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Review

Effects of prenatal cannabinoid use on the monoamine system in the fetoplacental unit: A systematic review of animal and human studies

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ABSTRACT

Background: The rapid increase in cannabis use during pregnancy—up by 170 % between 2009 and 2016—raises pressing concerns about its effects on fetal health, particularly on the delicate monoamine system within the fetoplacental unit, which is crucial for placental function and neurodevelopment.

Objective: This systematic review explores the impact of prenatal cannabinoid exposure on the monoamine system within the fetoplacental unit, with a focus on its implications for fetal development through the lens of the Developmental Origins of Health and Disease (DOHaD) framework.

Methods: A comprehensive search across multiple databases initially retrieved 18,252 papers. After rigorous screening, only 16 animal studies and 4 human studies met the inclusion criteria. Findings were synthesized to evaluate the effects of prenatal cannabis exposure on neurotransmitter regulation, receptor function, and gene expression.

Results: Although no studies directly addressed the monoamine system in the placenta, animal models revealed significant disruptions in neurotransmitter regulation and neurodevelopmental changes following prenatal cannabis exposure. Human studies suggested potential cognitive and behavioral risks for offspring exposed in utero.

Conclusion: This review exposes a critical gap in the literature on cannabis' effects on the placental monoamine system. While evidence points to notable neurodevelopmental risks, the scarcity of focused research underscores the need for further investigation to fully understand the implications of prenatal cannabis exposure.

1. Introduction

Cannabis sativa L is a phytochemically complex plant that has drawn significant interest within the pharmacological community, largely due to its diverse array of cannabinoid and terpenoid metabolites (Hourfane et al., 2023). In particular, tetrahydrocannabinol (THC) and cannabidiol (CBD) have attracted considerable attention for their distinct physiological effects - THC for its psychoactive effects and CBD for its broad therapeutic potential. Recent advancements in cannabis research have shown that it can have beneficial effects in treating diverse life-threatening medical conditions including chronic pain, epilepsy, and the side effects of chemotherapy, paving the way for the development of novel cannabis-derived pharmaceuticals (Doppen et al., 2022, Hasan, 2023). The interactions of cannabis compounds with the human monoamine system (MAS) are a vital topic of research in this context, especially in relation to neurochemical regulation (Kibret et al., 2023). The interaction of THC with cannabinoid receptors and the affinity of CBD for serotonin receptors highlight the intricate relationship between cannabis constituents and neurotransmitter dynamics (De Gregorio et al., 2019, Baltz and Le, 2020). MAS homeostasis during pregnancy is essential for optimal fetal neurodevelopment (Rosenfeld, 2021). It is postulated that internal and external challenges encountered during

Abbreviations: CBD, Cannabidiol; CBN, Cannabinol; DOHaD, Developmental Origins of Health and Disease; DRD2, Dopamine receptor D2; GD, Gestational Day; LD50, Lethal Dose; L-DOPA, L-3,4-dihydroxyphenylalanine; MAO, monoamine oxidase; MAS, monoamine system; SYRCLE, Systematic Review Centre for Laboratory Animal Experimentation; PND, Postnatal day; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; THC, Tetrahydrocannabinol; TH, tyrosine hydroxylase.

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pregnancy may trigger Developmental Origins of Health and Disease (DOHaD) (Arima and Fukuoka, 2020). Consequently, cannabis exposure during this critical period poses a potential risk to fetal neurodevelopment, with effects that may persist into adulthood (Hurd et al., 2019).

The MAS plays a key role in physiological and psychological responses across animal species, having evolved over millions of years (Walker et al., 1996, Goulty et al., 2023). It is a complex network consisting of neurotransmitters such as dopamine, serotonin, and norepinephrine as well as their receptors, transporters, and metabolic enzymes. Tightly regulated monoamine levels are crucial for control of mood (Castren, 2005, Ruhe et al., 2007), cognition (Kolla et al., 2016, Cools and Arnsten, 2022), and reward as well as bodily functions like sleep, appetite, and stress response (Lewis et al., 2021, Jiang et al., 2022). Dopamine, associated with pleasure and motivation, influences learning, attention, and motor control (Iversen and Iversen, 2007, Berke, 2018, Gershman and Uchida, 2019). Serotonin contributes to mood regulation, sleep-wake cycles, and emotional processing (Jouvet, 1999, Kanen et al., 2021), while norepinephrine affects alertness, arousal, and stress response (Goddard et al., 2010, Espana et al., 2016, Kjaerby, Andersen et al., 2022). Imbalances in the MAS have been observed in psychiatric and neurological disorders, including depression, anxiety, bipolar disorder, and schizophrenia (Delgado, 2000, Grace, 2016, Sigitova et al., 2017, Shao and Zhu, 2020). Accordingly, MAS modulation via medication, psychotherapy, or lifestyle adjustments has proven effective in managing various mental health conditions (Karrouri et al., 2021, Marx et al., 2023).

A growing body of research conducted over the past few decades, including contributions from our team, has emphasized the importance of maintaining monoamine homeostasis within the fetoplacental unit for optimal placental functions and fetal development (Bonnin et al., 2011, Bonnin and Levitt, 2011, Suri et al., 2015, Muller et al., 2017, Abad et al., 2020, Hanswijk et al., 2020, Karahoda et al., 2020, Karahoda et al., 2020, Horackova et al., 2022, Staud et al., 2023). The MAS is integral to neurodevelopment, affecting the process from its earliest stages in the fetus through to adulthood (Desan et al., 1988, Silberman et al., 2016, Hanswijk et al., 2020). It also significantly affects maternal emotional well-being and the developmental pathways involved in the intricate process of nurturing life (Rosenfeld, 2021). Disruptions in the delicate homeostasis of the MAS triggered by external challenges have been associated with significant health pathologies (Goeden et al., 2016; Becker et al., 2022; Levitan et al., 2022).

The effects of cannabinoids on the MAS in the brain have been comprehensively characterized, revealing that they regulate neurotransmitters and their transporters at both the gene and protein levels (Wing and Paton, 1978, Velenovska and Fisar, 2007, Schulze et al., 2012, Otten and Engels, 2013, van de Giessen et al., 2017, Grzywacz et al., 2020, Abame et al., 2021, Vaseghi et al., 2021). Cannabis use has also been linked to cognitive impairments including attentional disorders in children (Richardson et al., 2016, Corsi et al., 2020). However, the interactions between cannabinoids and the MAS in the placenta are poorly understood. This research gap is hugely significant because of the increasing use of cannabis in pregnancy and the lasting impact of cannabinoids even after brief exposure (Thompson et al., 2019, Kroon et al., 2021).

