tropical weeds (e.g., *Phyllanthus amarus* Schumach. & Thonn., *Blumea balsamifera* (L.) DC., *Mimosa pudica* L.) figure prominently in our shortlist as well. This might be an artefact of our specific search for the most widely used species, as most plant species shared by the three continents are pantropical weeds or cultivated species. However, as weeds typically contain high concentrations of bioactive compounds (Stepp, 2004), widely used medicinal plants need to be abundant and accessible (Stepp and Moerman, 2001) and rural women are often spatially limited in their search for herbal medicine (Towns et al., 2014), weeds and domesticated plants are readily available candidates for empirical testing of medicinal properties.

3.2. Mechanisms of action

All of the 59 most frequently mentioned plant species were used to treat menstrual pains. Each of these species was also used to treat irregular cycles, whereas 50 of them (85%) were also taken to induce (delayed) menstruation or to induce abortion (Supplementary file 1). This suggests that apart from their ability to ease painful menses, these species may also contain uterine contracting properties. Our review of pharmacological properties and/or mechanisms of action yielded 59 references for only 29 (49%) of the shortlisted species, including their synonyms (Supplementary file 2). In most studies, plant extracts were tested for their ability to reduce or induce contractions in isolated smooth muscle in vitro bioassays. In other studies, rodents were administered plant extracts to observe their abortive or other fertility effects. For the 29 shortlisted species for which we identified peer-reviewed research, 25 papers reported a spasmolytic effect for the species investigated, 13 papers reported a spasmogenic effect, 25 specified other mechanisms of action and four papers reported no effect. For some genera (e.g. *Aristolochia*) pharmacological properties were documented for species other than our shortlisted ones. For 25 (42%) of the frequently used species no scientific literature was found that supported traditional uses for menstrual morbidity or reproductive health.

3.3. Uterine spasmolytics

Biomedical treatment for dysmenorrhea prescribes inhibitors of the biosynthesis of prostaglandins (Ortiz de Montellano and Browner, 1985), and prostaglandins are used clinically to induce labor and as abortifacients (Lange, 1986). Essential oils often contain compounds that inhibit prostaglandin biosynthesis (e.g., quercetin, estragole, bisabolol, limonene, eugenol) and therefore could be effective as smooth muscle relaxants in the treatment of dysmenorrhea (Achterrath-Tuckermann et al., 1980; Ortiz de Montellano and Browner, 1985). Frequently used species for dysmenorrhea that contain such oils are *Citrus aurantiifolia* (Christm.) Swingle, *Ocimum gratissimum* L., *Zingiber officinale*, *Matricaria recutita* L., *Rosmarinus officinalis* L. and *Psidium guajava* L. Except for *Matricaria recutita*, all of these species have shown smooth muscle relaxant properties under laboratory conditions (Supplementary file 2). Fourteen of the 29 assayed shortlisted

species (48%) have reported spasmolytic effects on smooth muscle tissue.

3.4. Uterine spasmogenics

For nine of the 29 assayed plants (31%), laboratory tests showed smooth muscle contracting properties, but the mechanisms of action remained mostly unclear. These plants may help to relieve pre-menstrual pain by actually inducing the menstruation and thus shorten the period, which is also indicated by their traditional uses against fibroids, to cleanse the uterus after child birth, and, if taken in high doses, abortion. Results from clinical trials on humans were published only for *Leonurus japonicus* Houtt. (Supplementary file 2). This herb stimulated uterine contractions and reduced postpartum hemorrhage, and this corroborates its traditional use to induce menstruation and to expel the placenta after childbirth. Strong stimulant laxatives, such as the oil of *Ricinus communis* L. seeds and leaves of *Senna alata* (L.) Roxb. may not only stimulate peristaltic action, but also the smooth muscles of the uterus (Belew, 1999).

