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REVIEW

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Is it safe to consume traditional medicinal plants during pregnancy?

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The popularity of natural medicine is growing worldwide. Unlike conventional licensed medicines, herbal medicine practices are usually not supported by effectiveness, efficacy, or safety studies, which raise concerns about potential risks involved in their usage, particularly in high-risk patients such as pregnant women where teratogenicity is a concern. Despite a lack of science-based evidence, the use of herbal products for the management of pregnancy-associated challenges is common, due to the common notion that they are free of toxic effects and adverse reactions because they are "natural." The lack of concern about utilizing herbal remedies during pregnancy is strengthened by the lack of regulation in most countries for their marketing. However, plant-based remedies are not free of adverse reactions. Medicinal plants and herbal remedies contain substances that can be toxic to the human body and the fetus. Potential effects of indiscriminate use of medicinal plants are embryotoxicity, teratogenic, and abortifacient effects. Some plant constituents can cross the placenta and reach the fetus. Phytochemicals and their metabolites are known to induce stimulation of uterine contraction and hormone imbalance that could result in abortion. The alterations to the hormonal profile can affect conception, induce teratogenic activity, and halt the pregnancy or produce a congenital malformation. Due to the wide range of modes of action of phytochemicals, some medicinal plants may be safe to use during certain trimesters of pregnancy and harmful at other stages. This manuscript reviews available scientific information concerning potential health hazards associated with the consumption of herbal medicines during pregnancy, highlighting those herbs that should be avoided due to their potential abortifacient and/or teratogenic activity. We focused on plants that were tested by preclinical studies, and studies of these plants are summarized. Common therapeutic use of these herbs, estimated effects, toxicological effects, and animal studies of these plants is summarized. The literature reviewed suggests that consumption of the following medicinal plants should be avoided during pregnancy: *Abrus precatorius*, *Achyranthes aspera*, *Ailanthus excelsa*, *Aloe vera*, *Aristolochia indica*, *Areca catechu*, *Bambusa vulgaris*, *Cassia*

occidentalis, *Cicer arietinum*, *Cimicifuga racemose*, *Dolichandrone falcate*, *Ginkgo biloba*, *Hydrastis canadensis*, *Indigofera trifoliate*, *Lavandula latifolia*, *Maytenus ilicifolia*, *Momordica cymbalaria*, *Moringa oleifera*, *Musa rosacea*, *Oxalis corniculate*, *Phytolacca dodecandra*, *Plumeria rubra*, *Ricinus communis*, *Ruta graveolens*, *Stachys lavandulifolia*, *Senna alata*, *Trigonella foenum-graecum*, *Vitus agnus-castus*, and *Valeriana officinalis*.

KEYWORDS

abortifacient, antiimplantation, efficacy, estrogenic, medicinal plants, review, uterotropic

1 | INTRODUCTION

Since the beginning of human history, traditional medicine is documented to utilize plant-based remedies to treat complexities and challenges during pregnancy and childbirth. Traditional drugs are increasingly incorporated into modern medical practices, and in some parts of the world, they are preferably used by choice or out of economic necessity over synthetic medicines (Ahmed, Hwang, Hasan, & Han, 2018; Raymond & Grimes, 2012). In the preceding two decades, the utilization of traditional medicines has increased significantly worldwide (Barnes, McLachlan, Sherwin, & Enioutina, 2016; Enioutina et al., 2017). The prevalence of the use of traditional medicines is 5.9–48.3, 12, and 19% in Canada, United States, and the European Union, respectively (Eardley et al., 2012; Wu, Wang, & Kennedy, 2011).

Pregnancy is a state linked with considerable physiological changes resulting in various ailments and medical conditions, including nausea and vomiting, gastric disturbance, candida infection, labor induction, respiratory illnesses, and skin problems. Studies reveal that due to health concerns, women are inclined to avoid conventional drugs during pregnancy and to prefer herbal supplement treatments, regardless of the lack of science-based studies into their effects (Bayisa, Tatiparthi, & Mulisa, 2014; John & Shantakumari, 2015). In spite of this general tendency for caution, and an overall view that natural herbal treatment is safer, it is well known that natural drugs may demonstrate powerful pharmacological activities, which may negatively affect the fetus and the pregnancy. The adverse effects vary from teratogenicity to a higher tendency of bleeding and may affect neonatal hormones (Smeriglio, Tomaino, & Rombetta, 2014). In fact, in many traditional societies, herbal drugs are well known to have been used for inducing abortion; and abortifacient agents obtained from indigenous medicinal plants can considerably benefit the population of both developing and developed countries. For the majority of plant-based medicinal remedies in most countries, there are no specific guidelines for their use, and no science-based information is usually available for physicians.

Insufficient data are available about the frequency of prescribing and the use of natural drugs in pregnancy to date. According to a study by Nordeng and Havnen (2005), 39% of the pregnant women used medicinal plants which were probably unsafe. No sufficient information is available about the type and dosages of herbal remedies' consumption during pregnancy. This should be considered as a community health problem, as there are many gaps of information on the effects of these remedies during pregnancy. Pharmacoepidemiological research can assist, by generating an assessment of medicinal plants' use during pregnancy and characterizing management measures.

Contact with many substances throughout pregnancy may influence the fetus. This includes herbal treatments and supplements, conventional medicines, and environmental factors. Natural medicines are often the preferred treatment during pregnancy due to the belief that it is safer for the fetus as compared to synthetic drugs. The prevalence of natural medicine use in pregnant women is estimated to range between 7 and 55% in various ethnic groups and various social, geographical, and cultural settings (Eboh, Moyaki, & Okino, 2019).

The present manuscript summarizes information concerning effects of medicinal plants during pregnancy, focusing on abortifacient effects. We constructed a list of medicinal plants for which science-based studies, mainly preclinical, suggest potential unsafe use during pregnancy. Such information is needed to pin-point the potentially damaging effects of traditional plant-based remedies during pregnancy.

2 | METHODS

A systematic search of the literature, including academic articles, unpublished work, documents, and theses, was undertaken for the years 2010–2019. The search for studies on the use of traditional medicines during pregnancy and breastfeeding was conducted in Medline, Embase, AJOL, Google Scholar, and PubMed. Unpublished data were gathered from articles and publications identified in the systematic analysis on scholarly databases/libraries, medical research records, and regulatory bodies, as well as nongovernmental and informal communications. Keywords used for the search: abortifacient, abortion, adverse, attendant, birth, botanical, delivery, developing, drug, ethnobotan*, ethnomedicin*, ethnopharma*, expectant, folk, gestating, gravid, healing, and herb. Combinations and variations of keywords were also used. Search for terminology specific to repositories and groups of practitioners was conducted as well. We also searched for study products by browsing the bibliography and the Webby using the keywords above. The references lists of all relevant

articles were searched for the identification of relevant manuscripts. The articles identified by the search were individually assessed. The plant list (www.theplantlist.org) was reviewed for the medical plants' names.

2.1 | Extent of plant remedies' usage during pregnancy

Since antiquity, cultures throughout the world have used plant-based remedies for the relief and cure of many ailments. Archeological and historical records point at the usage of plants for medicinal purposes in numerous cultures including the Sumerians (5,000 years ago), the Chinese (2700 BC), Syria and Egypt (1500 BC), and India (1500–1400 BC) (Jamshidi-Kia, Lorigooini, & Amini-Khoei, 2018). Extensive use was also reported in North and South America by indigenous people (da Silva Costa, Bezerra, Norte, Nunes, & de Olinda, 2012).

