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St. John's Wort usage in treating of perinatal depression

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Introduction

Depression is a mental illness characterized by anhedonia, depressed mood, and neurovegetative and neurocognitive symptoms (Malhi and Mann, 2018), causing high disability and affecting the quality of life. Worldwide, about 280 million people suffer from depressive disorders, including major depressive disorder and dysthymia; this number has increased by over 28% with the pandemic (World Health Organization, 2022). Moreover, women are more susceptible to suffering from depression than men. In this regard, the gender gap might be explained by the influence of several factors such as biological (gen-environment interactions, hormonal oscillations, and stress response), psychological (personality traits, interpersonal orientation, and history of disorders), and environmental factors, which involved adversities during early life and sociocultural aspects (Kuehner, 2017). Pregnancy, postpartum, perimenopause, and menstrual cycle are some of the stages of a woman's life associated with vulnerability to developing depression (Cohen, 2003; Kessler, 2003; Soares and Zitek, 2008; Seedat et al., 2009; Schiller et al., 2015; Johann and Ehlert, 2022). For instance, pregnancy is a period in which women undergo several changes regulated by the ovarian hormones, which impact the fetus's development and shape the mother's brain to cope with this new situation (Frokjaer et al., 2015). These physiological changes that occur during pregnancy could also cause biological susceptibility in the mother to developing mental health disorders like depression, i.e., one in seven women who give birth develops postnatal depression (ACOG Committee, 2018). Considering that most of the global population uses herbal medicine because it is their primary source of health care or due to cultural influences (World Health Organization, 2013), it is not surprising that pregnant women prefer to consume natural products without medical supervision because they are perceived as safer for the fetus than allopathic medicine (Wake and Fitie, 2022). Yet, there is not enough evidence for their safety during pregnancy. An example in kind is one of the herbal remedies commonly used for depression: St. John's Wort.

Perinatal depression

Perinatal depression is defined as an episode of major depressive disorder during pregnancy or after childbirth [American Psychiatric Association (ed.), 2014]. It is

estimated that around 10% of pregnant women and women who recently gave birth experience an episode of depression (World Health Organization, 2022). This mental illness affects the mother and the child's emotional and behavioral development, mainly when maternal depressive symptoms persist (Kingston et al., 2018). For example, maternal depression is associated with poor self-care, malnutrition, maladaptive behavior, and pregnancy complications such as a high risk of preterm birth and low birth weight (Jarde et al., 2016). Also, newborns show poor neurobehavioral organization, less responsivity to caregivers and physiological changes, lower activity, cognitive and emotional alterations, and other symptoms related to the lack of mother-infant interaction (Emory and Dieter, 2006; Lefkovics et al., 2014). Thus, early mental health care interventions in obstetrics for pregnant and postpartum women are essential to prevent mother-infant adverse outcomes (Simas et al., 2018).

To this end, a variety of therapies for depression have already been used (Cuijpers and Karyotaki, 2021). For instance, selective serotonin reuptake inhibitors (SSRIs) constitute the first line of pharmacological therapies. SSRIs have shown improvement and remission in women suffering from moderate and severe postnatal depression (Molyneaux et al., 2018; Brown et al., 2021). Because of the risks reported during the development period, it is crucial to consider that this kind of treatment requires personalized care and monitoring to assure its effectiveness and most importantly, the safety and security of the fetus and the newborn (Bałkowiec-Iskra et al., 2017; Mesches et al., 2020).

Nevertheless, pregnancy and breastfeeding are the main reasons why women avoid or discontinue antidepressants, leading to the risk of relapse (Petersen et al., 2011; Payne, 2021). This has led to a search for alternatives, such as traditional medicine, including natural products, and the one that has been among; the most used for treating depression is the St. John's Wort (*Hypericum perforatum* L., Family Hypericaceae).