3.5. Other mechanisms of action

Our review also shows that it is not uncommon among women in the study area to use potentially toxic plants to induce their menses, for early stage abortion and/or terminate a pregnancy. In Cameroon, *Momordica charantia* L. is often called "Miss Efficient" because of its abortive properties (Noumi and Tchakonang, 2001). Seeds from wild *Momordica charantia* plants are frequently sold on West African markets as abortifacients (Quiroz et al., 2014; van Andel et al., 2012b). The fruit juice of the wild form of this species induces uterine bleeding, and the seeds of the vine have abortifacient activity, but may also cause serious birth defects, growth retardation or delayed mental development after birth in case the abortion has not effectively taken place (Leung et al., 1987; Ng et al., 1992). Women who take infusions of *Ruta chalepensis* L., frequently used for reproductive health in Latin America, may risk multiple organ failure and death (Ciganda and Laborde, 2003). Several *Aristolochia* species, widely used as medicines for a range of indications, are known to contain nephrotoxic and genotoxic aristolochic acids (Heinrich et al., 2009). More than 100 cases of nephropathy due to exposure to toxic aristolochic acids following the use of *Aristolochia fangchi* Y.C.Wu ex L.D.Chow & S.M.Hwang and *Aristolochia manshuriensis* Kom. have been described in the literature (Cosyns, 2003). However, concentrations of aristolochic acids may differ substantially among species within the genus. Crude methanol extracts of *Aristolochia manshuriensis* stems may contain up to 150-fold higher concentrations than those of *Aristolochia consimilis* Mast. When prepared according to traditional Surinamese recipes for reproductive health, aristolochic acids were no longer detectable in mixtures containing *Aristolochia consimilis* (Mouden, 2012).

Some of the species with a proven spasmolytic effect (e.g., *Zingiber officinale*, *Citrus* spp.) were also used to induce abortion or uterine cleansing, which could imply a dose-dependent reversal of effect. Differences in dose and additional species taken simultaneously as part of a traditional cure can vary widely, and are often difficult to establish from published ethnobotanical studies. Women in Benin (West Africa) used complicated herbal mixtures containing up to 31 species to treat several gynecological disorders simultaneously, varying from painful, irregular, or complicated menstruation to uterine fibroids and cysts (Towns and van Andel, 2014). Such practices complicate the study of the effect and safety of herbal medicines, as compounds from different species may have synergistic or counteracting effects. A few of the shortlisted species (e.g., *Ocimum gratissimum*) have properties that both

stimulate the uterus to contract and that inhibit contractions (Supplementary file 2). The net effect of the intake of such herbs by humans is not known.

3.6. Suspected adverse drug reaction reports in VigiBase™

Supplementary file 3 summarizes the number of reports identified in the WHO-UMC VigiBase™ database for single- and multiple-ingredient preparations of the species listed in Supplementary file 1. For single-ingredient herbal preparations, the database contained 894 reports for 17 (29%) of the 59 short-listed species listed. For *Persea americana*, *Senna occidentalis* (L.) Link and *Gossypium* ssp., reports only existed for multiple-ingredient preparations. Typically, the total number of reports for each of the species was low (1–10 reports: 9 species; 10–50 reports: 5 species; > 50 reports: 2 species). For several shortlisted genera, reports related only to one species within the genus (e.g., for genus *Ocimum*, all reports related to *Ocimum basilicum* L.). For single-ingredient preparations of the species, very few reports originated from Africa or Asia – regions comprising many low-income countries – with the exceptions of *Senna alexandrina* Mill. (10% of total number of reports for this species), *Ricinus communis* (29%), and *Rosmarinus officinalis* (41%). For 12 species, there were reports from the study area, mostly originating from one country. For example, for *Citrus aurantium* L., *Ocimum basilicum*, *Psidium guajava*, and *Matricaria recutita*, the great majority of the reports originating from the study area came from Cuba.

