UNIVERSITI PUTRA MALAYSIA

FISH OIL ANTIDEPRESSANT-LIKE EFFECTS ON INFLAMMATION AND SEROTONERGIC SYSTEM IN POSTPARTUM DEPRESSION RAT MODEL

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By

NURUL UYUN BINTI ABD AZIZ

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for the Degree of Doctor of Philosophy

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Chair : Mohamad Taufik Hidayat Baharuldin, PhD
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The pathophysiology of postpartum depression (PPD) was not well understood. Some studies however managed to strengthen the link between PPD with inflammation and neurochemistry alteration. PPD animals showed increased levels of pro-inflammatory cytokines and alleviated levels of neurotransmitter in brain. Fish oil supplementation reported to decrease the pro-inflammatory cytokines and increase brain neurotransmitter in many depression models of animals including PPD animal model. Fish oil intake reduced depression symptoms by modulating on the serotonergic neurotransmitter (serotonin) and regulation of inflammasome NLRP3 complex. Thus, it was postulated that antidepressant-like effects of fish oil in PPD animal model was influenced by serotonin modulation and NLRP3 inflammasome inhibition. The recent study designed the experiment into two batches (batch A (BA); investigated the effects of 10 days fish oil in PPD rats involvement with NLRP3 complex) and batch B (BB); investigated the effects of 10 days fish oil in PPD rats with the alteration of serotonin (5HT) concentration. The rats were induced to PPD model using hormone simulated pregnancy withdrawal (HSPW) regime for 23 days. The day after 23 days of induction was considered as PPD day 1. All supplements were given for 10 days consecutively. On day 2 and day 10 PPD, force swimming test (FST) and open field test (OFT) were conducted. Rats were sacrificed and brain tissue was collected for serotonin (5HT), histological and inflammasome NLRP3-dependent pro-inflammatory IL-1β analysis. Statistical analysis was evaluated using one-way analysis of variance (ANOVA) followed by the post hoc Tukey's multiple comparison test with $p<0.05$ was considered significant. The histological change has been observed using hematoxylin & eosin staining. The results showed that PPD rats without fish oil or fluoxetine showed increased immobility time in FST, NFκB/NLRP3/caspase-1/IL-1β cascade concentration, 5HIAA and 5HT turnover. Supplementation of fish oil or fluoxetine in PPD rats managed to ameliorate the effects of PPD in rats' hippocampus and PFC. However, the histological findings did not show any significant difference among groups. The

PCPA and WAY100135 challenged in PPD rats managed to prevent significant decreased of immobility time in PPD rats with fish oil compared to PPD rats with fish oil without PCPA and WAY100135 injection. It showed that 5HT alteration influenced the antidepressant-like effects of fish oil. Therefore, as a conclusion, the antidepressant-like effects of fish oil in PPD rats given for 10 days were influenced by the modulation of inflammation and serotonergic system.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk Ijazah Doktor Falsafah