Understanding the effects of cannabinoids on the placental MAS is crucial, as prenatal cannabis exposure has been linked to significant neurodevelopmental and behavioral effects. These include lasting cognitive impairments, externalizing behaviors, and an increased risk of psychotic symptoms. Prenatal cannabis exposure is also associated with adverse birth outcomes, such as low birth weight, small-for-gestational-age status (De Genna et al., 2022), and a higher risk of preterm birth, likely due to THC and CBD crossing the placenta and disrupting its function (Duko et al., 2023). However, evidence regarding structural birth defects remains inconclusive, with mixed findings on associations with the cardiac, central nervous system, and gastrointestinal malformations (Sujan et al., 2023).

As a transient organ with diverse physiological functions, the placenta plays a pivotal role in adapting to the dynamic changes and challenges of pregnancy (Burton and Fowden, 2015). Pathologies or external factors including drugs can compromise its functionality, leading not only to acute pregnancy complications but also to the onset of chronic conditions in adulthood (Rosenfeld, 2021), in accordance with the DOHaD framework. A thorough understanding of the biological factors responsible for disturbing its equilibrium during pregnancy is thus needed.

This review aims to comprehensively analyze existing research on the impacts of cannabis use during pregnancy on the MAS. By dissecting the complex interactions between cannabis compounds and the MAS we seek to enhance the broader understanding of cannabis pharmacology and its implications for maternal and fetal health.

2. Methods

2.1. Literature review methodology

We conducted a systematic review following the guidelines for Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Moher et al., 2009). Based on these guidelines, inclusion criteria were established to focus only on studies directly addressing gestational exposure and MAS-related outcomes such as neurotransmitter levels, receptor activity, or enzymatic function. Exclusion criteria eliminated review articles, editorials, and studies unrelated to gestational exposure to cannabinoids, as well as research focusing on other substances or physiological systems not involving the MAS. This approach ensured methodological precision and maintained focus on the specific research question.

On 1 July 2022, we initiated a search across the PubMed and Scopus databases, augmented by searches in Google Scholar and Web of Science, using the search string ((cannabis OR marijuana OR exocannabinoids) AND (pregnancy OR placenta OR MAS OR monoamine)). This initial search yielded a limited pool of records, prompting an expansion of our search terms to include ((tetrahydrocannabinol OR cannabidiol OR cannabivarin OR cannabigerol OR cannabinol) AND (pregnant OR reproduction OR dopamine OR noradrenaline OR serotonin) AND (human OR animal model)). The revised strategy led to the identification of significant studies. After removing duplicates, we reviewed the title, abstract, and full text of the remaining articles. We identified a number of independent studies that met our inclusion criteria, focusing on the effects of prenatal cannabis exposure on the monoamine system within the fetoplacental unit. Additionally, a manual search of reference lists from these articles and previous reviews allowed us to include further relevant studies that had been initially overlooked. The entire selection process is detailed in a flowchart (Fig. 1). This systematic approach ensured comprehensive coverage of the literature, thereby enhancing the reliability of our findings on the impact of prenatal cannabis exposure.

The selection process began with a review of titles containing our chosen keyword pairs, excluding duplicates, conference proceedings, editorial letters, and irrelevant gray literature. Eligibility for inclusion was assessed in two stages. First, we analyzed abstracts for relevance to the MAS and cannabis. The second stage was more focused, selecting articles that directly discuss the relationship between the MAS, cannabis, and pregnancy.

2.2. Risk of bias assessment

We rigorously assessed the risk of qualitative bias in animal model studies, with a specific focus on the effects of cannabis on the MAS during pregnancy. The assessment was conducted using the Systematic Review Centre for Laboratory Animal Experimentation (SYRCLE) risk of bias tool (Hooijmans et al., 2014), which was designed to identify

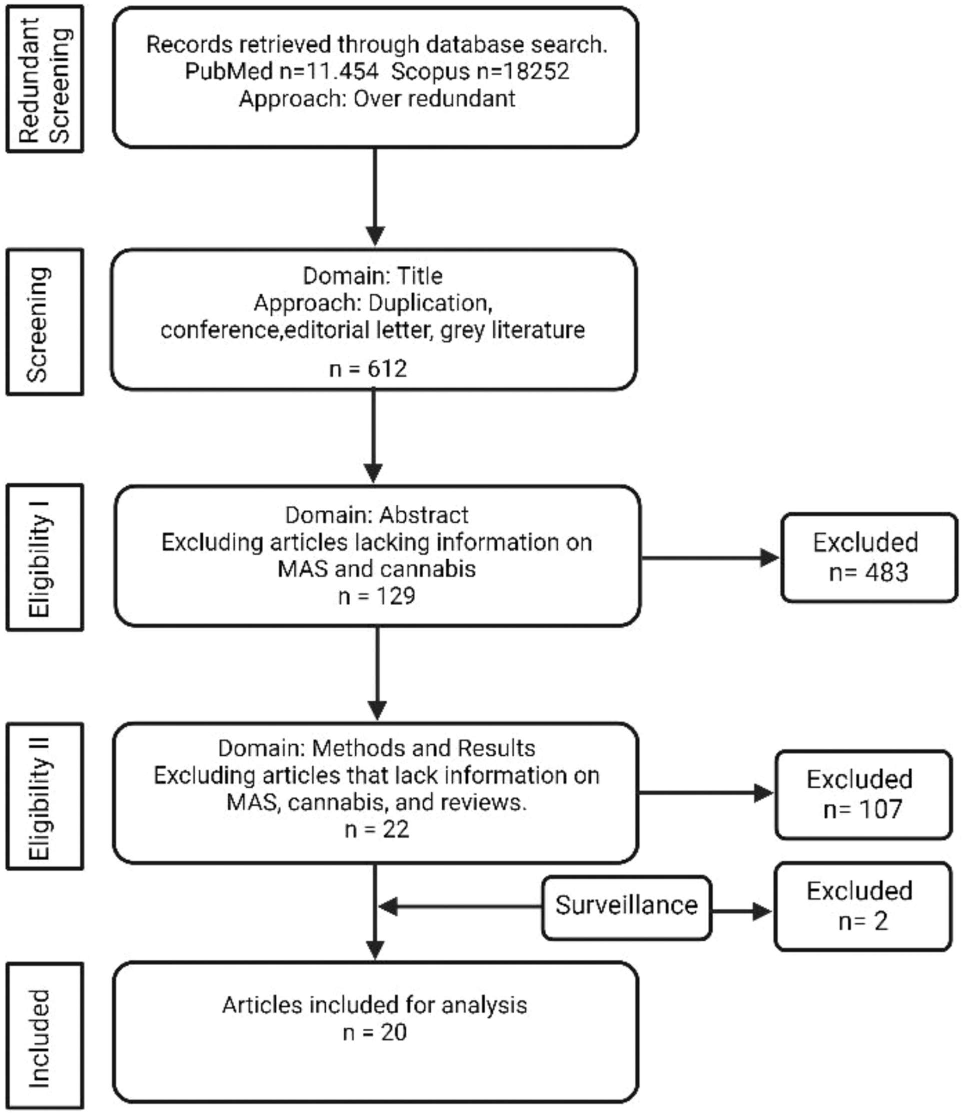

Fig. 1. Search and selection flowchart for prenatal cannabis studies. Flowchart outlining the systematic search, identification, and selection processes used to identify relevant studies.