In total, 1265 reports were identified for 14 species of interest that were components of multiple-ingredient preparations. For several other species with reports relating to multiple-ingredient preparations (*Citrus aurantium*, *Sesamum indicum*, *Zingiber officinalis*, *Matricaria recutita*, *Rosmarinus officinalis* and to a lesser extent *Caesalpinia sappan* L. and *Quassia amara* L.), the number of reports was substantially greater than that for single-ingredient preparations of these species. For multiple-ingredient preparations containing one or more of the species of interest, proportions of reports originating from Africa/Asia were notable for *Persea americana* (19%) and *Zingiber officinalis* (72%). In total, there were reports originating from the study area for ten species, mostly from one country. For example, for *Matricaria recutita* most reports came from Nigeria, while for *Aristolochia* spp. all reports came from China (Supplementary file 3).

The number and type of suspected ADR terms, coded and organized by system-organ-class (SOC) using MedDRA terminology, described in reports for single-ingredient preparations of the species of interest are also presented in Supplementary file 3. Valid VigiBase™ reports include at least one ADR term, and the reports for the species of interest contained on average two ADR terms from the same or other SOCs. Most suspected ADRs related to gastrointestinal disorders. For four species (*Senna alexandrina*, *Zingiber officinalis*, *Ricinus communis* and *Matricaria recutita*), substantial numbers of ADR terms were identified for many different SOCs. A very small number of suspected ADR terms related to the SOCs 'pregnancy, puerperium and perinatal conditions', and 'reproductive system and breast disorders'. These ADR terms were listed in reports related to the species *Senna alexandrina*, *Zingiber officinalis*, *Ricinus communis*, and *Matricaria recutita*. For the *Senna alexandrina* cases ($n=7$, from Portugal, Singapore, UK, USA), where given, indications for use were stated as constipation, bowel preparation, and gastric ulcer; one report related to a male. Numerous suspected ADRs were described in these reports, with several from the SOCs of interest, including umbilical artery hypoplasia, premature delivery of infant, uterine spasm, colpocele and others. In four of these reports, exposure to *Senna alexandrina* during pregnancy is stated or can be inferred (i.e. since premature delivery of infant is listed as a suspected ADR).

Typically, for these reports, details of the *Senna alexandrina* preparations used were very limited (usually only a proprietary product name) and few, if any, details of the dose and duration of use were provided. In several cases, the patient was taking numerous other medicines concurrently. For *Zingiber officinalis* (2 reports, both from Australia), indications were given as nausea and vomiting and unspecified arthritis, with the suspected ADRs reported as spontaneous abortion/cramps/hemorrhage, (following use of tablets of a proprietary product containing 1000 mg *Zingiber officinalis* rhizome equivalent standardised for [6]-gingerol 1 mg, 3 tablets daily for 21 days; outcome: unknown), and uterine hemorrhage (following use of two capsules of a proprietary ginger product (no further details provided); outcome: recovered), respectively. In the one report (from a Western country) for *Ricinus communis*, the indication for use was labor induction, and a single oral dose of 20 ml was ingested. The suspected ADRs were uterine rupture, anaphylactoid shock of pregnancy, and cardiac arrest; the outcome was that the patient (mother) died.