Effects of St. John's Wort during pregnancy and postnatal period

Hypericum perforatum (HP), known as St. John's Wort, is a plant commonly found in Europe and Asia. It is traditionally used as an alternative therapy to manage depression (Sarris, 2018) and contains many biological compounds, such as flavonoids, hyperforin, and hypericin. These bioactive compounds inhibit the synaptosomal uptake of serotonin, dopamine, and noradrenaline and have affinity for GABAergic and glutamatergic system receptors (Butterweck, 2003). Although HP has shown clinical effectiveness and safety for mild or moderate depression, similar to SSRIs (Apaydin et al., 2016; Ng et al., 2017), some clinical and preclinical studies have reported side-effects and pharmacological interactions associated with HP that might compromise health (Rodríguez-Landa and Contreras, 2003). In this regard, little is known about

its effectiveness and safety for treating perinatal depression, which presents a significant health risk since pregnant and breastfeeding women prefer natural products because of their "innocuousness" compared to conventional medicine (Frawley et al., 2015). Thus, it is critical to further study these aspects of HP.

Clinical evidence has shown that HP usage during the first trimester of pregnancy is not associated with malformation, prematurity, or increased rates of stillbirth (Moretti et al., 2009). Nevertheless, some reports indicate that low levels of hyperforin were detected in breast-milk samples from mothers taking HP. Even after the breastfeeding period, infants' plasma levels of hyperforin and hypericin were at the lower limit of quantification. Additionally, no side effects were detected, neither in newborns nor mothers (Klier et al., 2002, 2006). Nonetheless, infants breastfed by mothers taking HP for around 2 months showed colic, drowsiness, and lethargy (Lee et al., 2003). On the other hand, pregnant women consuming HP before the 17th gestational week do not show pregnancy outcomes such as shortened gestational age, preterm birth, abnormal circumference head, low weight, and Apgar scores. However, the authors showed higher rates of malformation in the newborns compared to those detected in the general population (Kolding et al., 2015).

In this sense, data obtained through animal models are controversial (Table 1). On the one hand, rodent females subject to 2 weeks of daily human equivalent doses of HP, or even superior, during gestation and/or postnatal period do not display any behavioral, emotional, and physical long-term outcomes in offspring (Rayburn et al., 2000; Cada et al., 2001). On the other hand, male offspring exposed to HP during pregnancy exhibited less weight at birth. Another study showed that daily HP consumption during gestation, or 2 weeks before conception, did not affect the growth and physical development of mouse offspring (Rayburn et al., 2001). Besides, no toxicity signs were detected in offspring when double human equivalent doses of HP were administered during the 9th to 15th day of pregnancy, the period of organogenesis (Borges et al., 2005).

Moreover, *in vitro* studies have shown that the ethanolic extract of HP does not modify the placental cell viability, differentiation, and metabolic activity, indicating no cytotoxic or genotoxic effects of HP (Spiess et al., 2021). On the contrary, pups from mothers exposed to HP before mating, during the gestation or breastfeeding period, have focal hepatocyte damage such as hepatocyte hyaline degeneration, fibrosis, and cellular disorganization, which increased when higher doses were used (Garrovo et al., 2004). In the same way, Kahyaoglu et al. (2018) reported that exposure to HP before conception decreases the pregnancy rates and the number of fetuses. In addition, HP exposure during gestation caused an increase in gestation duration and low birth weight. In fact, the histological analysis indicated inflammation in the liver and focal necrosis in each lobe, as well as a morphological alteration in the kidney, possibly

TABLE 1 Effects of the exposure to SJW and/or its bioactive compounds during the prenatal and postnatal periods in the offspring.