potential biases in experimental animal research. This allowed each candidate publication to be analyzed thoroughly across eight key dimensions of potential bias, ensuring a comprehensive evaluation of methodological soundness. Each of the 16 selected articles was assessed independently, providing a robust foundation for our analysis. We assigned qualitative ratings to each dimension of potential bias, using a color-coded system for clarity and intuitive understanding: High risk of bias was indicated in red with a capital 'X', low risk was marked in green with a '+ ' sign, and unclear or indeterminate risk was represented in yellow with a '-' sign. These evaluations were visualized using the RobVis tool (McGuinness and Higgins, 2021), providing a structured and accessible presentation of the bias risks of each included study along each dimension.

2.3. Strengths and limitations

This systematic review of articles published between 1984 and 2023 aims to elucidate what is currently known about the intricate relationship between prenatal cannabis exposure and the MAS within the feto-placental unit. A commitment to methodological rigor was maintained throughout the review process by adhering stringently to the PRISMA guidelines, ensuring a standard of excellence. A notable strength of the review is the extensive scope achieved by integrating data from both animal and human research. This facilitates a deeper and more nuanced understanding of the potential effects of prenatal cannabis exposure.

Despite the above, some limitations may influence our interpretation of results. The lack of differentiation between gestational stages in animal studies could have caused us to miss crucial developmental periods, thus potentially limiting the generality of our findings. Moreover, the pool of human studies was relatively small, which narrowed the range of insights we could draw. This is important because ethical concerns relating to clinical trials present challenges in gathering direct evidence and the subjective nature of self-reported data in human studies introduces biases resulting from underreporting driven by factors such as societal judgment, legal repercussions, and stigma linked to personal choices. This issue is particularly relevant in pregnant women reporting cannabis use, where factors affecting the accuracy and transparency of self-disclosure to healthcare providers come into play.

In summary, while our systematic review sheds significant light on the effects of prenatal cannabis exposure on the MAS, we encourage readers to interpret the findings with a measured perspective. The strengths of this review, notably its methodological rigor and comprehensive analysis, need to be considered alongside the mentioned limitations in order to fully evaluate the presented data on the potential impacts of cannabinoids on the fetoplacental unit.

3. Results

We performed a comprehensive literature search to identify publications addressing the effects of cannabis on the MAS during pregnancy without limiting our search by publication year. In this way we identified 20 highly relevant studies, of which 16 used animal models and 4 examined the experiences of pregnant women. Intriguingly, despite our thorough and stringent selection process, we found a striking gap: not a single study specifically explored impacts on the placenta. Fig. 1 presents a flowchart generated in accordance with the PRISMA guidelines that illustrates our search methodology and article selection process.

Table 1
Summary of key parameters in animal studies investigating cannabis use during pregnancy in animal models.

Authors	Cannabinoid	Dose	Strategy	Animal Model	Strain	Route of administration	Vehicle	Main Conclusions
(Dalterio, Steger et al. 1984)	THC CBN CBD	50 mg/kg Single dose	Prenatal GD 18	Mice	ND	Oral	Sesame oil	Alterations in endocrine function and brain neurotransmitters
(Walters and Carr, 1986)	Crude Marijuana Extract	20 mg/kg Daily dose	2 weeks Prenatal – 20 days Post natal	Rat	Sprague -Dawley	Oral	Sesame oil	Reduced body and brain weights in offspring, along with lower tyrosine hydroxylase activity
(Walters and Carr, 1988)	Δ8-THC Δ9-THC CBD	1 mg/kg Δ8-THC 10 mg/kg Δ9-THC 10 mg/kg CBD	2 weeks Prenatal – 20 days Post natal	Rat	Sprague -Dawley	Oral	Sesame oil	The chemical entourage of marijuana produces a distinct impact on brain catecholamine mechanisms compared to THC or CBD.
(Rodriguez de Fonseca et al., 1991)	Hashish extract (11.8 %THC, 5.7 % CBN and 9,7 % CBD)	20 mg/kg Daily dose	Prenatal GD 5–24 days postnatal	Rat	Wistar	Oral	Sesame oil	Sex-specific disruptions in dopaminergic systems across various rat brain regions suggest the potential for long-term neurological consequences.
(Molina-Holgado et al. 1993)	Δ9-THC	5 mg/kg Daily dose	Prenatal GD 13- postnatal 7	Rat	Wistar	Oral	Sesame oil	Acute and maternal THC exposure show route-dependent regional effects on central 5-HT systems.
(Bonnin et al., 1995)	Δ9-THC	5 mg/kg Daily dose	Prenatal GD 5 – GD 14 /16	Rat	Wistar	Oral	Sesame oil	Perinatal THC exposure can influence the expression of crucial proteins for brain development at early fetal stages
(Garcia et al., 1996)	Δ9-THC	5 mg/kg Daily dose	Prenatal GD 5 to postnatal 24	Rat	Wistar	Oral	Sesame oil	Perinatal THC exposure alters responsiveness to dopamine antagonists, reduces ambulatory activity, and affects dopaminergic D2 receptors
(Bonnin et al., 1996)	Δ9-THC	5 mg/kg Daily dose	Prenatal GD 5 to postnatal 1–2	Rat	Wistar	Oral	Sesame oil	Perinatal THC exposure results in irreversible changes in TH gene expression and catecholamine synthesis in adulthood
(Garcia-Gil et al., 1998)	Δ9-THC	5 mg/kg Daily dose	Prenatal GD 5- Postnatal 24	Rat	Wistar	Oral	Sesame oil	Perinatal THC exposure did not affect DAT and TH gene expression as animals matured
(Suarez, Bodega et al. 2000)	Δ9-THC	5 mg/kg Daily dose	Prenatal GD 5- Postnatal 21	Rat	NS	Oral	NS	Glial changes caused by THC may underlie CNS dysfunctions following prenatal cannabinoid exposure.
(Gonzalez et al., 2003)	Δ9-THC	5 mg/kg Daily dose	Prenatal GD 5- Postnatal 24	Rat	Wistar	Oral	Sesame oil	Perinatal THC exposure leads to morphine preference in adult females.
(Frau, Miczan et al. 2019)	Δ9-THC	2 mg/kg Daily dose	Prenatal GD 5 – GD 20	Rat	Sprague -Dawley	Subcutaneous	-	Male offspring from THC-exposed dams exhibit unique molecular changes in dopaminergic neurons of ventral tegmental area.
(Sagheddu et al. 2021)	Δ9-THC	2 mg/kg Daily dose	Prenatal GD 5 – GD 20	Rat	Sprague -Dawley	Subcutaneous	-	Prenatal cannabis exposure sensitizes male pre-adolescent rat dopaminergic systems for later psychotic-like outcomes
(Traccis, Serra et al. 2021)	Δ9-THC	2 mg/kg Daily dose	Prenatal GD 5 – GD 20	Rat	Sprague -Dawley	Subcutaneous	-	Prenatal cannabis exposure leads to sex-specific effects on mesolimbic dopamine activity, causing susceptibility in males but resilience in females to THC
(Di Bartolomeo et al., 2021)	Δ9-THC CBD	5 mg/kg Δ9-THC 30 mg/kg CBD Daily dose	THC Prenatal GD 15 – PND GD 9 + CBD PND 19–39	Rat	Sprague -Dawley	Oral and intraperitoneal	-	Exposure at a non-toxic dose of cannabinoids leads to lasting neurobehavioral and molecular changes in rat offspring
(Pinky, Majrashi et al. 2021)	Δ9-THC	2 mg/kg Daily dose	Prenatal GD 3 – GD 21	Rat	Sprague -Dawley	Subcutaneous	-	WIN55,212–2 administration lowered oxidative stress markers and impacted mitochondrial Complex I and IV activities.