4. Discussion

4.1. Why do women in low-income countries use plants to induce menses?

In high-fertility populations, a regular menstrual cycle with clear, free-flowing blood is seen as a sign of good health and fertility (Madhavan and Diarra, 2001). In many cultures, both physical and social health depends on unimpeded flow of bodily fluids (Sobo, 1996; van Andel et al., 2012a; Van de Walle and Renne, 2001). Irregular, delayed or painful menses, and dark or foul-smelling blood are seen as symptoms of reproductive malfunction caused by the presence of 'dirt' or 'blockages' in the womb (Levin, 2001; Madhavan and Diarra, 2001; van Andel and Ruysschaert, 2011; Williamson et al., 2009). Delayed menses, even for weeks, are not necessarily regarded as a sign of pregnancy (Sobo, 1996). It often remains difficult to interpret whether the use of particular herbs is intended to prevent or terminate a pregnancy or promote fertility. In some Islamic beliefs, inducing a delayed menstruation is considered an abortion only after 120 days (Hull and Hull, 2001). The underlying motivation for the frequent use of remedies to regulate the menses is health-related, as cleansing of the womb is seen as a method to clean impurities and increase fertility, rather than reducing it by terminating a pregnancy (Levin, 2001; Madhavan and Diarra, 2001). In many societies, menstruating women are believed to be unclean, and not expected to cook or handle any sacred object at such times (Michel et al., 2006; Van de Walle and Renne, 2001). They are not allowed to participate in religious ceremonies and perform rituals, as they are thought to spoil whatever they touch (Iwu, 1993). Controlling the timing and the duration of their menses in a society that considers menstrual blood unclean and offers few other possibilities for family planning or menstrual hygiene may be another reason for women to take herbal remedies that work as uterus contractors. Health workers and scientists in the field should be aware of such ideas about reproductive health and menstruation. Specific questions about herbs as abortifacients can result in failure to disclose use, even if women are talking frankly about pregnancy termination, since they may not consider the induction of menses in the early months of pregnancy as being an abortion (Hull and Hull, 2001). When informants report plants used to treat dysmenorrhea or regulate menstruation, researchers should inquire about the perceived efficacy and side effects of these treatments and ask their informants whether these plants also induce menstruation and whether they are considered as safe to be taken during pregnancy.

4.2. Is it healthy to cleanse your womb with plants?

Although the practice is illegal and dangerous in many low-income countries, some researchers argue that (early) abortion could be seen as more accessible than hormonal contraceptives (Williamson et al., 2009). Others argue that herbal medicine used in management of dysmenorrhea will increase alternatives for women and healthcare providers to manage this type of ailment (Gwekwe and Monera, 2012). Through training and scientific evaluation of putatively effective remedies, it may be possible for some traditional medicines to meet standards for quality, efficacy and safety such that they can be regarded as an acceptable alternatives to modern pharmaceuticals (Lindsey et al., 1998). However, the question remains whether it is safe to treat dysmenorrhea by using plants that contract the uterus and induce menstruation rather than through a uterine-muscle relaxant effect.

Further, plants employed to 'cleanse the womb' may result in heavy bleeding (Harlow and Campbell, 2000). Unsafe abortions are a significant cause of maternal mortality and morbidity in the world (World Health Organization, 2011), and the treatment of incomplete and septic abortions puts substantial pressure on scarce healthcare resources (Coeytaux, 1988). Several studies from low-income countries report that a common reason for delay in seeking surgical termination of pregnancy is repeated attempts to bring on the menses through ingestion of traditional medicines or hazardous substances (Ciganda and Laborde, 2003; Siedlecky, 2001; World Health Organization, 2011). Many of those herbal preparations are not strong enough to expel the fetus entirely and it is these incomplete abortions that often lead to dangerous complications (Siedlecky, 2001). In a study in Ivory Coast, a high number of previous pregnancies and the ingestion of plants to provoke abortion were factors associated with the highest risk for maternal death (Goyaux et al., 1999). Our review has pointed out that the same species taken to treat dysmenorrhea are often also taken as abortifacients, which limits their suitability for integration into modern healthcare as abortion or induction of menstruation is not a desired side-effect of alleviating menstruation or pain or womb cramps in general.

Reduction of menstrual morbidity constitutes an important challenge for reproductive health services in low-income countries (Harlow and Campbell, 2004), and there is a great need for scientific evaluation of the efficacy and safety of herbal medicine employed for menstrual disorders. To improve the reproductive health of the consumers of these herbs, is also essential to disseminate this scientific information among local healthcare providers, women's groups and traditional healers to avoid unneeded morbidity from harmful remedies. The widespread and frequent use of herbal remedies to treat menstrual complaints necessitates giving research into the risks and benefits of these medicinal plants a higher priority in reproductive health programs.