	Method/test	Presentation/extract	Source	Exposure period	Treatment	Effect of the treatment/exposure	References
Human							
Breastfeeding women	Adverse events	Herbal supplement of SJW	Not mentioned	Lactation	Not mentioned	No adverse effects Isolated cases: colic, drowsiness, lethargy	Lee et al., 2003
Breastfeeding women	Mass spectrometry (LC-MS/MS)	Herbal supplement of SJW (300 mg)	Jarsin®, Lichtwer Pharma GmbH, Germany	Lactation	300 mg SJW/3 times daily	HP: ↓ levels/breastmilk ↓ Levels/infant plasma (limit of quantification)	Klier et al., 2002
Pregnant women	CES-D, PO	Herbal supplement of SJW (tablets, teas, tincture, or granules)	Not mentioned	Gestation	Pregnant women exposed to SJW Depressed women with a disease/conventional drugs Healthy women exposed to teratogens Healthy women	**ne**: depression status, malformation rates, birth and prematurity rats	Moretti et al., 2009
Pregnant women	Pregnancy outcomes	Herbal supplement of SJW	Not mentioned	17 and 32 gestational weeks	Not mentioned	**ne**: gestational age, preterm birth, head circumference, length, birth weight, and Apgar scores ↑ Malformation incidence	Kolding et al., 2015
Animal model							
CD1 mouse	EPM/EB/FS/H/LA/ MA/NG/RC/SV/SP	Herbal supplement of SJW (0.3% hypericin)	Basic Organics, Inc., Columbus, Ohio, USA	Gestation/2 w before conception	0.75 mg SJW mixed with each gram of feed	↓ Birth weight of male offspring ↓ Motor coordination (PND3) **ne**: EB, LA, FS, EPM, SP	Rayburn et al., 2000
CD1 mouse	BM/PMM/RC	Herbal supplement of SJW (0.3% hypericin)	Basic Organics, Inc., Columbus, Ohio, USA	Mating/gestation	0.75 mg SJW mixed with each gram of feed	↓ Birth weight of male offspring (PND1) Delay eruption upper incisors (PND11) **ne**: BM, PMM, RC	Rayburn et al., 2001

(Continued)

TABLE 1 (Continued)

	Method/test	Presentation/extract	Source	Exposure period	Treatment	Effect of the treatment/exposure	References
Sprague-Dawley rat	PMM, OFT, ASR, CMT, MWM, EPM	Standardized SJW (0.3% hypericin, 300 mg plant/capsule)	NaturPharma in American Fork, UT, USA	Gestation/lactation	0.18, 0.90, 1.80 or 4.50 g of SJW/kg chow.	↓ Birth weight (PND56/78) **ne:** Brain weight **ne:** OFT, ASR, CMT, MWM, EPM	Cada et al., 2001
Wistar rat	Histological analysis (hematoxylin and eosin staining)	Methanol extract (0.3% total hypericin)	Not mentioned	2 weeks before mating/gestation/ lactation	SJW 100 or 1000 mg/k/day	*Pups exposed (100 mg/k/day):* Hepatocyte damage (vacuolization) *Pups exposed (1000 mg/k/day):* Hepatocyte: hyaline degeneration/disorganization arrays Lobular fibrosis ↓ Glomerular size ↓ Bowman's space Hyaline tubular degeneration	Garrovo et al., 2004
Wistar rat	BM, organs weight, RC	Dry extract of Jarsin (0.4% hypericin)	Galena Quimica e Farmacêutica Ltda, Brazil	Gestation (9th—15th day)	18 mg/kg/twice a day	**ne**: Ambulation, piloerection No diarrhea and deaths. **ne**: Maternal body and organs weight **ne**: Implantation and reabsorption rates and # of fetuses/rat	Borges et al., 2005
Wistar rat	Histologic analysis (hematoxylin and eosin staining)	SJW herb extract	Pharmacy store, SOLGAR Istanbul, Turkey	1 weeks before mating/gestation/ lactation	300 mg/kg in water *ad libitum*	Inflammation, focal necrosis (lobes), deteriorating cell layout in pups' liver Hydropic and vacuolar degeneration in fetuses ↓ Diameter of glomeruli Bowman capsule distance was absent Hydropic and hyaline degeneration in tubules	Kahyaoglu et al., 2018

(Continued)

TABLE 1 (Continued)