3.1. Cannabinoid administration during pregnancy in animal models

3.1.1. Type of cannabinoids used

Our review of animal model studies revealed that THC has been the main focus of research in this field: many of the included studies dealt exclusively with this cannabinoid. Its effects have been studied both alone and in conjunction with other psychoactive substances including cocaine, morphine, apomorphine, quinpirole, and methamphetamine. Studies have also investigated the effects of different THC-containing substances and derivatives including unrefined marijuana extracts and synthetic variants such as HU-210 and WIN 55,212. In addition to this heavy focus on THC there has been a notable recentuptick in interest in other phytocannabinoids such as CBD and cannabinol (CBN). While these studies are comparatively few in number, their existence reflects a growing curiosity about the wider array of compounds within cannabis plants. This shift from a primary focus on THC's psychoactive attributes to an exploration of other phytocannabinoids marks a significant evolution in the field.

3.1.2. Animal selection

Rats were clearly the preferred animal model in cannabis research, being used in 15 of the 16 animal studies. The remaining animal study used mice. The rat studies generally used either the Wistar or the Sprague-Dawley strain, both of which are frequently used because their shared key physiological and biological traits make them ideal for research in toxicology and pharmacology. Detailed scientific reasons for using one of these strains rather than the other are rarely given; instead, the decision seems to be mainly guided by the preferences of individual researchers or the protocols of their institutions. Both Wistar and Sprague-Dawley rats are equally viable for this type of research, so the choice often comes down to factors such as availability or the guidelines of a particular research facility.

3.1.3. Route of administration, strategy and vehicle

Cannabinoids were administered orally in a majority (11 out of 16; 68.75 %) of the included animal studies. Injections were used in the remaining 5 studies (31.25 % of the total). Of these studies, four used subcutaneous injections while one combined oral and intraperitoneal injection methods. Further details can be found in Table 1. In animal models, cannabinoid treatment typically spans gestation days 5–20. Table 1 specifies the first and last days of treatment, with analyses conducted the day after the final dose. Sesame oil was the preferred vehicle in most of the studies using oral administration, but one publication did not specify what vehicle was used. Despite its widespread use as a carrier in over-the-counter products for human and animal consumption, sesame oil can cause unpredictable absorption patterns that may complicate the task of understanding cannabis pharmacology. A self-nano-emulsifying drug delivery system (SNEDDS) formulation eliminated this issue , ensuring consistent and reliable CBD absorption (Izgelov et al., 2020).

3.1.4. Sources and doses dilemmas

Cannabis was historically classified as a Schedule I substance (Sonnenreich, 1970), which imposed stringent restrictions on its research and use. This classification primarily confined cannabinoid research to government-supplied sources. However, since 1996 there has been a notable transition towards commercially produced cannabinoids, allowing contemporary researchers to access a broader range of research-grade compounds. This evolution reflects a gradual liberalization of cannabis research regulations. The cannabinoid dosages used in biomedical research have also changed significantly over time. Studies conducted in the 1980s used a wide range of dosages, reflecting a period of extensive experimentation (Freeman and Lorenzetti, 2020). However, since the year 2000 there has been a trend towards a more uniform dosage, typically around 5 mg/kg (Table 1). This standardization, which was influenced by the National Institute on Drug Abuse's guidelines and is mirrored in commercial THC/CBD pharmaceuticals such as Epidiolex and Marinol, has occurred across a wide range of biomedical fields and is not limited to research on the effects of cannabis in pregnancy (Lim et al., 2017).

3.1.5. Historical milestones on cannabis research in pregnant animals

Decades of research have provided some notable insights into the effects of cannabinoids on the MAS during pregnancy. Fig. 2 summarizes what has been learned about this issue to date from animal models, showing that the most important findings can be grouped into four primary domains that include the influence of cannabinoids on MAS components including neurotransmitters, receptors, and enzymes; their effects on animal development, with a specific emphasis on sex-specific outcomes; and the influence of cannabinoids on behavior. Table 1 summarizes the methodological approaches used in the animal studies as well as their main conclusions; it should be noted that our presentation provides a thematic rather than strictly chronological summary of the field's key and foundational contributions.

Dalterio *et al.* found that maternal exposure to THC, CBN, and CBD disrupted pituitary-gonadal feedback, hormone levels, and neurotransmitters in pregnant mice, impacting male offspring's neuroendocrine development, reproductive outcomes, and neurodevelopment via the hypothalamo-pituitary-gonadal axis. CBN and CBD also markedly altered brain and hypothalamic neurotransmitter concentrations (norepinephrine, dopamine, serotonin), unlike THC. The study concluded that both psychoactive and non-psychoactive cannabinoids can induce lasting changes in male offspring's neuroendocrine and reproductive functions (Dalterio et al., 1984).