According to estimates by the World Health Organization (WHO), traditional medicine is considered the main foundation of health care by 65–80% of the world population (WHO, 2013). Worldwide, there are thousands of prescribed traditional plant remedies (Teng, Peng, Ong, & Qu, 2017). In a multinational study of 23 countries in Europe, North and South America, and Australia, 28.9% of the women reported herbal remedy use during pregnancy. The highest rates of herbal remedy users were reported for Russia (69.0%), Poland (49.8%), and Australia (43.8%) (Kennedy, Lupattelli, Koren, & Nordeng, 2013). Studies indicated that up to 45% of pregnant women use traditional remedies at least once during pregnancy. The percentage of pregnant women that use plant-based remedies was reported to be up to 73% in Ethiopia (Laelago, Yohannes, & Lemango, 2016), 20% in Uganda (Nyeko, Tumwesigye, & Halage, 2016), 34% in Australia (Frawley et al., 2013), 58% in the United Kingdom (Holst, Wright, Haavik, & Nordeng, 2011), 40% in Norway (Nordeng, Bayne, Havnen, & Paulsen, 2011), and 27.3% in Egypt (Orief, Farghaly, & Ibrahim, 2014). A study conducted in Australia showed that use of medicinal remedies is the second most used therapy by pregnant women and is exercised by 12% of the pregnant women (da Silva Costa et al., 2012). In rural areas in North America, 95.8% of the surveyed women reported to use at least one kind of medication, 92.8% of the women that reported to use medications self-medicated, and 45.2% of the surveyed women reported that they used plant-based remedies during pregnancy (Glover, Amonkar, Rybeck, & Tracy, 2003). With the prevalence of traditional medicine use during pregnancy in many countries estimated to be between 7 and 55% (Eboh et al., 2019), the World Health Organization encourages the integration of traditional medicines into health care systems (WHO, 2013).

Plant-based remedies are used during pregnancy to improve the well-being of the mother or to treat pregnancy-related problems. The most common indications reported to be treated with herbal remedies are preparations for and/or facilitation of labor, nausea and vomiting, urinary tract infections, gastrointestinal problems, flu, pain, prevention of miscarriage, anxiety, and edema (Ahmed, Nordeng, Sundby, Aragaw, & de Boer, 2018; John & Shantakumari, 2015; Kennedy et al., 2013; Teni et al., 2017).

The species of medicinal plants used during pregnancy vary with geographical location and ethnicity. For example, the most frequently used herb by pregnant women in rural areas of West Virginia, United States, is peppermint (18.0%) for the treatment of nausea, followed by cranberry juice for urinary tract infections (Glover et al., 2003). In a study conducted in Australia, the most frequently consumed herbs were found to be raspberry leaf (21.6%), *Hydrastis canadensis* L., *Zingiber officinale* Rosc. *Echinacea*, and *Hypericum perforatum* (Adams et al., 2009). In the Tumpat district, Malaysia, the prevalence of using at least one variety of herbal medicine by pregnant women was 51.4%, and the most frequently used plant remedy was coconut oil, which was consumed by 64% of these women. The third trimester of pregnancy was the most common period of consuming herbal remedies, and the recurrent indication (90%) was to assist labor (Rahman, Sulaiman, Ahmad, Daud, & Hamid, 2008).

The general population and pregnant women of developing countries are very much dependent on herbal therapy (Ali-Shtayeh, Jamous, Jamous, & Salameh, 2013; Jaradat & Adawi, 2013), and a large percentage of the pregnant women consider herbal medicines as effective for their ailments. Regardless of the wide spread of medicinal plant usage during pregnancy in developing and developed countries, science-based information about their potential therapeutic and undesirable effects is restricted.

2.2 | Potential health risks associated with plant remedies during pregnancy

Throughout the plant kingdom, plants have evolved an immense chemical diversity, including many phytochemicals with varied biological potentials. The wide range of biological activities, include both positive-therapeutic as well as negative-damaging effects on human health, including during pregnancy. Plants and plant products are often used carelessly during pregnancy due to the common notion that they are free of toxic effects and adverse reactions because they are "natural." Sixty percent of the participants in a survey in Brazil declared that they do not believe that plant remedies have toxic effects (Olivera & Goncalves, 2006), and about 39% of the women who reported use of medicinal plants or herbal formulations during pregnancy were unaware of potential undesirable effects of the plants (Chan, Xia, & Fu, 2007; Nordeng & Havnen, 2005). These results point at the need for the development of measures focused on science-based, responsible, risk-free use of medicinal plants and herbal medical products.

The common public belief that ingestion of herbal medicine during pregnancy is safe brings about an increased use during pregnancy without motivation on the part of the patient to acquire prior information about potential health issues (Frawley et al., 2015). In Oslo, Norway, over 78.3% of the women surveyed had very little information about the use of natural medicines, even though 31.3% had taken natural drugs during pregnancy (Nordeng & Havnen, 2005). The lack of

concern regarding utilizing herbal products during pregnancy is exacerbated by the lack of regulation for their marketing. In most countries, natural medicines are sold as nonprescription drugs, which make them easy targets for self-medication. Consumers believe that traditional medicines are free of side effects and rarely report to clinicians about the use of traditional medicines (Brown, 2017). Likewise, pregnant women, who believe that herbal medicines do not have negative or toxic effects, do not tend to consult health care professionals about plant-derived remedies (Clarke, Rates, & Bridi, 2013). Reflecting on the ignorance of consumers, many health care professions do not have sufficient knowledge of potential benefits, efficiency, effects, and safety of plant remedies (Xu & Levine, 2008). Consequently, folklore and folk practices, rather than scientific studies, are often the source of information for the patients on indications, efficacy, and safety of medicinal plants and herbal medicines. It is therefore not surprising that many women have reported that the decision to use traditional remedies was based on suggestions from friends or family or on their own initiative. Only few women reported that the suggestion to use natural medicine came from clinicians (Dante, Bellei, Neri, & Facchinetti, 2014; Kennedy et al., 2013).

Is it safe to consume traditional medicinal plants during pregnancy? Information regarding the safety and effectiveness of traditional medicine during pregnancy is skimpy (Abdullah, Mahmood, & Ahmed, 2017), and there are numerous concerns about the use of traditional herbal remedies by pregnant women (Kıssal, Güner, & Ertürk, 2017). Common reported adverse effects of medical remedies during pregnancy are the stimulation of uterine contraction and abortion. Some natural medicines were reported to cause loss of pregnancy by uterine contraction or to induce hormone imbalance that could result in abortion (Sjöström et al., 2007), and various traditional medicines contain constituents that can cross the placenta, reach the fetus, and affect the fetus (Gilmartin, Vo-Tran, & Leung, 2018).

Several medicinal plants alter hormone concentration, composition, or action in the human body, including during pregnancy. The induced alterations to the hormonal profile can affect conception, induce teratogenic activity and halt the pregnancy, or produce a congenital malformation (a birth defect). Plants which contain compounds having estrogenic activity can directly control pituitary action through peripheral modulation of follicle-stimulating and luteinizing hormones. Furthermore, some plants may interrupt the synchronized development of the endometrium and ovum, while others may have antiprogestational or abortifacient effects. Various plants are known to be used to induce abortion (Artimani, Shabanian, Heidari-Soureshjani, Asadi-Samani, & Luther, 2017). Table 1 summarizes results of scientific studies that tested abortifacient potential of plants. The studies, conducted with animals (rats, mice, or rabbit), demonstrate abortifacient activity of 13 medicinal plants.