KESAN ANTI-KEMURUNGAN MINYAK IKAN KE ATAS KERADANGAN DAN SISTEM SEROTONERGIK KEPADA MODEL TIKUS KEMURUNGAN POSTPARTUM

Oleh

NURUL UYUN BINTI ABDUL AZIZ

Januari 2020

Pengerusi : Mohamad Taufik Hidayat Baharuldin, PhD
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Patofisiologi bagi kemurungan postpartum (PPD) tidak difahami sepenuhnya. Beberapa kajian walau bagaimanapun berjaya mengaitkan PPD dengan inflamasi dan perubahan neurokimia. Haiwan PPD menunjukkan peningkatan paras sitokine pro-inflamasi dan merendahkan paras neurotransmiter di dalam otak. Suplementasi minyak ikan dilaporkan mampu mengurangkan sitokin pro-inflamasi dan meningkatkan neurotransmiter otak dalam banyak model kemurungan haiwan termasuklah model haiwan PPD. Pengambilan minyak ikan dapat mengurangkan gejala kemurungan dengan mengubahsuai neurotransmiter serotonergik (serotonin) dan regulasi komplek inflammasome NLRP3. Oleh itu, ia telah diandaikan bahawa kesan antidepresan minyak ikan kepada model haiwan PPD dipengaruhi oleh modulasi serotonin dan perencatan komplek inflammasome NLRP3. Kajian terkini ini mengubah reka bentuk eksperimen kepada 2 kelompok (kelompok A (BA) ; mengkaji kesan 10 hari minyak ikan ke atas tikus PPD dengan penglibatan komplek NLRP3) dan kelompok B (BB); mengkaji kesan 10 hari minyak ikan ke atas tikus PPD dengan pemindaan kepekatan serotonin (5HT). Semua tikus diaruhinduksi dengan model PPD menggunakan aruhan pengunduran hormone bagi kehamilan (HSPW) selama 23 hari. Hari yang selepas hari 23 induksi dianggap sebagai hari 1 PPD. Semua supplemen diberikan selama 10 hari berturut-turut. Pada hari ke 2 dan 10 PPD, ujian paksa renang (FST) and ujian lapangan terbuka (OFT) telah dijalankan. Tikus dikorbankan dan tisu otak telah dikumpul untuk ujian analisis serotonin (5HT), histologi and pro-inflamasi IL-1β yang bergantung kepada inflammasome NLRP3. Analisa statistik dibuat menggunakan menggunakan analisis varian satu hala (ANOVA) diikuti dengan ujian perbandingan pelbagai Tukey post hoc dengan nilai $p<0.05$ dianggap signifikan. Perubahan histologi dilihat menggunakan pewarnaan hematoxylin & eosin. Keputusan tikus PPD tanpa minyak ikan ataupun fluoxetine menunjukkan peningkatan masa immobilisasi dalam ujian FST, kepekatan lata NFκB/NLRP3/caspase-1/IL-1β, 5HIAA and perolehan 5HT. Supplementasi

minyak ikan atau fluoxetine di tikus PPD rats berjaya memperbaiki kesan PPD bagi hippocampus and PFC tikus. Walaubagaimanapun kajian histologi tidak menunjukkan perubahan yang signifikan. Pemberian PCPA dan WAY100135 kepada tikus PPD berjaya menghindari penurunan signifikan masa immobilisasi tikus PPD yang diberi minyak ikan apabila dibandingkan dengan tikus PPD yang tidak disuntik dengan PCPA dan WAY100135. Ini menunjukkan alterasi 5HT mempengaruhi kesan antidepresan minyak ikan. Oleh itu, sebagai kesimpulan, kesan antidepresan minyak ikan terhadap tikus PPD selama 10 hari dipengaruhi oleh modulasi inflamasi dan sistem serotonergikAbstrak merupakan ringkasan keseluruhan tesis dan wajib diberi perhatian rapi sepertimana bahagian tesis yang lain.

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LIST OF ABBREVIATIONS

UPM	Universiti Putra Malaysia
MDD	Major depressive disorder
PPD	Postpartum depression
HSPW	Hormone simulated pregnancy withdrawal model
FST	Force swim test
OFT	Open field test
EPM	Elevated plus maze test
5HT	Serotonin neurotransmitter, 5-hydroxytryptamine
SSRIs	Selective serotonin reuptake inhibitors
CUMS	Chronic unpredictable mild stress
FLX	Fluoxetine
FO	Fish Oil
5-HT1A	Serotonin 1A receptor
SERT	Serotonin transporter
NLRP3	Nod-like receptor family pyrin domain containing 3
NLR	Nod-like receptor
ASC	Adaptor apoptosis-associated speck-like protein
IL-1β	Interleukin 1-β
Nf-κB	Nuclear factor kappa B
DHA	Docosahexaenoic acid
EPA	Eicosapentaenoic acid
BDNF	Brain-derived neurotrophic factor
5HIAA	5-hydroxyindolacetic acid
PFC	Prefrontal cortex
H&E	Hematoxylin & eosin
WHO	World Health Organization
IL-16	Interleukin 6
TRP	Tryptophan
TPOH	Enzyme tryptophan hydroxylase
MAO	Enzyme monoamine oxidase
HPA	hypothalamic-pituitary-adrenal axis
GR	Glucocorticoid receptor
DNA	Deoxyribonucleic acid
CAM	Complimentary and alternatives medicine
ALA	α-linolenic acid
AHA	American Heart Association
H	hours
±	Plus minus

PM	Post meridiem (after midday)
OVX	Ovariectomized
USA	United State of America
PBS	Phosphate buffer saline
°C	Degree celcius
g	Gram
ELISA	Enzyme-linked immunosorbent assay
cm	Centimeter
%	Percentages
ng/mL	Nanogram per mililitres
pg/mL	Pikogram per mililitres
UPM	Universiti Putra Malaysia