Walters *et al.* showed that crude marijuana extracts had direct effects on the catecholamine mechanism in rats. This resulted in reduced body and brain weights in offspring, diminished tyrosine hydroxylase (TH) activity, and altered dopamine D2 receptor binding in the striatum, all of which were associated with chronic exposure during pregnancy and lactation (Walters and Carr, 1986). The same authors subsequently investigated the effects of the isolated cannabinoids THC and CBD, revealing potential disruptions in neurochemical balance for extended periods after drug exposure (Walters and Carr, 1988). Importantly, these effects diverged from those observed in previous studies using crude marijuana extracts, suggesting variations in brain catecholamine development linked to factors such as dosage dependency and chemical interactions. Recent research has accordingly underscored the importance of studying marijuana's effects within its chemical entourage rather than focusing solely on individual isolated cannabinoids (Hanus and Hod, 2020).

Rodriguez de Fonseca *et al.* showed that pre- and post-natal exposure to hashish extracts that retain the chemical complexity of marijuana had sex-specific effects on the development of nigrostriatal, mesolimbic, and tuberoinfundibular dopaminergic neurons, affecting male offspring more significantly than females (Rodriguez de Fonseca et al., 1991). The authors posited that these modifications could have enduring effects that extend into adulthood. However, later studies focused mainly on the effects of isolated cannabinoids, leading to neglect of the potential effects of the chemical entourage of cannabis. Another study on prenatal and perinatal Δ9-THC exposure in rats yielded similar conclusions about the potential long-term effects of cannabinoids on the MAS (Molina-Holgado et al., 1993). This psychoactive cannabinoid affects the serotonergic system with clear regional specificity within the brain, potentially influencing postnatal innervation patterns and functional organization.

Early studies focused on the effects of cannabinoid consumption on the dopaminergic system and its interactions with TH, a key enzyme responsible for the synthesis of L-DOPA - a precursor of dopamine, norepinephrine, and epinephrine. Notably, Bonin *et al.* found that Δ9-THC had gene modulating effects during early brain development, particularly affecting the *TH* gene within catecholaminergic neurons (Bonnin et al., 1995, Bonnin et al., 1996). Their findings suggest that

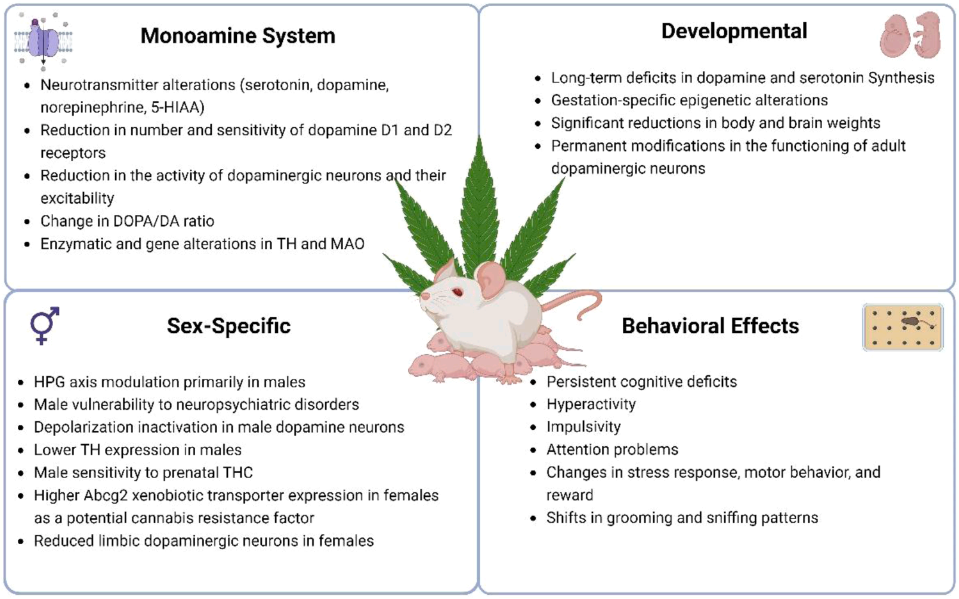

Fig. 2. Impact of cannabis on the MAS in animal models during pregnancy. This figure summarizes the key findings of our systematic review of 16 animal-based studies, focusing on the effects of cannabis on the fetoplacental unit and the MAS. It details significant observations in animal development, sex-specific responses, and behavioral implications, providing a comprehensive overview of current knowledge about these issues. Created with **BioRender.com**

cannabinoids could induce changes in the production of proteins crucial for neurodevelopment. The concurrent studies of Garcia *et al.* clarified THC's influence on dopamine metabolism and its lasting consequences by revealing subtle shifts in midbrain dopaminergic neuron sensitivity following perinatal Δ9-THC exposure (Garcia et al., 1996). These modifications have broad implications and could affect a wide range of dopamine-related processes including stress responses, motor behavior, and reward mechanisms by modifying the synthesis, reuptake, breakdown, and receptor interactions of dopamine. The identified shifts in dopaminergic sensitivity highlight a potential link between perinatal Δ9-THC exposure and the long-term health outcomes outlined in the DOHaD framework.

Similarly, Suarez *et al.* observed sex-related differences in TH expression with the potential to disrupt dopaminergic neuron maturation in males following perinatal THC exposure, suggesting potential irreversible long-term disruptions of dopamine metabolism that could have repercussions in adulthood (Suarez et al., 2000). In contrast, Garcia-Gil *et al.* found no long-term effects on dopamine metabolism, regardless of sex (Garcia-Gil et al., 1998). Their report contradicts the findings of Gonzalez *et al.*, who concluded that perinatal Δ9-THC treatment predominantly reduced dopaminergic neuron activity in females, indicating sex-specific effects on neurobiology and behavior (Gonzalez et al., 2003).

Despite the significance of serotonin in neurodevelopment, the first report on the effects of cannabinoids on its metabolism during pregnancy was published just three years ago by Pinky *et al.*, who studied effects on the key enzyme monoamine oxidase (MAO). The synthetic cannabinoid WIN55,212–2 was shown to have neuroprotective potential because it reduced oxidative stress and levels of pro-apoptotic factors such as caspase-3, pERK, and pJNK, although its overall neuroprotective properties are the subject of some debate. WIN55,212–2 also reduced MAO activity but caused no apparent modulation of TH expression, in contrast to previous findings (Pinky et al., 2021).

Over the years, research into the effects of cannabinoids when combined with other drugs has yielded intriguing insights into behavioral outcomes. An ethological analysis conducted by Meyer and Kunkle indicated that cocaine predominantly drove behavioral changes, overshadowing the influence of THC (Meyer and Kunkle, 1999). More recently, Frau *et al.* introduced pregnenolone as a potential remedy to counteract the molecular and synaptic alterations resulting from prenatal cannabis exposure, showing that it had a notable impact on dopamine functions and associated behaviors (Frau et al., 2019). Building on this work, Sagheddu *et al.* showed that prenatal cannabinoid exposure had a distinct impact on male rats, leading to reduced activity in ventral tegmental area (VTA) dopamine neurons (Sagheddu et al., 2021). This reduction enhanced sensitivity to D2 receptor activation and increased vulnerability to acute stress, influencing sensorimotor gating. The most recent results published by Traccis *et al.* underscored the sex-specific consequences of prenatal cannabis exposure: male offspring exhibited greater susceptibility to cognitive and emotional issues, while females seemed more resilient. Notably, preadolescent females exposed to prenatal THC maintained normal dopamine function and coped effectively with stress, pleasure, and learning (Traccis et al., 2021).