Substances in medicinal plants, or their metabolites, may be toxic to the human body and the fetus. They can induce immediate negative effects that can be directly correlated with their ingestion. Alternatively, the effects can develop over time and, although potentially asymptomatic, can entail severe clinical consequences, sometimes fatal (Lapa, Souccar, Lima-Landman, Godinho, & Nogueira, 2004). Medicinal plants were suggested to exert two types of adverse effects. The first is inherent to the consumed plant and includes toxicities related to an overdose and/or interaction with other drugs. The second is related to extrinsic factors such as the quality of the product, which may interfere with the merit of herbal therapy (Calixto, 2000).

2.2.1 | Timing of herbal remedies' consumption

The timing of herbal remedies' consumption during pregnancy is relevant. Taking herbal medicines during different trimesters of pregnancy may cause diverse effects. Because of the wide range of modes of action of medicinal plants, some may be safe to use during certain trimesters of pregnancy but harmful at other stages. This is well acknowledged in traditional medicine for some plants, but information for most plants is lacking. For example, in Tanzania, it is common to consume certain herbs during labor and the first trimester (Mbura, Mgaya, & Heggenhougen, 1985). A study from Malaysia reported that the majority (79.6%) of the surveyed patients took herbal medicines only in the third trimester and mainly to facilitate labor (Rahman et al., 2008). Gallo et al. (2000) reported that in Toronto, Canada, 54% of surveyed pregnant women used *Echinacea* spp. at the first trimester, and only 8% throughout the pregnancy. In a study carried out in Alexandria, 52.4% of the pregnant women were reported to use *Zingiber officinale* Rosc. during the first trimester and 51.6% used *Trigonella foenum-graecum* L., at the third trimester (Orief et al., 2014). Herbal remedies appear to be used mainly during the first and third trimesters to prevent and solve labor difficulties and to stimulate and ease delivery (John & Shantakumari, 2015; Pallivalapila et al., 2015). Consumption during the first trimester is often for the treatment of nausea, and gastrointestinal disorders and, during the third trimester, is commonly aimed to ease delivery (Nyeko et al., 2016; Onyiapat et al., 2017). However, the use of herbal remedies throughout pregnancy is not uncommon, and several studies have identified a lack of temporal trends in their consumption during pregnancy (Tang, Lee, Binns, Hui, & Yau, 2016).

2.2.2 | Standardization

Another concern related to utilization of traditional plant medicines is standardization. Production of traditional medicines does not need to follow the same safety and regulatory procedures by the FDA or equivalent governmental agencies as synthetic medications. Consequently, the value and potency of traditional medicines can differ within and between batches of the same product and between products from various pharmaceutical producers, due to quantitative and qualitative variability in chemical composition including therapeutic agents (Anwar, Al Disi, & Eid, 2016; Bernstein, Gorelick, & Koch, 2019; Gardner & McGuffin, 2013).

TABLE 1 Summary of scientific studies on abortifacient potential of plants

Plant name	Geographic origin of the plant	Traditional medical use	Use in which part of the world	Estimated effect	Toxicological effect	Animals used in the study	References
Plumeria rubra (Frangipani)	India	Antiasthmatic, laxative	Mexico, India	Abortifacient activity was 100% at a dose of 200 mg/kg b.w. (alcoholic extract)	No toxicity symptoms were reported at 200 mg/kg b.w.	Female albino rats	Dabhadkar & Zade, 2012
Indigofera trifoliata L.	North and South Carolina	Antiinflammation, antileprotic, expectorant	India, Australia, Vietnam	Abortifacient activity was 92.3% at a dose of 400 mg/kg b.w (alcoholic extract)	No toxicity even at the highest dose of 4,000 mg/kg b.w.	Rats	Dinesh & Varsha, 2013
Phytolacca dodecandra L'Herit	Southern Africa, Ethiopia	Antiinfective. Antidysmenorrheal, anthelmintic, antirabies, antianthrax, abortifacient	Uganda, Madagascar, Ethiopia	Abortifacient activity was 100% at a dose of 500 mg/kg b.w. (aqueous extract)	Sleepiness, shivering, excessive urination, and reduced appetite were observed at the dose of 2048 mg/kg. No death was reported	Wistar Rats	Namulindwa, Nkwangu, & Oloro, 2015
Musa rosacea (Herb Smith)	India, Philippine	Anticancer and abortifacient	India	Preimplantation and postimplantation loss was 50.8 and 83.3%, respectively, at a dose of 500 mg/kg b.w. (alcoholic extract)	No toxicity symptoms were reported at the dose of 500 mg/kg b.w.	Female rats	Srikanth, Swamy, Rao, & Rao, 2013
Oxalis corniculate L.	India, Mexico	Antiscorbutic, refrigerant	India	Abortifacient activity was 78.5% at a dose of 200 mg/kg b.w. (petroleum ether extract)	No toxicity symptoms were reported at the dose of 200 mg/kg b.w.	Albino rat	Sharangouda & Patil, 2007
Avicennia marina subsp. australasica (Walp.) J.Everett	Australia, India	Antioxidant, abortifacient	India, Pakistan	Preimplantation and postimplantation loss was 54.69 and 86.21%, respectively, at a dose of 500 mg/kg b.w. (alcoholic extract)	No toxicity symptoms were reported at the dose of 500 mg/kg b.w.	Rats	Srikanth, Rao, & Swamy, 2015
Stachys lavandulifolia Vahl	Iran	Antianxiety, antiasthmatic, antiinflammatory, antioxidant and antimicrobial	India, South Anatolia	Abortifacient activity was 29.8% at a dose of 200 mg/kg b.w. (alcoholic extract)	Hepatic and renal toxicity were reported at the dose of 140 mg/kg b.w.	Mice	Jafarzadeh, Rafieian-Kopaei, Samani, & Asgari, 2012
Momordica cymbalaria Hook F.	India	Antidiabetic and neuroprotective	South East Asia, India	Abortifacient activity was observed at a dose of 500 mg/kg b.w. (alcoholic extract)	No toxicity symptoms were reported at the dose of 500 mg/kg b.w.	Rats	Koneri, Balaraman, & Saraswati, 2006

(Continues)

TABLE 1 (Continued)