CHAPTER 1

INTRODUCTION

1.1 Introduction

Depression is increasingly recognised as a serious, worldwide public health concern. It is associated with emotions instability and the symptoms of negative though, behavioural changes as well as lack of motivation. Depression influences 300 million people and making it a leading cause of disability worldwide (World Health Organization, 2017). The screening of depression among children and adult including postpartum women has been recommended in some developed countries as it is costly regarding health care allocation and management (Maurer, Raymond & Davis., 2018). The most familiar problems regarding on depression that occur in women after birth is postpartum depression (PPD) which could affect 10-20% women (Pawluski, Lonstein & Fleming, 2017). PPD women often suffers from anhedonia, dysphoria, hopelessness, anxiety and sleep disturbances. In worse cases, PPD leads to increase risk of suicide and infanticide (Trujillo et al., 2018). The symptoms seen in PPD women are more likely apparent in major depressive disorder (MDD). Thus, PPD is considered as among the subtypes of MDD. A very good management is crucial as poor management leads to interference of a good life of postpartum women such as their relationship with their partners, infants, families and societies (Pawluski et al., 2017).

Development of PPD has been associated with many factors which vary from the status of mental health of the mothers during pregnancy, the status of ovarian hormones level after birth and the status of social interaction of the mothers with families and societies (Palumbo, Mirabella & Gigantesco, 2017) . Among all the above status, the rapid change of ovarian hormones from pregnancy to afterbirth condition has played a significant role in PPD development (Craft et al., 2010). Changes in ovarian hormones concentration during pregnancy to afterbirth condition leads to onset of PPD symptoms. An animal model has been used employing the concept of hormonal changes. Hormone simulated pregnancy withdrawal model (HSPW) is one of the models used in inducing the PPD in rodents. Animal studies applying this concept of reduction of ovarian hormones after birth demonstrated increased risk factors in PPD (Arbabi, Baharuldin, Moklas, Fakurazi, & Muhammad 2014, Shukkoor, Saleem, Baharuldin, Jais, Manan, Moklas, & Basir, 2017).

HSPW model showed less antidepressant activity in behavioral test in force swim test (FST). The passive behavior (immobility time) observed during FST was high while the active behavior (swimming and climbing time) was low (Stoffel & Craff.,

2004; Arbabi et al., 2014 & Shukkoor et al., 2017). The HSPW animals also showed increased level of anxiety in open field test (OFT) and elevated plus maze test (EPM) (Suda, Segi-Nishida, Newton, & Duman, 2008). Increased anxiety is one of the features of postpartum depression (Ross, Evans Sellers & Romach, 2003). Increased pro-inflammatory cytokine IL-1β has been seen in HSPW rats (Arbabi et al., 2014). In addition, HSPW model has decreased the level of serotonergic neurotransmitter, serotonin (5HT) as well (Shukkoor et al., 2017).

A key aspect of monoaminergic neurotransmitter impairment in depression is the modulation of serotonin. The issues of serotonin modulation in depression received considerable critical attention where several researchers have reported the involvement of serotonergic neurotransmission serotonin and its receptors in the mechanism of antidepressant drugs. Several attempts have been made to link serotonin receptors as a target for many antidepressant drugs due to its involvement in many diseases such as in depression and anxiety. Serotonergic receptors can be further divided into a few subgroups and the most common serotonin receptor associated with depression is serotonin 1A receptor (5-HT1A). This receptor is responsible in modulating neuronal, glial cells proliferation and maturation (Whitaker-Azmitia, 2001) and the dysfunctional of 5-HT1A receptor can lead to depressive behaviour (Albert, Vahid-Ansari, & Luckhart, 2014; Vahid-Ansar et al., 2017; Cao et al., 2019). Besides, a study with agonist of 5HT1A receptor has managed to show possible antidepressant effects (Kosari-Nasab et al., 2019).

Impaired monoaminergic neurotransmitter and modulation of inflammatory biomarkers in the brain are important components in the PPD, which play a key role in depression (Szewczyk, Kotarska, Siwek, Olech & Kuter, 2017). Although extensive research has been carried out on serotonergic system involvement in depression, fewer studies are available regarding serotonergic neurotransmitter modulation with PPD. Fluoxetine is one example of antidepressant drug from selective serotonin reuptake inhibitors (SSRIs) group used in treating depression and PPD.