Our systematic review of 16 animal studies reveals a complex relationship between prenatal cannabis exposure and the monoamine system (MAS) in the fetoplacental unit. These studies demonstrate significant disruptions in neurotransmitter regulation, influencing developmental processes and leading to sex-specific outcomes. The interplay between cannabinoids and key neurochemical pathways, such as dopaminergic and serotonergic systems, appears to drive changes in behavior and neurodevelopment. Fig. 2 provides a visual summary of these findings, offering a broad perspective on how prenatal cannabis exposure impacts fetal development through these intricate biochemical mechanisms.

3.1.6. Bias risk assessment

The findings summarized above are drawn from sixteen rigorously chosen animal studies on the developmental impact of prenatal cannabis exposure on the MAS that were published between 1984 and 2021. To evaluate potential bias in these studies, we applied a strategy that captures eight key bias dimensions ranging from selection bias to ethical considerations in order to evaluate the current state of research on this topic (Fig. 3). The term 'dimensions' reflects their multifaceted and continuous nature, unlike the fixed and singular 'categories.' The evaluation focused on the animal studies because human self-report studies are subject to a high level of inherent bias (Althubaiti, 2016). Overall, the studies had a low risk of bias and a high degree of methodological consistency, offering clear insights into cannabis' developmental

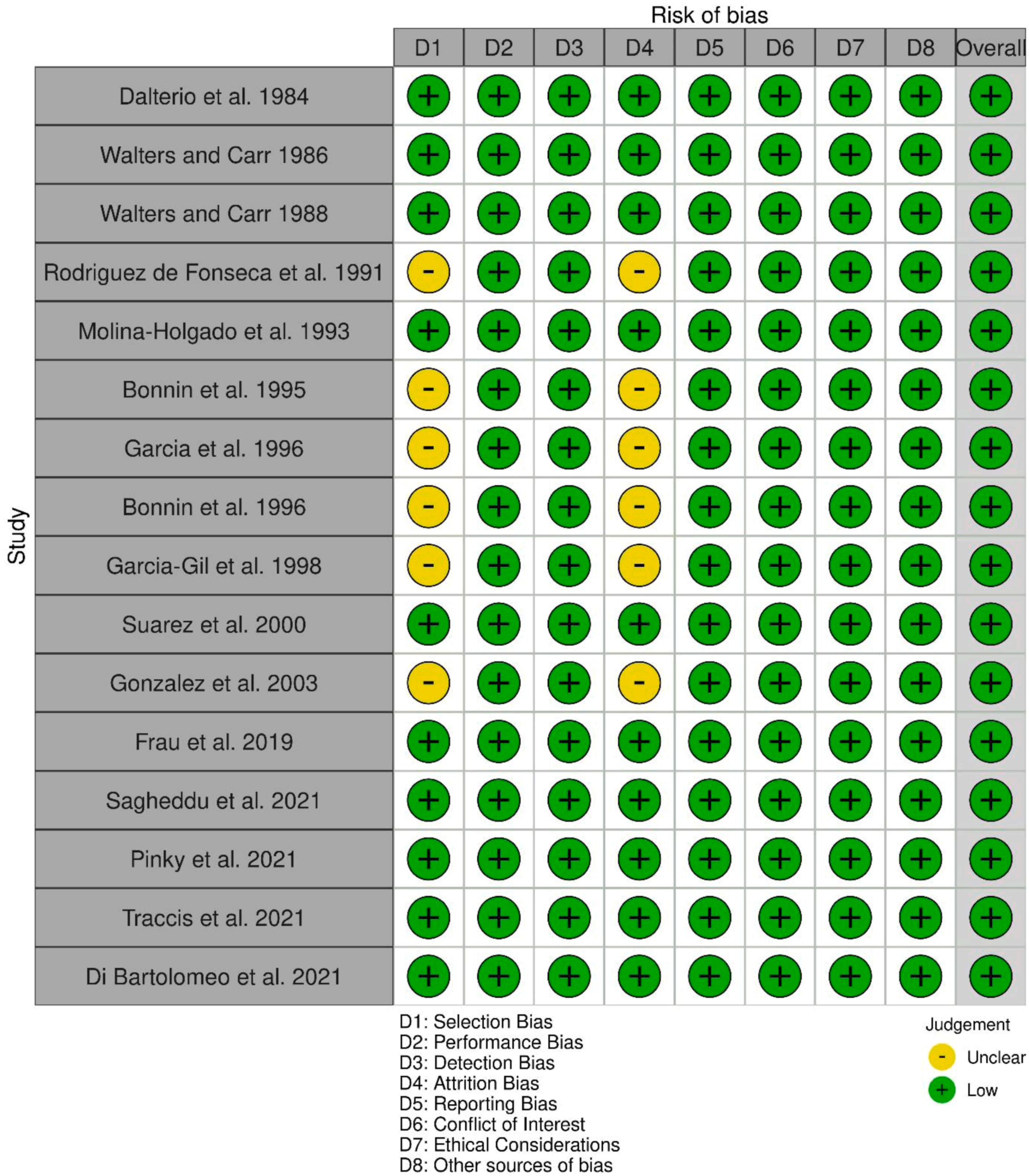

Fig. 3. Analyzing bias risks in animal studies on cannabinoid effects on the monoamine system during pregnancy. Traffic light plot showing the results of generic assessments generated using RobVis with the Cochrane colors palette.

impacts. This attests to the methodological and ethical rigor of research in this field and indicates that our findings can contribute meaningfully to the understanding of cannabis' prenatal effects.