Plant name	Geographic origin of the plant	Traditional medical use	Use in which part of the world	Estimated effect	Toxicological effect	Animals used in the study	References
Cicer arietinum Linn.	India	Diuretic, antiinflammatory, and anthelmintic	Malaysia, Iran, India	Abortifacient activity was 83.7% at a dose of 400 mg/kg b.w. (aqueous extract)	There were no toxicity symptoms at the dose of 4,000 mg/kg b.w.	Albino rats	Wikhe, Zade, Dabadkar, & Patil, 2013
Dolichandrone falcata (Wall. ex DC) Seem	India	Anticancer, antioxidant, and anxiolytic	India	Abortifacient activity was 100% at dose of 400 mg/kg b.w. (alcoholic and aqueous extracts)	There were no toxicity symptoms at the dose of 4,000 mg/kg b.w.	Albino rats	Wikhe, Zade, Dabhadkar, & Pare, 2012
Ricinus communis L.	India, Pakistan	Antileprotic, antisyphilitic, and emetic	India, Korea, Algiers, India, Pakistan	Abortifacient activity was 100% at the dose of 6.25 mg/kg of ricin-A chain or the castor bean extract	Toxicity symptoms reported were diarrhea and weight loss	Rabbits	Salhab, Al-Tamimi, Maha, & Shomaf, 1998
Bambusa vulgaris	Indochina, Southern China, Nigeria, United States, and Europe	Astringent, emmanogogue, refrigerant, and abortifacient	Pakistan, India, Brazil, Tanzania	Abortifacient activity was 100% at the dose of 500 mg/kg (aqueous extract)	No toxicity symptoms were reported at the dose of 500 mg/kg	Rabbits	Yakubu & Bukoye, 2009
Senna alata (PROTA)	Nigeria	Wound healing and laxative	Florida, Bangladesh, Pakistan, India	Abortifacient activity was 100% under 500 and 1,000 mg/kg b.w. (aqueous extract)	Diarrhea and tiredness	Rats	Yakubu et al., 2010

2.2.3 | Regulations

Apart from the biological effects of the phytochemicals, medicinal plants and plant-based remedies that their production is not controlled by regulation in most countries may contain various contaminants that may harm the fetus or the pregnancy. For example, various traditional medicines were found to contain high levels of heavy metals such as lead, which can accumulate in the body to toxic levels. Quality control in the formal herbal industry is needed (Mensah et al., 2019; Ozioma & Chinwe, 2019).

2.2.4 | Lack of science-based studies

Studies on effectiveness and safety during pregnancy of most of the traditional medicines are lacking or at best partial. A meta-analysis showed that *Zingiber officinale* Rosc., is efficacious and safe for the treatment of nausea and vomiting during pregnancy (Moradi, Taleb, & Saeidi, 2008). An increased occurrence of preterm labor and threatened miscarriages has been documented with the use of *Matricaria chamomilla* L. and *Glycyrrhiza glabra* Linn., (Cuzzolin et al., 2010). In a review of traditional medicines prescribed for morning sickness, *Mentha piperita* L., and *M. chamomilla* L., were reported to be risky in 6% of the studies, and *Rubus idaeus* L., leaves and *Z. officinale* Rosc., were reported unsafe in 15 and 12% of the studies, respectively (Wilkinson, 2000). High consumption of *M. piperita* L. is unsafe during early pregnancy due to its emmenagogue activities (John & Shantakumari, 2015). *T. foenum-graecum* L. should also be taken with care during pregnancy because of its antihyperglycemic activity and its stimulation of oxytocin secretion that induces uterine contraction (Orief et al., 2014).

No doubt, similar to supplements and synthetic medicines, herbal medicines as well should be used with care during pregnancy as they may be harmful to the fetus or the mother (Bercaw, Maheshwari, & Sangi-Haghpeykar, 2010). Some medical professionals do not advocate traditional medicines during pregnancy as safety has not been established by clinical studies (Chuang et al., 2009). When prescribed based on science-based knowledge, natural medicines can be safe, with uncommon occurrence of life-threatening episodes (Al-Rawi & Fetters, 2012). However, careless, untested use of natural medicines during pregnancy, or interaction of natural medicines with synthetic drugs that can have adverse reactions, can be harmful to the mother and the fetus (Holst et al., 2011).

2.3 | Management of some pregnancy-related challenges with herbal remedies

Some common challenges faced during pregnancy are nausea and vomiting. Up to 90% of all pregnant women suffer from nausea and vomiting, and many prefer to avoid conventional medicine due to potential risks to the fetus (Darvishpor et al., 2018). Examples of two medicinal plants which are used to assist with these conditions are Ginger and *Mentha piperita* L. Ginger is commonly used for indigestion, motion sickness, pregnancy-associated morning sickness, nausea, and vomiting. The impact of ginger consumption as an antiemetic in nausea and vomiting during pregnancy has been extensively investigated in clinical studies (Giacosa et al., 2015), and a dose of 1 g/day was found effective with no significant side effects (Firouzbakht, Nikpour, Jamali, & Omidvar, 2014). However, at higher doses, it increases production of gastric acid and can decrease platelet aggregation which can result in increased risk of bleeding especially if taken with herbs having similar effects (Cassileth & Deng, 2004). Later studies showed that the use of ginger during pregnancy was not associated with an increased risk of congenital malformations, still birth/perinatal birth, low birth weight, or preterm birth (reviewed by Nikkhah Bodagh, Maleki, & Hekmatdoost, 2018). The mechanism of ginger action involves its ability to increase the in gastroduodenal motility, which possibly reduces nausea and vomiting. The consumption of ginger orally after food intake or in a fasting state increases motility of the gastroduodenal tract (Chrubasik, Pittler, & Roufogalis, 2005), which was suggested to be the mode of action for reducing nausea and vomiting (Viljoen, Visser, Koen, & Musekiwa, 2014). *Mentha piperita* L., has been used since ancient time during pregnancy for the treatment of gastrointestinal disorders, common cold and respiratory conditions, muscle pain, headache, and neuralgia. It is also used for the treatment of pregnancy-induced nausea (Joulaeerad, Ozgoli, Hajimehdipoor, Ghasemi, & Salehimoghaddam, 2018) and as an antiulcer medicine in pregnancy (da Silva et al., 2016; Klafke et al., 2016).

2.4 | Herbs considered unsafe for use during pregnancy

The present section summarizes available science-based information about medicinal plants which are considered unsafe during pregnancy. The botanical family of each plant is written in parentheses near the plant name.

2.4.1 | *Abrus precatorius* L. (Fabaceae)

A. precatorius L., commonly known as jequirity bean or rosary pea, is a herbaceous flowering plant found in India, Africa, and China. Its leaves, pods, roots, and seeds are considered to have an abortifacient activity. The main active phytochemicals in the plant are trigonelline, squalene, precabrine, abrusic acid, abrine, abrin, hypaphorine, and abraline (Roy et al., 2012). It is used in traditional medicine for the treatment of diarrhea, dysentery, gonorrhea, general pain, hoarseness, aphthae of mouth, cancer, syphilis, spermatorrhea, inflammation, tuberculosis, asthma, headache, stomatitis, fever, eye diseases, wounds, skin diseases, itching, leucoderma, and superficial infection caused by *Staphylococcus aureus* (Garaniya & Bapodra, 2014). Its biological activities are aphrodisiac (Garaniya & Bapodra, 2014), anthelmintic (Selvadurai, Dhana Raju, Rao, & Kirubha, 2016), antidiabetic

(Sawant, Randive, & Kulkarni, 2017), antimicrobial (Mobin, Saeed, Ali, Saeed, & Ahmed, 2018), and immunomodulant (Tilwari, Shukla, & Pathirissery, 2011). Garaniya and Bapodra (2014), reported that *A. precatorius* L. has abortifacient activity. Methanol/chloroform extract (50 mg/mL) of *A. precatorius* L. seeds given subcutaneously to rats was inactive. Aqueous extract (125 mg/kg) of *A. precatorius* L. seeds given intragastrically to pregnant rats was active (Sethi, Nath, & Singh, 1990). Alcohol extract (200 mg/kg) of *A. precatorius* L. seeds, given orally to pregnant hamsters and pregnant rats, was inactive and active, respectively (Popli, 1977). Oral administration of petroleum ether extract of *A. precatorius* L. seeds was inactive in rats (Prakash, 1976).