4.3. Reports on suspected ADRs

The data extracted from VigiBase™ indicate that this resource contains only small numbers of reports originating from tropical regions for the species of interest in this paper. VigiBase currently contains around 8.5 million reports; in 1999, around 0.5% of the total number of reports (2 million) related to herbal medicines. Our searches for reports associated with particular plant species yielded few reports from Africa, Asia and our defined 'developing' countries subset, and this underpins previous findings (Farah et al., 2000) that the proportion of 'herbal' reports originating from these areas, as a proportion of all 'herbal' reports worldwide in VigiBase™, remains low. The reason(s) for the typically low

numbers of reports for the species of interest are not known, but a likely explanation is under-reporting of suspected ADRs for herbal medicines (Barnes, 2003), and in particular from low-income countries. This is exacerbated by the absence, or currently limited capacity, of national schemes for reporting of suspected ADRs in some of these countries, and/or a lack of promoting the reporting of suspected ADRs associated with herbal medicines. Nevertheless, there are currently 117 countries participating in the WHO International Drug Monitoring programme, but many African nations have only become Members or Associate Members of the WHO International Drug Monitoring programme in the last 5 to 10 years (Uppsala Monitoring Centre, 2013). Even when reporting of ADRs associated with herbal medicines occurs, typically reports use vernacular or other types of names that can lead to ambiguity with respect to the species implicated (Farah et al., 2006).

As a substantial proportion of the population in low-income countries relies on herbal and other traditional medicines as its main form of healthcare (World Health Organization, 2013), the very low number of reports from these areas of suspected ADRs associated with herbal medicines is of concern, since signals of safety concerns associated with these preparations could go undetected. In spite of the well-known nephrotoxic properties of the genus *Aristolochia*, VigiBase™ contains only eight reports (four in females) of suspected ADRs associated with single-ingredient preparations of any species within this genus, (*Aristolochia fontanesii*, n=4; *Aristolochia kaempferi*, n=1; *Aristolochia* spp. not specified, n=3), of which six included ADR terms from the renal and urinary disorders SOC. In one report, a 53-year-old male developed acute renal failure and other symptoms after 64 days' use of *Aristolochia* sp. (not specified) for an unspecified indication; the patient was also taking other herbal and conventional medicines. In a second case, a 12-year-old girl developed nausea and vomiting after using *Aristolochia kaempferi* root 1.5 g daily for 2 to 3 days for an open head wound. For the other cases, no further details on the *Aristolochia* preparations used, their dose and duration of use were provided in the reports.

Our finding that there are no reports in VigiBase™ originating from our study area that list suspected ADR terms related to the SOCs 'pregnancy, puerperium and perinatal conditions' or 'reproductive system and breast disorders' for the species of interest further strengthens our argument that signals of safety concerns associated with herbal medicines could be missed. Plants used for menstrual disorders and/or as abortifacients could cause ADRs that are not necessarily limited to pregnancy- or reproductive-system effects. Furthermore, there are obvious potential risks for women and, where herbal medicines are used in pregnancy (for example to ease birth), for the developing fetus, either directly (i.e. foetotoxicity or teratogenicity) or indirectly, through toxicity to the mother, which may impact the health of the developing fetus or subsequent development of the child (Bone, 2005). Nevertheless, anxiety of teratogenicity of modern pharmaceuticals is a common reason for women in developed countries to use complementary and alternative medicine during pregnancy (Hall et al., 2011). The report from a Western country describing a female who experienced uterine rupture, anaphylactoid shock of pregnancy, and cardiac arrest following oral administration of 20 ml of *Ricinus communis* oil for labor induction is of particular concern since the patient died. Castor oil (made from *Ricinus communis* seeds) has a folklore reputation as an emmenagogue and for inducing labor (Williamson, 2003), and has been investigated clinically in this respect (Garry et al., 2000). In the latter study, which was non-randomised, women received a single, oral dose of 60 ml castor oil or no treatment. All women who received castor oil reported nausea after ingesting the preparation, which is expected with high doses (Sweetman, 2011). No other ADRs were reported, although cases of amniotic fluid embolism (Steingrub et al., 1988) and

meconium-stained amniotic fluid (Mitri et al., 1987) have been described following castor oil ingestion (30 ml, dose not stated, respectively) during labor.