Furthermore, in recent years, there has been an increasing interest in bringing together the immune system in depression that potentially improved the therapeutic outcomes (Haapakoski, Ebmeier, Alenius & Kivimaki, 2016). How immune system decreased the risk factors and aetiology of depression are currently debated. Depression is associated with the changes of inflammatory transcriptional factor Nf-κB in brain tissues. It was shown for the first time that inflammasome nod-like receptor family pyrin domain containing 3 (NLRP3), a protein complex consisted of intracellular sensor in cytosol, a nod-like receptor (NLR), an adaptor apoptosis-associated speck-like protein (ASC) and a

precursor of procaspase-1 potentially involved in the modulation of neuroinflammation regarding on depression (Zhang et al., 2015).

The pathophysiology mechanism of inflammasome complex NLRP3 is related to high level of pro-inflammatory cytokines production, which is interleukin 1-β (IL-1β). The protein inflammasome complex helps in IL-1β production by assisting the maturation and cleavage of pro-IL-1β to mature IL-1β. Increased of IL-1β level in blood and brain tissues pro-inflammatory has increased the risk factors in depression development (Leonard, 2018). It is suggested that inflammasome complex NLRP3 has become a new target for therapeutic intervention of depression (Bhattacharya & Jones, 2018). Modulation of NLRP3 complex associated with modulation of IL-1β concentration and maybe useful in therapeutic modulation of depression. However, association between NLRP3 and IL-1β in PPD is not well studied. Therefore, the study on relationship of inflammation and depression could bring a new hope in treating depression.

PPD women are reluctant to seek for medicinal helps and consume anti-depressant drugs. They believed that the anti-depressant drugs gave bad side effects to the infants as it can be transferred to the infants through breastfeeding. Therefore, the supplementation of alternatives medicine is warranted and preferable. Fish oil is one of the popular alternatives supplementation given to postpartum mothers. Supplementation of fish oil is recommended as a preventive measure instead of as a treatment itself (Ellulu et al., 2015). However, the antidepressant-like study on fish oil, which is enriched with omega-3 fatty acids, is still controversial as there are less reports that could define the site of action for omega-3 fatty acids in treating depression especially in postpartum-induces model (dos Santos Vaz et al., 2017). Fish oil possesses good anti-inflammatory properties and can potentially decrease the risk factors of depression. Previous studies indicated the therapeutic potential of fish oil ingestion in many diseases such heart disease, depression and anxiety (Siscovick et al., 2017; Parletta et al., 2019).

Fish oil is rich in omega-3 fatty acids. Omega-3 fatty acids are mostly consumed through fish oil supplementation and diet. Omega-3 fatty acids, which have many benefits towards health can be found numerously in marine life such as in seafood, fishes and algae in a form of long-chain fatty acids: docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). A study by Laino et al. (2010) showed a potential benefit of fish oil in treating depression especially in patients with depression resistance to conventional treatment by combining the therapeutic approaches of current antidepressant with omega-3 fatty acids (Laino, Fonseca, Sterin-Speziale, Slobodianik, & Reinés, 2010). Beydoun et al. (2013) study that based on Epidemiologic Studies-Depression scale indicated

the relationship between the high intakes of omega-3 fatty acids with low risk of elevated depressive symptoms.

It is shown that antidepressant-like effect of fish oil is associated with serotonergic system together with the activation of serotonin receptor, 5HT1A (Vines et al., 2012). Post synaptic receptor of 5HT1A in hippocampus is involved with its antidepressant-like effects (Carabelli et al. 2015). Fish oil supplementation also potentially reduced peripheral pro-inflammatory cytokines (Borsini et al. 2017). Fish oil has been observed to modulate central inflammation and activation of serotonin receptors and neurotransmitter (Carabelli et al., 2015). The neuroprotective effects of fish oil have been seen in bulbectomy rat's model. The ingestion of fish oil had increased hippocampal brain-derived neurotrophic factor (BDNF) and 5-HT, which are the two major regulators of neuronal survival and long-term plasticity in brain structure in bulbectomy rats (Pudel et al. 2014). In PPD animal models, supplementation of fish oil decreased the immobility time in FST indicating its antidepressant-like effects (Arbabi et al., 2014). In other study, the potential benefits of fish oil in controlling or modulating inflammation-associated depression has been demonstrated (Shi et al., 2017).

To obtain therapeutic approaches regarding diseases involving neurology, fish oil was studied on several factors such as its anti-inflammatory effects, antioxidant effects and also neurotropic processes (Jia, Heng, Yang & Gao, 2014; Shi et al., 2015). In addition, it was observed that the benefits of fish oil regarding on mood disorders are influenced by serotonergic system as well as kynurenine pathway making fish oil as a promising therapeutic approach in mood disorders (de Gomes et al., 2018).