2.4.2 | *Achyranthes aspera* L. (Amaranthaceae)

A. aspera L., commonly known as "devil's horsewhip" or "chaff-flower," is spread throughout the world as a common weed or an introduced species. It is used in traditional medicine in many countries including Australia, India, and Kenya. The leaves, seeds, and roots of *A. aspera* L. are considered to have abortifacient properties. The active phytochemicals in the plant include achyranthine, inokosterone, saponins, oleanolic acid, betulinic acid, ecdysterone, and ursolic acid (Pai, Upadhya, Hegde, Joshi, & Kholkute, 2016). It is traditionally used to treat abdominal pain, kidney stones, respiratory tract infections, boils, and inflammation-related disorders (Bhosale, Yegnanarayan, Pophale, & Somani, 2012). Reported biological activities for the plant material or its extracts are antiinflammatory, expectorant, blood purifier, antispasmodic, and diuretic (Asif, Jabeen, Atif, Majid, & Qamar-Uz-Zaman, 2014). Methanol solution leaf extracts demonstrated abortifacient activity in rats (Shibeshi, Makonnen, Zerihun, & Debella, 2006).

2.4.3 | *Ailanthus excelsa* Roxb. (Simaroubaceae)

A. excelsa Roxb. Common name: "tree of heaven," is a large tree distributed in Sri Lanka and India. The stem, bark, and leaves are considered to have abortifacient activity. Its bioactive constituents include ailanthione, glaucarubinone, glaucarubol, isovalerate, and dehydroglaucarubol (Rashed, Said, & Ahmed, 2013). It is traditionally used for the treatment of jaundice, heart diseases, tumors, gastric problems, inflammation, and asthma (Mani & Rathore, 2016). It appears to have a diverse range of biological activities, including antiinflammatory, antiasthmatic, hepatoprotective, and antioxidant (Said et al., 2010). Antiimplantation and early abortifacient activities were observed in female rats which received alcoholic extracts of the plant (Dhanasekaran, Suresh, Sethuraman, Rajan, & Dubey, 1993). Inhibited implantation and terminated pregnancy were received in Wistar albino rats which received a methanol solution extract of the stem-bark at the dose of 200 mg/kg (Mani & Rathore, 2016).

2.4.4 | *Aloe vera (Aloe barbadensis* miller) (Asphodelaceae)

This plant is found in Sudan, eastern and southern Africa, and the Mediterranean region and is cultivated in Venezuela, America, South Africa, India, Pakistan, Bangladesh, Haiti, Bonaire, southern California, and Aruba. *Aloe vera* gel is prescribed as a topical management for burns, wounds, and other skin diseases (Sajjad & Sajjad, 2014). It contains phenolic contents, flavonoids, glycosides, triterpenoids, steroid, tannin, and alkaloids (Patel, Patel, & Dhanabal, 2012). It is antiseptic, antiviral, analgesic, immune modulator, antifungal, antihelmintic, aphrodisiac, antioxidant, antiinflammatory, antimicrobial, purgative, and emollient. A topical use of *A. vera* gel is considered safe during pregnancy with no known pregnancy-related adverse effects. Liposome-encapsulated *A. vera* gel extract was superior to *A. vera* gel extract in decreasing the severity of melasma in pregnancy due to their ease in percolation; it lightens the melasma, with only mild side effects (Ghafarzadeh & Eatemadi, 2017). *A. vera* latex, which is administered orally for its strong laxative potential may cause stimulation of uterus contraction and abortion and should be avoided during pregnancy (Cuzzolin et al., 2010).

2.4.5 | *Allium sativum* L.: Garlic (Alliaceae)

Garlic is native to central Asia and northeastern Iran and is used worldwide for thousands of years as a food flavoring and as a traditional medicine. Enzymes, such as allinase, peroxidase, and myrosinase, are its important active constituents. When a garlic clove is crushed, allinase converts Alliin into allicin (Mikail, 2010), a thiosulphate compound with antioxidant potential (Otunola, Afolayan, Ajayi, & Odeyemi, 2017) that crosses the placenta. It is known as an antiprotozoal, antibacterial, antifungal, antineoplastic, immunostimulant, antiinflammatory, antioxidant, hepatoprotective, antifertility, antiulcerogenic, anticataract, and antinociceptive. Garlic is used to lower preeclampsia and hyperlipidemia during pregnancy; no complications were reported in clinical and animal studies, at doses lower than 1 g (reviewed by Rouhi-Boroujeni et al., 2017). Garlic is therefore likely safe to use during pregnancy when taken in the amounts typically found in food. However, excessive consumption of garlic may augment the threat of pregnancy loss, uterine contraction, and hemorrhage (Braun & Cohen, 2015).

2.4.6 | *Aristolochia indica* L. (Asclepiadaceae)

A. indica L., is a creeper plant found in Southern India and Sri Lanka. It is traditionally used for the treatment of indigestion, fever, irregular menstruation, and inflammation (Mathew, Kaitheri, DinakaranVachala, & Jose, 2011), and the roots and stems are considered to have abortifacient properties. It contains a range of bioactive components including savinin, aristolochic acid, secoishwaran, aristolic acid, methyl aristolate, coumaric

acid, naphthoquinone, aristolindiquinone, and magnoflorine (Kuo, Li, & Wu, 2012). It was demonstrated to have a range of biological activities including stimulant, antibacterial, mast cell stabilizer, and antipruritic (Venkatadri et al., 2015). The abortifacient activity of aristolic acid, found in the roots of the plant, was 100% at a dose of 60 mg/kg on administering it on the seventh day of pregnancy; and 20 and 25% at a dose of 60 mg/kg, respectively when administered on the 10th and 12th day of pregnancy (Yeung, Li, & Ng, 1991).

2.4.7 | *Areca catechu* (Linn) (Arecaceae)

A. catechu is a species of palm commonly found in the tropical Pacific, Asia, and parts of east Africa. It is considered to have originated in the Philippines but is widespread in cultivation in southern China, Taiwan, India, Bangladesh, the Maldives, Ceylon, Cambodia, Laos, Thailand, Vietnam, Malaysia, Indonesia, New Guinea, islands in the Pacific Ocean, and the West Indies. It is traditionally used for the treatment of gingivitis, diarrhea, urinary disorder, small pox, cholera, syphilis, dysentery, fractured bone, and gastric ulcer (Lee et al., 2016). The roots, kernel, seeds, and leaves are considered to have abortifacient activity, and the main bioactive phytochemicals are aracaidine, arecoline, guvacine, isoguacine, and alkaloids (Amudhan, Begum, & Hebbar, 2012). Biologically, these components demonstrate antibacterial, antimicrobial, antifertility, astringent, anthelmintic, and antidepressant activities (Adilijiang et al., 2016). Abortifacient effects of *A. catechu* were reported for female rats; administering doses of 100 and 300 mg/kg of the plant extract from the 6th to the 15th day of pregnancy induced 75% abortion rate (Shrestha et al., 2010).