	Method/test	Presentation/extract	Source	Exposure period	Treatment	Effect of the treatment/exposure	References
In vitro model							
JEG-3 Cell line	Biological assays	SJW extract standardized (0.3% hypericin) purified hypericin	Homeocan®, Montreal, QC, Canada Sigma-Aldrich (St. Louis, MO, USA)	–	SJW (25–250 mg/mL) Hypericin (7.5 ng/mL and 75 ng/mL)	↓ Viability/JEG-3 cells (SJW 150 and 250 mg/ mL) **ne**: hCG production (SJW 25 mg/mL or hypericin 7.5 and 75 ng/mL) ↑ [Ca2þ]i of JEG- 3 cells (SJW and hypericin) ↓ TCTP (SJW) ↑ CaBP28K, TRPV-6 (hypericin) ↓ PMCA1/4 (hypericin)	da Conceição et al., 2010
GST-pi/ human placenta at term	EA, PCD	Hypericin	Fluka® (purity: ∗95 %, HPLC), Germany.	–	Hypericin (0.1, 0.2, 0.4, 60 0.6, 0.8, 1.0, 1.2, 1.6, 3.2, 6.4 mM)	70% inhibition of GST-pi (1 mM hypericin) Total inhibition of GST-pi (8.5 mM hypericin)	Dalmizrak et al., 2012
ES cells NIH/3T3 cell line	Biological assays RT- PCR	Hyperforin	Sigma-Aldrich, St. Louis, MO, USA	–	Hyperforin (0.01–10 mM)	↓ Cell viability/ ES cells, NIH/3T3 cells (dose-dependent) Inhibition of ES and NIH/3T3 cell proliferation. ↑ Expression Oct4 and Sox2 ↓ Expression GATA6, TTR, BMP4, NPPA	Nakamura et al., 2013
åBeWo cell line	Biological assays	*H. perforatum* herb (70% EtOH)	Dixa, St. Gallen Switzerland	–	0.03, 0.1, 0.3, 1, 3, 10, 30, and 100 μg/mL	Cytotoxicity (30-100 μg/mL) ↓ Cell viability ↑ Apoptosis (100 μg/mL)	Spiess et al., 2021

ANF: ASR, acoustic startle response; BM, body measurements; BMP4, bone morphogenetic protein 4; CaBP28K, cytosolic calcium binding protein; CES-D, center for epidemiologic studies depression scale; CMT, complex maze test; ea, enzymatic assay; EPM, elevation plus maze; EB, exploratory behavior; FS, forced swim; GATA6, GATA binding protein 6; GST-pi, glutathione S-transferase-pi; H, homing; HP, hyperforin; LA, locomotor activity; MA, male aggression; MWM, morris water maze; ne, no effect; NG, negative geotaxis; NPPA, natriuretic peptide type A; Oct4, Octamer-binding transcription factor 4; OFT, open field test; PCD, protein concentration determination; PMCA1/4, plasma membrane Ca^{2+}-ATPase 1 and 4; PMM, physical maturation milestone; PND, postnatal day; PO, pregnancy outcomes; RC, reproductive capabilities; SJW, St. John's Wort; Sox2, SRY-box containing gene 2; SV, separation vocalization; SP, social play; TCTP, translationally controlled tumor protein; TPRV6, transient receptor potential; TTR, transthyretin.

caused by oxidative stress, since inducible nitric oxide synthase was elevated in a dose-dependent effect. Moreover, da Conceição et al. (2010) found that HP or hypericin, one of the active compounds, modifies calcium transit in trophoblast-derived cells. It seems that HP and hypericin alter the expression of specific transporters. For instance, HP caused a down-regulation of the Translationally Controlled Tumor Protein (TCTP).

In contrast, hypericin caused a down-regulation of the plasma membrane Ca^{2+}-ATPase 1 and 4 (PMCA1/4) and an up-regulation of transient receptor potential (TPRV6) and the cytosolic calcium-binding protein (CaBP28K). These data indicate that HP and its biologically active compounds trigger an imbalance in the Ca^{2+} influx in trophoblast differentiation. Moreover, hypericin competitively inhibits GST-pi, an enzyme that functions in the placenta's detoxification. The latter effect indicates that hypericin could be one of the components contributing to the toxic effects reported in the literature (Dalmizrak et al., 2012), although further work is needed.