3.2. Pharmacological effects of prenatal cannabis exposure on human monoaminergic system

Despite the scarcity of research in this field, which is heavily influenced by bioethical considerations concerning research on pregnant women (Lyerly, 2022), four pivotal studies have collectively shed light on the intricate relationship between prenatal cannabis exposure and neurodevelopmental outcomes, with a particular emphasis on dopamine within the broader MAS. Table 2 summarizes the principal findings from human studies on cannabis use during pregnancy. Mirochnick *et al.* conducted a comprehensive examination of neurotransmitter dynamics, highlighting a significant association between maternal marijuana use and elevated plasma norepinephrine levels in infants (Mirochnick et al., 1997). Infants exposed to both cocaine and marijuana had higher plasma norepinephrine levels (1164 pg/mL) than those exposed solely to cocaine (812 pg/mL) or neither substance (667 pg/mL). These findings remained robust even after careful adjustment for potential confounders. Moving from the systemic level to the neural, Wang *et al.* explored the impact of maternal marijuana use on gene expression in the fetal brain, revealing distinct changes in D2 mRNA expression in the amygdala basal nucleus that were particularly pronounced in male fetuses (Wang et al., 2004). Groundbreaking work by DiNieri *et al.* underscored the prenatal period's sensitivity to environmental influences, revealing the downregulation of dopamine receptor D2

Table 2
Key findings on cannabis use during pregnancy from human studies.

Authors	Study Design & Participants	Exposure & Methodology	Main Findings
(Mirochnick et al. 1997)	Cross-sectional study, newborns	Analyzing norepinephrine plasma levels within 24–72 hours postpartum in infants exposed to prenatal cocaine and marijuana.	Exposure to cocaine and marijuana during pregnancy led to heightened plasma norepinephrine levels in newborns when compared to those not exposed. Infants exposed to both substances exhibited the highest NE levels together with distinct behavioural changes.
(Wang et al. 2004)	Cross-sectional study, fetal brains	Examining in utero marijuana exposure in relation to the expression of CB1, D1, and D2 receptors in key brain regions, including the striatum, amygdala, and hippocampus.	Prenatal marijuana exposure may impair mesocorticolimbic neural systems involved in regulating emotional behavior. Male fetuses exposed to cannabis showed reduced D2 mRNA expression in the amygdala. Notably, specific gene alterations were observed in distinct brain regions.
(DiNieri et al. 2011)	Animal study (rats) and human subjects	Impact of prenatal cannabis exposure on mRNA expression of dopamine receptor D2 (DRD2) in the ventral striatum.	Prenatal cannabis exposure resulted in reduced DRD2 mRNA expression in the human ventral striatum. Additionally, enduring epigenetic alterations in DRD2 were observed, suggesting a potential connection to addiction and psychiatric disorders.
(Fransquet, Hutchinson et al. 2017)	Longitudinal study, neonates	Assessing the impact of extensive first-trimester cannabis use on neonates, with a specific focus on DRD4 promoter DNA methylation and its association with ADHD.	Maternal cannabis use during pregnancy led to specific DNA methylation changes in infant DRD4 promoter CpG sites. However, these associations did not remain significant after correcting for multiple testing, leaving broader links between prenatal substance use and infant DRD4 methylation inconclusive.

(DRD2) mRNA expression in the ventral striatum, a crucial brain reward center. Importantly, this work also showed that prenatal THC exposure induced epigenetic changes in the *Drd2* gene, ultimately influencing adult behavior (DiNieri et al., 2011). Lastly, Fransquet et al., 2017 ventured into the epigenetic realm, uncovering distinct DNA methylation patterns within the DRD4 promoter region in neonates exposed to maternal cannabis use. Collectively, these four seminal studies provide profound insights into the effects of prenatal cannabis exposure on neurodevelopment, particularly within the MAS, which plays a key role in shaping neural processes during this critical period (Fransquet et al., 2017).

4. Discussion

Regulation of the MAS plays a pivotal role in maintaining cognitive integrity, and prenatal disruptions of this system are linked to profound long-term sequelae (Suri et al., 2015). This review sought to elucidate the direct impacts of cannabis use in pregnancy on the MAS in the fetoplacental unit, a critical yet underexplored facet of perinatal toxicology. Extensive research over the years has produced considerable knowledge about how cannabinoids disturb the delicate equilibrium of neurotransmitters, thereby influencing hormonal cascades and subsequently affecting behavioral characteristics (Augustin and Lovinger, 2022). By summarizing and synthesizing results derived from animal and human model studies, this systematic review has shed light on the current state of knowledge about the relationship between prenatal cannabis exposure and the MAS in the fetoplacental unit, providing valuable insights into the neurodevelopmental implications of such exposure. Importantly, our analysis revealed a notable research gap: there have been no direct investigations into the effects of cannabis on the placental MAS.

The review also revealed two methodological limitations of existing research on prenatal cannabis exposure and its effects on the MAS, namely the heavy use of uniform dosages and a reliance on administration methods that may not reflect those used during recreational drug consumption. Both the tested dosage ranges and the route of administration can profoundly affect the results obtained in pharmacological research. Many of the included studies used uniform dosages, which is beneficial for regulatory compliance and facilitating comparative analysis but may inadvertently limit the scope of cannabinoid research. In particular, given that cannabis has a high lethal dose (LD50) and very variable consumption patterns, an emphasis on lower dosages in research raises the possibility that the full pharmacological range of cannabinoid exposure may not be adequately studied. The heavy use of uniform dosages may reflect an indirect influence of regulatory frameworks on scientific exploration. Given the biphasic dose-response nature of cannabinoids (Calabrese and Rubio-Casillas, 2018, Hodges et al., 2020, Kitdumrongthum and Trachootham, 2023), it is imperative to broaden the spectrum of investigation to fully understand their pharmacological impact.

The route by which a drug is administered can also profoundly affect its pharmacokinetics and body disposition. Although smoking is the most common consumption method, its underrepresentation in the selected studies highlights a disconnect between research settings and real-world practices. The bioavailability of cannabis when smoked ranges from 30 % to 50 %, which is significantly higher than the 6–20 % achieved through oral administration, a disparity primarily due to differences in absorption and the effects of first-pass metabolism (Huestis, 2007). In contrast, while not typically used by consumers, intravenous, intraperitoneal, and subcutaneous routes are frequently utilized in pharmacological studies, offering valuable insights. Intravenous administration provides minimal variability between individuals and a rapid post-administration concentration decline (Englund et al., 2012), while the subcutaneous route is chosen for its slow and sustained release (Kim et al., 2017). However, neither method mirrors the typical consumption patterns of cannabis users, indicating a misalignment between research methods and real-world usage.

Investigations using animal models have predominantly explored the effects of cannabis on dopamine levels during gestation, with effects on serotonin receiving less attention. This trend is mirrored in human studies: all four articles that satisfied the review's stringent selection criteria examined cannabis' influence on catecholamine metabolism, with particular emphasis on dopamine. A thorough analysis of publications listed in PubMed confirmed this tendency, revealing that dopamine has received much more attention than serotonin across many fields of biomedical research in both animal and human studies. The journey of dopamine, from its recognition as a neurotransmitter in the early 20th century to the pivotal moment of its chemical structure's elucidation in the 1950s, has significantly shaped the direction of these studies (Costa and Schoenbaum, 2022). Moreover, the development of advanced research tools and its evident clinical relevance, especially in motor function and neurological disorders such as Parkinson's disease, has propelled it into the scientific limelight (Marsden, 2006). In contrast, serotonin's role as a neurotransmitter was recognized much later, in the mid-20th century (Whitaker-Azmitia, 1999), and a paucity of research tools together with its initial characterization as a primarily peripheral hormone regulating gut function delayed exploration of its effects in the central nervous system (Banskota et al., 2019).