2.4.8 | *Cassia occidentalis* L. (Leguminosae)

C. occidentalis L. is an Ayurvedic medicinal plant used as a traditional remedy for the treatment of fungal infections and hepatic ailments (cirrhosis, hepatitis, jaundice) (Sadiq et al., 2012). The plant extracts have antibacterial, antifungal, antimalarial, antiinflammatory, antioxidant, hepatoprotective, and immunosuppression activity (Vijayalkshmi et al., 2013). The principle phytochemical constituents include achrosin, aloeemodin, emodin, anthraquinones, anthrones, apigenin, aurantiobtusin, campesterol, cassiollin, chryso-obtusin, chrysophanic acid, chrysarobin, chrysophanol, and chrysoeriol (Yadav et al., 2010). Its antibacterial effects against *salmonella typhi* and *E. coli* have been demonstrated in in vitro studies. It was demonstrated to increase placental weight in rats and therefore may have therapeutic applications (Auharek, do Carmo Vieira, Cardoso, Oliveira, & Cunha-Laura, 2013). However, it should be avoided during pregnancy because it exerts laxative activity which may stimulate abortion (Bin-Hafeez, Ahmad, Haque, & Raisuddin, 2001). Perinatal exposure of goats at the early pregnancy caused fetal death and reabsorption. And high dose–induced tissue damage in the mother (vacuolation of liver cells and kidneys) and myocardium bone necrosis (Samavati, Ducza, Hajagos-Tóth, & Gaspar, 2017).

2.4.9 | *Chamaemelum nobile* (L.) All.

Chamomile (Asteraceae). Chamomile grows in Argentina, Egypt, Bulgaria, Poland, Hungary, Germany, England, France, Belgium, Portugal, and Spain. It contains sesquiterpenes, flavonoids, catechins, coumarins, polyacetylenes, phenolic acids, triterpenes, and steroids. It is commonly used for the treatment of mental stress, flatulent dyspepsia, dysmenorrhea, nausea and vomiting during pregnancy, and anorexia. It is used as an antiinflammatory, sedative, antispasmodic, antiemetic, carminative, spasmolytic, and anxiolytic (reviewed by Al-Snafi, 2016). The essential oil extracted from *C. nobile* L. has antioxidant properties (Al-Snafi, 2016). Animal studies have shown that the flavonoid component, apigenin, exhibits anxiolytic activity by binding to benzodiazepine receptors (Viola et al., 1995), and it also causes relaxation of intestinal smooth muscles (Forster, Niklas, & Lutz, 1980). Chamomile is considered, by traditional medicine, to be safe in pregnancy, lactation, or childhood, and no adverse effects have been noted in human trials; however, it is contraindicated to be used along with sedative, anxiolytic drugs, and alcohol (O'Hara, Kiefer, Farrell, & Kemper, 1998). Since chamomile is an oxytocic drug, that is, a stimulant of uterine contraction (Anderson & Johnson, 2005), care should therefore be exercised concerning dosages and at sensitive periods during pregnancy.

2.4.10 | *Cimicifuga racemosa* (L.) Nutt. (synonym *Actaea racemosa* L.) (Ranunculaceae)

Commonly known as fairy candle, black bugbane, black snakeroot, or black cohosh, this is a flowering plant common to North America. The roots and rhizomes were used in traditional medicine by Native Americans. The plant contains triterpenes, tannins, volatile oils, and phenolic acid (Gödecke et al., 2009). It is traditionally prescribed for the management of painful menstruation, premenstrual syndrome, and menopausal manifestations (Lieberman, 1998). It is also usually prescribed to induce labor in late pregnancy (Dog, 2009). Some studies reported an estrogenic or estrogen receptor–binding effect, but more recent studies reported that it does not (summarized by Wuttke & Seidlová-Wuttke, 2015). It was reported to suppress endogenous luteinizing hormone secretion to have no effect on follicle-stimulating hormone levels (Düker, Kopanski, Jarry, & Wuttke, 1991). Usage during pregnancy should be avoided because it stimulates uterus contractions (Dugoua, Seely, Perri, Koren, & Mills, 2006).

2.4.11 | *Ginkgo biloba* (Ginkgoaceae)

The *G. bilboa* tree, also known as ginkgo, gingko and "maidenhair tree," is cultivated in America, Europe, and Asia. It contains ginkgotoxin, cyanogenic glycosides, organic acids, ginkgolides, bilobalide, proanthocyanidins, kaempferols, quercetin, isorhamnetin, and rutin (Mei et al., 2017). It is traditionally used for the treatment of urinary tract disorders, tinnitus, dementia, edema, sexual dysfunction,

connective tissue disorders, intermittent claudication, age-associated memory impairment, altitude sickness, light-induced retinal damage, antidepressant-induced sexual dysfunction, erectile dysfunction, macular degeneration, premenstrual syndrome, vertigo, asthma, bronchitis, cough, scabies, skin sores, circulatory disorders, and brain disorders. Leaf extracts are associated with spontaneous bleeding, although contradictory research findings also exist (reviewed by Mei et al., 2017). Ginkgo leaf extracts demonstrated antiplatelet activity in animal studies (Kudolo, Dorsey, & Blodgett, 2002) and the ability to prolong bleeding during delivery in in vitro studies. It was reported by herbal toxicology and drug interaction compendium that the leaves possess emmenagogue activity and can induce hormonal changes (Brinker, 2000). However, in evidence-based medicine literature, it is not considered to possess the aforementioned activities. Consumption of roasted ginkgo seeds is considered safe during pregnancy; however, raw seeds are of a concern during pregnancy (Namulindwa et al., 2015).

2.4.12 | *Hydrastis canadensis* L. (Ranunculaceae)

H. canadensis is a reach source of alkaloid phytochemicals. The main active constituent of *H. canadensis* (Goldenseal) is berberine, which has antidiarrheal activity. It contains cardiac glycosides, sugar, amino acids, balsams, resins, terpenes, saponins, anthroquinone, flavonoids, tannins, steroids, phlobatannins, phenolics, anthocyanosides, and alkaloids (reviewed by Mandal et al., 2020). It is used for the treatment of ringworm, scabies, itches, skin diseases, abscess, throat infection, itch, wounds, pyrexia, bone fracture, rheumatism, hematuria, diabetes mellitus, leprosy, hemoglobin disorders, asthma, tuberculosis, typhoid fever, liver disorders, inflammation, edema, constipation, scorpion bite, snake bite, hepatitis and, asthma. It is an immunosuppressant, hepatoprotective, antioxidant, antiinflammatory, antimalarial, antifungal, and antibacterial. Few studies have also suggested the possible neurotoxic, hepatotoxic, and phototoxic activities of goldenseal extract and its alkaloids (reviewed by Mandal et al., 2020). It is contraindicated in pregnancy and in lactating mothers due to its uterine-stimulant effects (Ernst, 2002; O'Hara et al., 1998). The uterine-stimulating effects of goldenseal are suggestive that its use during pregnancy or nursing and administration to under puberty females shall be avoided.

2.4.13 | *Lavandula latifolia* Medik (Lamiaceae)

Lavender grows in France, Spain, Italy, and North Carolina. It is an abortifacient and is used either in a dried form or as an essential oil extract for the treatment of various ailments as well as for cosmetic purposes. It contains camphor, linalool, borneol, 1,8-cineole, α- and β-pinene, camphene, terpinen-4-ol, phellandrene, transcaryophyllene, limonene, and more (Wells, Truong, Adal, Sarker, & Mahmoud, 2018) as well as many phenolics. The essential oils are usually obtained from the flowers and foliage by steam distillation. Lavender essence is safe and effective in aromatherapy by reducing pain in women after cesarean section (Hadi & Hanid, 2011), episiotomy (Vakilian, Atarha, Bekhradi, & Chaman, 2011), and perineal discomfort after labor (Sheikhan et al., 2012). Its consumption is contraindicated in pregnancy due to its emmenagogue potential, that is, stimulation of blood flow in the pelvic area and uterus as well as menstruation (Ernst, 2002).