Thus, this study attempts to show the possible mechanisms of action of fish oil antidepressant-like effects in PPD rats. The aims of this study project are focused on trying and establishing what serotonergic neurotransmitter and NLRP3 inflammasome complex did in PPD rats regarding fish oil supplementation. The investigation was focused on antidepressant-like effects fish oil supplementation for 10 days in HSPW model (Figure 1.1) with the involvement of serotonergic neurotransmitter, 5HT, its metabolites, 5-hydroxyindolacetic acid (5HIAA) and its turnover rate (5-HIAA/5-HT) as well as inflammasome NLRP3 cascade that are responsible for IL-1β pro-inflammatory production in prefrontal cortex (PFC) and hippocampus. The antidepressant-like effects of fish oil supplementation have been observed in FST, a standard model test used in the antidepressant screening. Neurochemical analysis involved measurement of 5HT, 5HIAA and 5HT turnover as well as IL-1β dependent NLRP3 inflammasome cascade (NfκB/NLRP3/caspase-1/IL-1β) in both PFC and hippocampus. In addition, the brain tissue PFC and hippocampus were collected for light histological analysis using hematoxylin & eosin staining (H&E). This

study helps in providing a detailed understanding on the pathophysiology of fish oil antidepressant-like effects in postpartum depression model in animals.

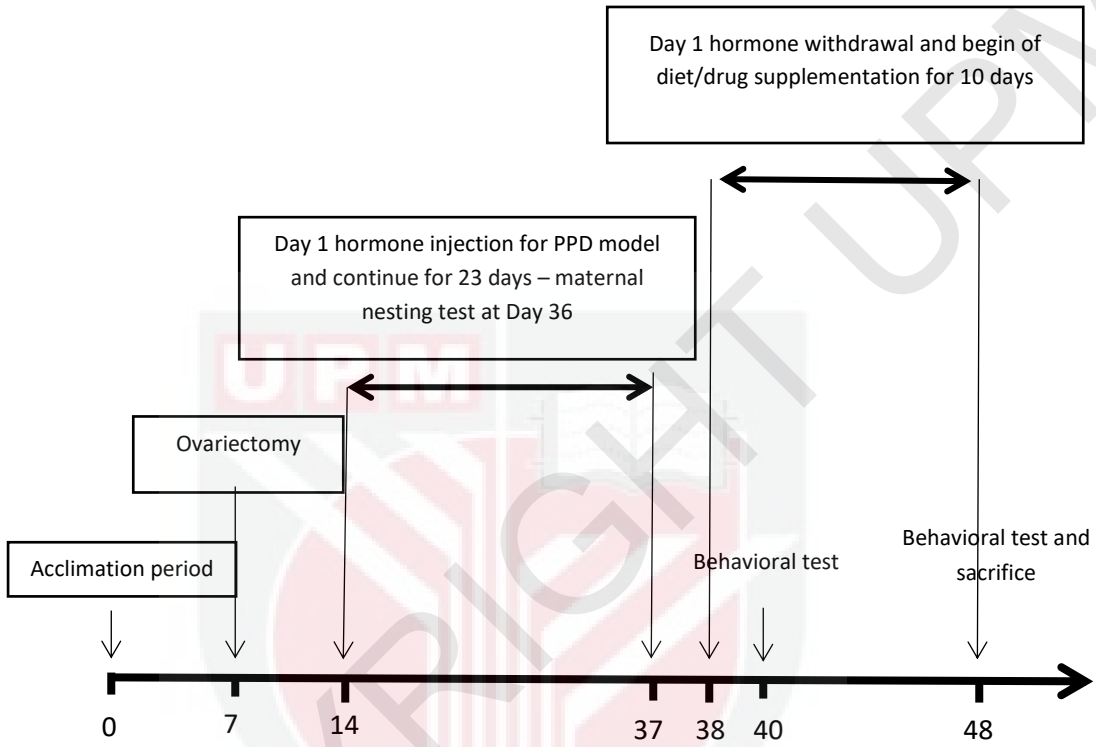

Figure 1.1: Timeline of experiment procedure

Legend: The figure above showed the timeline of the study. Begin at day 0, the rats were acclimatized and followed by ovariectomy. After one week recovery period from ovariectomy, the rats were induced into postpartum depression model at day 14. The induction involved the injection of ovarian hormones for 23 days starting from day 14 until day 38. On day 37, the maternal nesting behavior was conducted to observe for maternal simulated pregnancy period of rat. The rats with positive result of maternal simulated pregnancy period were withdrawn from the ovarian hormone injection on day 38. The postpartum depression period was calculated starting at day 38 until day 48. Treatment with fish oil or fluoxetine was given starting from day 38 until day 48 as well. On day 48 rats were sacrificed and brain tissues were collected for biochemical analysis.