Concluding remarks

Perinatal depression is a common complication caused by vulnerability from all the physiological changes occurring during pregnancy up to the postnatal period. Thus, untreated depression is not an option since adverse health outcomes can affect the mother, the fetus, and even the neonate (Dubovicky et al., 2017). Nevertheless, it is expected that women do not want to use antidepressant drugs before getting pregnant or even drop pharmacological treatment during pregnancy due to the relation between the consumption of antidepressants and the long-term effects on the fetus or neonate (Bałkowiec-Iskra et al., 2017; Dubovicky et al., 2017). Thus, to avoid unnecessary risk to the newborn, they resort to the use of complementary alternative medicine, including natural products like medicinal plants. However, natural medication such as HP is not regulated by high-quality standard processes, unlike allopathic drugs.

Consequently, there is no correct indication of drug interactions, doses, or side effects, to name a few. For instance, HP has around ten components, including hypericin and hyperforin, which appear to be the main ones responsible for its antidepressant effect and its putative effectiveness for mild and moderate depression (Ng et al., 2017). Nevertheless, as Linde et al. (2005) indicate, we have to consider recent studies due to the improvement of trial quality, and the selection of the patient regarding diagnosis.

In this regard, the results must be received with caution, as some evidence mentioned above is contradictory. Some reports indicate that using HP for perinatal depression does not represent a risk to the mother or child. The main active compounds of HP were barely detected in breast milk and the child's serum (Klier et al., 2002). Nevertheless, the participants

did not consume the same commercial presentation of the product, and even, they only indicated a standardized extract of HP. The key risk factor is the lack of information about the precise drug concentration or its metabolites, as, in contrast, conventional medications are highly standardized. Moreover, some reports indicate that HP has several drug interactions with other drugs, which interact with P450 cytochrome and P-glycoprotein (Borrelli and Izzo, 2009). For that matter, HP could interact with allopathic antidepressants, increasing their effects and causing a serotonergic syndrome (Izzo, 2004), which could affect the mother and the offspring.

In addition, recent evidence from animal models and *in vitro* studies indicate that HP could cause serious toxicologic effects in the fetus and newborns at doses equivalent to those used for humans and that these toxicological outcomes, such as morphological alterations in the liver and kidneys, are more evident at high doses (Kahyaoglu et al., 2018). In this regard, recent systematic analysis assessing the antidepressant effect of HP during pregnancy and lactation, highlights the limitations of preclinical studies; such as the lack of botanical verification and extract characterization, the ambiguous dosage selection, and the low quality of the methodology and design (Avila et al., 2018), to name a few. Perhaps, the deleterious effects of HP were more prominent in studies in which the experimental procedures were controlled; this allowed to explore modifications at the cellular level and in structural tissues, as well as the expression of essential proteins related to the metabolism of the drugs involved. Overall, it is believed that herbal medicine is safer because it is "natural," but this is not entirely accurate. Therefore, it is essential to consider that herbal medicine's prescription during gestation or lactation could be unsafe without medical supervision (see Dante et al., 2013). Consequently, more evidence to assure the safety of the consumption of HP as an alternative treatment for perinatal depression is needed to better understand all its pros and cons and make better decisions. To this effect, the main recommendation is the development of obstetrical strategies and programs that offer pregnant women care and support by medical professionals. In the same vein, it is medical professionals who should provide reliable information about the use of herbal treatments such as HP and constant monitoring of the mother and the fetus/newborn to guarantee timely assistance. Finally, the development of regulatory programs to assure safety and effectiveness of herbal medicine constitutes a true challenge that must be addressed.

Author contributions

TM-J conceived and wrote the original draft. CJ-P and RCZ reviewed the manuscript and provided expertise and feedback.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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