2.4.14 | *Maytenus ilicifolia* Mart. ex Reissek (Celastraceae)

M. ilicifolia Mart. ex Reissek is traditionally used for the treatment of gastric ulcers, dysentery, and cancer (de Araújo et al., 2013). Phytocomponents in its leaves and roots are considered to have abortifacient activity. The principle active chemicals in the plant are triterpenes, flavonoids, and tannins (Leite et al., 2010) which biologically were reported to have gastroprotective, anticancer, abortifacient, and antiinflammatory activities (Jorge, Leite, Oliveira, & Tagliati, 2004). A study with pregnant rats identified no clinical signs of maternal toxicity under the administration of 15.11 mg/kg b.w. plant extracts. There were no fetus anomalies or malformation, with no effects on reabsorption, number of implantations, and dead and live fetuses. The study indicated that *M. ilicifolia* does not interfere with development of the embryonic fetus and is nontoxic throughout gestation or during the organogenic period (Cunha-Laura et al., 2014).

2.4.15 | *Moringa oleifera* (Moringaceae)

M. oleifera is a fast-growing tree, native to tropical and subtropical regions of South Asia, cultivated mainly in semiarid, tropical, and subtropical areas. The main bioactive compounds in this plant are glycosides, acetylated carbamate, moringine, tocopherol, kaempferol, quercetin, sitosterol, pterygospermin, spirochin, and thiocarbamate (Asiedu-Gyekye, Frimpong-Manso, Awortwe, Antwi, & Nyarko, 2014). It is traditionally used for the treatment of gouts, sore throat, respiratory tract infections, splenomegaly, sexual disorders, and diabetes mellitus (Anthanont, Lumlerdkij, Akarasereenont, Vannasaeng, & Sriwijitkamol, 2016). The reported biological activities of *M. oleifera* are antigout, appetizer, aphrodisiac, abortifacient, and anticancer (Michl et al., 2016). Dried powder of leaf extract, administrated orally as an aqueous solution at a dose of 175 mg/kg body weight on 5–10 days after mating, was demonstrated to have a 100% abortifacient activity in albino rats (Sethi, Nath, Shukla, & Dyal, 1988).

2.4.16 | *Phytolacca dodecandra* (PROTA) (Phytolaccaceae)

P. dodecandra, commonly known as, African soapberry, gopo berry, or endod, is native to tropical Africa, Southern Africa, and Madagascar. It

has been cultivated by Africans for centuries, particularly in Ethiopia and Eritrea. It is traditionally used for the treatment of ascariasis, gonorrhea, malaria, rabies, jaundice, and eczema. It contains phenolic compounds, tannins, triterpenoids, steroids, alkaloids, and saponins (Matebie, Zhang, & Xie, 2019). Its biological activity is vermifuge, laxative, expectorant, diuretic, antitussive, antifungal, antidote, antibacterial, antiasthmatic, abortifacient, antitumor, and antimalarial (Getachew, Balkew, & Gebre-Michael, 2016). The abortifacient activity of aqueous leaf extracts was confirmed in a study with Wistar rats (Namulindwa et al., 2015).

2.4.17 | *Plumeria rubra* L. (Apocynaceae)

P. rubra L. is native to Mexico, Central America, Colombia, and Venezuela and is currently widely cultivated in subtropical and tropical climates worldwide. Its common names include frangipani, red paucipan, red-jasmine, and temple tree. It is traditionally used for the treatment of pyrexia, inflammation, itches, and anxiety (Chatterjee et al., 2013), and the biological activities associated with this plant are antiinflammatory, antiallergic, and larvicidal (Patil, Patil, Borase, Salunke, & Salunkhe, 2012). The parts used for traditional medicine are the roots. It contains alkaloids, tannins, simple phenolics, flavonoids, steroids, and saponins (Lawal, Ogunwande, & Opoku, 2014). A study with female rats revealed significant abortifacient activity of chloroform, ethyl acetate, alcohol, and aqueous extracts of this plant. The number of live fetuses was significantly reduced, and alcoholic extract induced 100% abortion with 200 mg/kg dose (Dabhadkar & Zade, 2012). Clinical toxicity symptoms were not observed during the study period.

2.4.18 | *Ricinus communis* L. (Euphorbiaceae)

R. communis L., the castor bean, or castor oil plant, is a perennial flowering plant indigenous to Eastern Africa, the southeastern Mediterranean Basin, and India. It is widespread throughout tropical regions and widely grown worldwide as an ornamental plant. Seeds of the plant are the source of castor oil. They contain 40–60% oil that is rich in triglycerides, mainly ricinolein and ricin—a water-soluble toxin, that is present in lower concentrations also throughout the plant (Akande, Odunsi, & Akinfala, 2016). Since ancient times, castor oil has been used as a folk medicine, and it is used in several countries to terminate unplanned pregnancies. Castor seeds are consumed by Mexican women to induce permanent sterility, and Indian women consume the seeds after delivery as a contraceptive for 9 months. Castor oil was reported to induce labor in 57.7% of the treated women within 24 hours after dosing (Garry, Figueroa, Guillaume, & Cucco, 2000). At a dose of 59 mL, it can induce painful, irregular uterine contraction, vomiting, and diarrhea which may lead to dehydration that can affect the mother and fetus (Davis, 1984). It can stimulate the passage of meconium and results in neonatal respiratory distress due to meconium aspiration, and medical consultation is thereby advised prior to administration during pregnancy (O'sullivan, Hehir, O'brien, & Morrison, 2010). *R. communis* exhibits estrogen-like activity which is attributed to its anticonceptive activity (Okwuasaba et al., 1991), and it exhibited an antifertility activity in an animal model, which might explain its long-established usage to evade unnecessary pregnancies. Further studies are needed (Makonnen, Zerihun, Assefa, & Rostom, 1999).

2.4.19 | *Ruta graveolens* Linn. (Rutaceae)

Commonly known as rue, common rue or herb-of-grace, this plant is commonly found and used as a medicinal plant in the Mediterranean region. Due to its medicinal value, it is also used in traditional medicine in South Africa, India, China, and South America. It is used traditionally for the treatment of dermatitis, rheumatism, hypertension, spasms, inflammation, thrombogenesis, edema, rheumatic pain, eczema, psoriasis, varicose veins, tendon strains, dislocation, intestinal and stomach problems, eye problems, and pain. It is insecticidal, antidiabetic, antiinflammatory, analgesic, and antibacterial. *R. graveolens* is a rich source of secondary metabolites mainly: coumarins, alkaloids, volatile oils, flavonoids, and phenolic acids including also rutin, gravacridondiol, rutacridone epoxide, methoxypsoralen, psoralen, and quercetin (Malik, Moraes, do Amaral, & Ribeiro, 2016). Rutin has emmenagogue potential and is involved in the stimulation of the basal fiber of the uterus (Miguel, 2003). It is contraindicated in lactating or pregnant women because it stimulates uterus contraction and causes abortion. According to Ritter, Sobierajski, Schenkel, and Mentz (2002), this plant contains photosensitizers and poisonous substances, which stimulate uterus motility, resulting in abortion. Teratogenicity studies conducted with this plant prove its toxicity; oral administration of *R. graveolens* extract interfered with preimplantation development and embryo transport and resulted in high proportion of abnormal embryos (Gutiérrez-Pajares, Zúñiga, & Pino, 2003; Ritter et al., 2002).