The data obtained from VigiBase™ have recognized limitations. Not least, the information shown comes from a variety of sources, and the likelihood that the suspected adverse reaction is drug-related is not the same in all cases (WHO-UMC Caveat Statement). The species of interest is not necessarily the only preparation that was being used by the person experiencing the suspected ADR(s), and in many cases individuals were using more than one preparation, including both herbal and conventional medicines. A bias towards under-reporting of suspected ADRs associated with herbal medicines has been described (Barnes, 2003; Barnes et al., 1998; Biscoe et al., 2002; Green et al., 1999; Wingfield et al., 2002).

There is an awareness at the national and international levels of the need to improve safety monitoring for herbal medicines. The WHO has published guidelines on pharmacovigilance of herbal medicines that include practical advice on how some of the many challenges can be approached, including the need to expand the source of case reports, such as from providers of traditional herbal medicines (World Health Organization, 2004). This document followed the WHO-UMC's initiation of a traditional medicines surveillance scheme aimed at stimulating reporting of ADRs associated with herbal and other traditional medicines to national pharmacovigilance centers, and at improving the quality of such reports (Farah et al., 2006). Other approaches to enhancing traditional herbal medicines pharmacovigilance have also been proposed. For example, ethnobotanical or ethnopharmacological studies, typically used to collect data on uses, doses/dosages, sources and methods of preparation of traditional herbal medicines, could supplement spontaneous reporting data by also collecting data on individual's experiences with unexpected and adverse reactions (Rodrigues and Barnes, 2013).

5. Conclusions

Our review shows that more than 2000 plant species are used in Latin America, the Caribbean, sub-Saharan Africa and South and Southeast Asia to treat menstrual disorders, which reflects the importance of menstruation as a major reproductive health issue among women in these regions. Most species were used to treat painful menstruation, to induce or regulate menses, and/or to provoke an abortion. The most widely used genera were *Citrus*, *Senna*, *Phyllanthus* and *Gossypium*. For less than half of the 59 the most salient species, literature was available on their pharmacological properties and/or mechanisms of action. From the tested species, 48% appear to work as uterine spasmolytics and may ease uterine cramps and contractions, while 31% as uterine spasmogenics, and may ease menstrual pains by inducing the menses. Researchers should be careful to interpret the frequent use of plants to induce menses as abortion practises, as in many cultures, the regular cleansing of the womb is seen as a method to clean impurities and increase fertility.

Less than a third of the 59 most salient plant species used for menstrual morbidity by women in the study area occur as ADR reports in VigiBase™, and the few reports that come from this area only list a very limited number of suspected ADRs relating to pregnancy, puerperium, perinatal, reproductive and/or breast disorders associated with herbal medicines. Nonetheless, at least some of the frequently used species are known to contain toxic substances, and may expose women and/or a developing fetus to serious health risks if taken in high doses. Our findings indicate the need for different methods, perhaps using an ethnobotanical approach to collecting data on experiences of suspected ADRs, to explore whether ADRs of particular interest occur among women

using herbal medicines as emmenagogues. There would also appear to be a need for ongoing activity and commitment to raising awareness of and facilitating reporting of suspected ADRs using a mechanism through which reports will reach national pharmacovigilance centers and, ultimately VigiBase™ itself. In summary, until the objective to guarantee safe and culturally acceptable access to medicines for use in anticonception and for treatment of menstrual morbidity has been reached, women in low-income countries will continue using traditional remedies. Menstrual complaints and research into the risks and benefits of medicinal plants used to treat these ailments should be given a higher priority in reproductive health programs that respect traditional knowledge, local perceptions and preferences. We hope that the results from our review will lead to a better understanding of plant use for menstrual disorders among women in low-income countries and contribute to the development of safe and effective treatments for menstrual morbidity in this region.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at <http://dx.doi.org/10.1016/j.jep.2014.06.049>.

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