In the second half of the 20th century, THC held a central role in biomedical cannabis research, leading to extensive characterization of its impact on behavior at the expense of research on other cannabinoids. However, a notable shift occurred in recent years, especially in 2021: a thorough PubMed search for this year revealed that the number of publications focusing on CBD research (1004 reports) surpassed that for THC (825 reports). This significant change indicates evolving research priorities and a growing recognition of CBD's potential health benefits and greatly reduced psychoactivity when compared to THC.

Research using animal models has clarified the effects of cannabis use during pregnancy, demonstrating that cannabinoid exposure can disrupt pituitary-gonadal feedback mechanisms and thus potentially cause hormonal imbalances. THC has a unique profile in this respect, having only a limited impact on neurotransmitter levels and inducing diverse responses that depend on the timing and context of exposure (Halbout et al., 2023). This complexity is partly due to the interplay between stress-induced alterations and the impact of THC on dopamine levels (Bloomfield et al., 2016), which implies nuanced interconnections between prenatal exposure and stress-related mechanisms. While there has been little research on the effects of prenatal cannabis exposure on the MAS in humans, the literature offers some valuable insights. In particular, newborns exposed to marijuana exhibited elevated norepinephrine levels, which indicates a potential modulation of sympathetic tone and highlights the importance of adequate levels of norepinephrine for proper brain function maturation (Wang et al., 2015).

Studies on cannabinoid and dopamine receptor expression have uncovered complex neural circuits affecting emotional regulation. For example, results obtained using a model of mesencephalic dopaminergic neurons indicated that persistent reductions in dopamine receptor D2 mRNA expression, which can be induced by cannabis exposure, may signify long-term epigenetic changes (Brami-Cherrier et al., 2014). This finding is consistent with results from animal studies. There have also been many important discoveries relating specifically to the impact of prenatal cannabis exposure. However, despite the increasing use of cannabis among pregnant women, little evidence exists regarding its safety, particularly during pregnancy and lactation (Lo et al., 2022). Numerous reports have established a connection between prenatal cannabis use and adverse outcomes, including epigenetic changes, abnormal gene regulation, persistent health conditions, behavioral disruptions, and psychiatric disorders (Olyaei et al., 2022). Unfortunately, only a few studies analyzed in this review have explored the potential link between MAS modulation during pregnancy and the potential development of chronic ailments in adulthood as described by the DOHaD theory.

The integration of findings from human and animal studies has revealed concerning evidence of cannabinoid-induced perturbations in the MAS, with significant implications for the fetoplacental unit. There is thus a clear need for effective strategies to mitigate these risks and protect the neurodevelopmental process. It will also be important to thoroughly characterize the complex interactions between cannabinoids and the MAS during prenatal development; these interactions are crucial determinants of several processes whose disruption poses risks to the fetoplacental unit including hormonal regulation, neural network formation, and behavioral patterns. The observed variability in responses across different species, developmental stages, and genetic backgrounds further illustrates the complexity of these effects and necessitates carefully nuanced interpretation of data in this area.

Our exhaustive literature search revealed a conspicuous absence of studies on the placenta's vulnerability to cannabis exposure, highlighting a critical gap in our current understanding of cannabis-related risks. This indicates a need for targeted research to decipher the nuanced interplay between cannabis exposure and placental function, which will be essential for informing public health strategies and mitigating potential developmental toxicities. The roles of the MAS in the brain are well-documented, but its significance in the placenta and implications for fetal development have received less attention. However, recent experimental studies by several groups, including ours, have unveiled the pivotal role of the MAS in the placenta, showing that it plays a vital role in regulating serotonin and tryptophan levels to meet the needs of fetal development (Bonnin et al., 2011, Karahoda et al., 2020, Staud et al., 2023). Additionally, our most recent findings indicate that CBD modulates tryptophan catabolism pathways in the placenta, influencing serotonin homeostasis and the balance between neurotoxic and neuroprotective metabolites (Portillo et al., 2024). Given the rising prevalence of cannabis use among pregnant women and the crucial role of the MAS in the fetoplacental unit and fetal programming, it is imperative to understand the interactions between cannabis and MAS in the placenta.

Future research should examine the long-term effects of prenatal cannabinoid exposure on the MAS and the fetoplacental unit in adolescence and adulthood. It would also be very desirable to investigate strategies for addressing and potentially reversing the adverse effects of cannabinoids on the MAS. Such research will significantly deepen our understanding of the long-term implications of prenatal cannabis exposure in the fetoplacental unit but will require a comprehensive and multi-disciplinary approach. The results of these investigations may facilitate the development of effective measures to counteract the adverse effects of cannabis exposure during pregnancy, thereby safeguarding the health and integrity of the fetoplacental unit and its neurodevelopmental processes.

5. Conclusion

This systematic review reveals the profound effects of prenatal cannabis exposure on the monoamine system, emphasizing significant disruptions in neurotransmitter regulation, receptor dynamics, and neurodevelopmental processes. Animal studies consistently demonstrate sex-specific vulnerabilities, with male offspring showing heightened sensitivity to dopaminergic perturbations. On the other hand, human research provides evidence of epigenetic modifications and altered neurotransmitter activity, though constrained by ethical and methodological challenges. A striking research gap was identified: the lack of studies investigating the effects of cannabinoids on the placental MAS, a critical interface in fetal neurochemical regulation. This omission leaves unanswered questions about how placental mechanisms mediate or exacerbate the impacts of cannabis on fetal development. Furthermore, the reliance on standardized dosages and administration routes that do not reflect real-world consumption practices underscores the need for refined experimental designs that capture the complexity of maternal cannabis use. Addressing these gaps is imperative as cannabis use during pregnancy becomes increasingly prevalent. Future research must prioritize elucidating the placental MAS's role in mediating fetal exposure and explore strategies to mitigate potential harm. These efforts will provide the scientific foundation necessary for informed public health policies and clinical guidelines to protect maternal and fetal well-being in an evolving landscape of cannabis accessibility.

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CRediT authorship contribution statement

Staud Frantisek: Writing – review & editing, Supervision, Funding acquisition, Formal analysis, Conceptualization. **Synova Tetiana:** Writing – original draft, Investigation, Conceptualization. **Portillo Ramon:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Data curation, Conceptualization.

Declaration of Competing Interest

The authors have nothing to declare.

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