2.4.20 | *Trigonella foenum-graecum* L. (Fabaceae)

Fenugreek is an annual leguminous herb, found in Iran, Switzerland, Germany, Egypt, and Africa and is widely cultivated in India. The seed is an important source of vitamin C; it contains 50% fiber, as well as β-carotene, thiamine, riboflavin, nicotinic acid, and folic acid. It is abortifacient and emmenagogue. It contains oxytocin, which stimulates uterine contraction and induces labor, and can lower blood sugar levels, and hence precaution should be taken during pregnancy (reviewed by Yadav & Baquer, 2014). The uterine and lactation-stimulating properties were suggested to result from the presence of steroids such as saponins in the seed, which may be related to similar stimulant effect of the hormone oxytocin or similar compounds on uterus and milk ducts (Bingel & Farnsworth, 1991). Aqueous extract of fenugreek was demonstrated to have potential teratogenic effects in humans and animals, and seed consumption during pregnancy has been associated with a range of congenital malformations, including

hydrocephalus, anencephaly, and spina bifida. (Khalki, M'hamed, Bennis, Chait, & Sokar, 2010; Samavati et al., 2017). Prenatal exposure of mice to a high dose of fenugreek seeds caused growth retardation and altered neurobehavioral performance in the postweaning period (Khalki, Bennis, Sokar, & Ba-M'hamed, 2012).

2.4.21 | *Valeriana officinalis* L. (Caprifoliaceae)

Valerian is a perennial plant cultivated in the temperate areas of America, Japan, Eastern Europe, Germany, Holland, Belgium, France, England, and Asia. It is used as a hypnotic, sedative, anxiolytic, anticonvulsant, and antidepressant drug. The rhizomes of *V. officinalis* contain several components with demonstrable pharmacological activities, including sesquiterpenoids (valerenic acid), epoxy iridoid esters (valepotriates, valtrate, didravaltrate), amino acids [arginine, γ-aminobutyric acid (GABA), glutamine, tyrosine], and alkaloids (reviewed by Nandhini, Narayanan, & Ilango, 2018). The ethanol solution and aqueous extracts of the valerian root prevent the reuptake of GABA (Ortiz, Nieves-Natal, & Chavez, 1999). Valerian is traditionally contraindicated in pregnancy, but there are no studies to support this. Results from animal studies revealed that consumption of valerian at the second trimester of pregnancy can cause zinc deficiency in the fetus due to alterations in zinc homeostasis, which can increase the risk of neurobehavioral defects, such as learning, attention, and memory defects (Golub, Keen, Gershwin, & Hendrickx, 1995; Golub, Takeuchi, Keen, Hendrickx, & Gershwin, 1996). In a study conducted with mouse consumption of valerian by pregnant mice, it did not affect volume of the cerebral cortex, brain weight, and concentrations of copper in the fetal brain (Mohamoudin, Rajei, Haghir, Banihashemia, & Hami, 2012).

2.4.22 | *Vitus agnus-castus* L. (VAC) (Verbenaceae)

V. agnus-castus, also called vitex, chaste tree (or chastetree), chasteberry, Abraham's balm, lilac chastetree, or monk's pepper, is native to the Mediterranean region and is widely cultivated in warm temperate and subtropical regions throughout the world. It has estrogen-like activity and is used to treat various gynecological disorders, mainly in Europe and the Middle East (reviewed by Niroumand, Heydarpour, & Farzaei, 2018). The fruits contain a wide range of compounds including essential oils, flavonoids, iridoid glycosides, and diterpenoids such as agnuside, isoflavonoids, and phenolic compounds. The main active components are flavonoids including casticin, apigenin, vitexin, isovitexin, luteolin, orientin, isoorientin, santin, 6″-caffeoylisoorientin, and its methyl 5-*O*-demethyltangeretin (Niroumand et al., 2018). A woman that consumed *V. agnus-castus* while undergoing in vitro fertilization, during an unstimulated cycle, was reported to show significant derangement of ovarian and gonadotrophin levels (Cahill, Fox, Wardle, & Harlow, 1994). According to a systematic review, *V. agnus-castus* induces mild and reversible adverse effects (Posadzki, Watson, & Ernst, 2013); most common were nausea, mild gastrointestinal discomforts, fatigue, menstrual disorders, dry mouth, acne, pruritus, and erythematous rashes (Dugoua, Seely, Perri, Koren, & Mills, 2008; Posadzki et al., 2013). It was therefore suggested that *Agnus castus* may lead to ovarian hyperstimulation and may enhance the threat of miscarriage. Use of *V. agnus-castus* is contraindicated during pregnancy due to cellular studies that exhibited progesteronic and estrogenic properties of the plant (reviewed by Niroumand et al., 2018).

3 | CONCLUSION

Despite the lack of science-based information concerning effects of specific medicinal plants during pregnancy, herbal remedies are extensively used by pregnant women in both developing and developed countries throughout the world. Is it safe to consume traditional medicinal plants during pregnancy? To answer this question, one should consider specific herbal preparations. Since herbal medicine practices are based on a large number of medicinal plants, and various plant parts that differ greatly in chemical composition and hence in the potential effect on the human body; an answer to this question should address separately each plant, plant part, and mode of medical application. The majority of traditional herbal medicines have not been comprehensively investigated for their effects during pregnancy, and very little, insufficient, data are available about the effects of most medicinal plants during pregnancy. Available clinical and preclinical studies identified teratogenic and abortive effects of some commonly used medicinal plants or their derivatives, and this should raise a warning flag against the assumption that plants and their derivatives are harmless solely because they are natural. There is a need to expand the research base on medicinal plants and remedies used in pregnancy, to generate science-based data of therapeutic and harmful effects. Until sound data are available for a specific plant and plant preparations, it should be considered unsafe throughout pregnancy and to educate the public and practitioners accordingly.

Results reviewed in the present manuscript suggest that the consumption of the following plants should be avoided during pregnancy due to a range of potential damaging effects:

- Abortifacient activity: *A. precatorius*, *A. aspera*, *A. excelsa*, *A. vera*, *A. indica*, *A. catechu*, *Bambusa vulgaris*, *C. occidentalis*, *Cicer arietinum*, *Dolichandrone falcate*, *Indigofera trifoliate*, *M. ilicifolia*, *Momordica cymbalaria*, *M. oleifera*, *Musa rosacea*, *Oxalis corniculate*, *P. dodecandra*, *P. rubra*, *R. communis*, *R. graveolens*, *Senna alata*, and *Stachys lavandulifolia*.
- Stimulation of uterus contraction: *A. sativum (with excessive dosages)*, *Chamaemelum nobile* (with high dosages), *Cimicifuga racemose*, *H. Canadensis*.
- Emmenagogue potential: *Lavandula latifolia*
- *Antiplatelet activity* and the ability to prolong bleeding during delivery: *G. biloba*
- Teratogenic effects: *R. graveolens*, *T. foenum-graecum*

- *Progesteronic and estrogenic properties* that enhance the threat of miscarriage: *V. agnus-castus*.
- *Risk of neurobehavioral defects* due to potential zinc deficiency in the fetus: *V. officinalis*.
- Anticonceptive activity: *R. communis*

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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