1.2 Problem statement

Pathophysiology of postpartum depression (PPD) is not well understood. PPD was associated with inflammation modulation as well as serotonergic pathways alteration. The supplementation of fish oil, a good anti-inflammatory agent has given the antidepressant-like effects in depression by influencing the serotonin and pro-inflammatory cytokines concentration as well. Fish oil intake has been shown to control the depression risk factors by increase the level of serotonin concentration and decreasing the pro-inflammatory cytokines concentration. However, the result regarding on antidepressant-like effects of fish oil in postpartum depression model with the involvement of serotonergic neurotransmitter and inflammation is not well understood. There was lack of studies investigating on the mechanism of action of fish oil in its antidepressant-like effects in postpartum depression. Thus, this study was conducted to highlight an initial association between ten days administration of fish oil anti-depressant like effects with the involvement of serotonergic neurotransmitter, serotonin and neuroinflammation (NLPR3 complex which controlling the IL-1β pro-inflammatory cytokines production) in postpartum depression rats.

1.3 Hypothesis

1. The antidepressant-like effects of ten days fish oil supplementation in postpartum depression rats' model observe during behavioral force swim test (FST) is influenced the decrease of immobility time and increase of swimming and climbing time.
2. The antidepressant-like effects of ten days fish oil supplementation in postpartum depression rats' model is influence by IL-1β-dependent NLRP3 inflammasome concentration in brain prefrontal cortex (PFC) and hippocampus.
3. The antidepressant-like effects of ten days fish oil supplementation in postpartum depression rats' model is influence by alteration of serotonin concentration in brain prefrontal cortex (PFC) and hippocampus observe in force swim test.
4. The antidepressant-like effects of ten days fish oil supplementation in postpartum depression rats' model is influence by alteration of serotonin receptor 5HT1A observe in force swim test.
5. The antidepressant-like effects of ten days fish oil supplementation in postpartum depression rats' model is influence the histological changes of prefrontal cortex and hippocampus.

1.4 Objectives

1.4.1 General Objective

To investigate the antidepressant-like effects of fish oil in postpartum depression model in rats for ten days administration on modulation of serotonergic neurotransmitter and inflammasome complex NLRP3.

1.4.2 Specific Objectives

1. To determine the antidepressant-like effects of ten days fish oil supplementation in postpartum depression rats' model on behavioral changes during force swim test (FST).
2. To determine the antidepressant-like effects of ten days fish oil supplementation in postpartum depression rats' model on IL-1β-dependent NLRP3 inflammasome cascade concentration in brain prefrontal cortex (PFC) and hippocampus.
3. To determine the antidepressant-like effects of ten days fish oil supplementation in postpartum depression rats' model on behavioral changes during force swim test (FST) involving the alteration of serotonin concentration in prefrontal cortex (PFC) and hippocampus.
4. To determine the antidepressant-like effects of ten days fish oil supplementation in postpartum depression rats' model on behavioral changes during force swim test (FST) involving on serotonin receptor 5HT1A.
5. To observe the antidepressant-like effects of ten days fish oil supplementation in postpartum depression rats' model prefrontal cortex and hippocampus histological changes if any.

REFERENCES

Adinolfi, E., Giuliani, A. L., De Marchi, E., Pegoraro, A., Orioli, E., & Di Virgilio, F. (2018). The P2X7 receptor: a main player in inflammation. *Biochemical pharmacology*, 151, 234-244.

Ahmed, M., & Azmat, A. (2017). Decreased brain serotonin turnover rate following administration of Sharbat-e-Ahmed Shah produces antidepressant and anxiolytic effect in rats. *Metabolic brain disease*, 32(6), 1785-1790.

Aishwarya, S., Rajendiren, S., Kattimani, S., Dhiman, P., Haritha, S., & AnanthaNarayanan, P. H. (2013). Homocysteine and serotonin: Association with postpartum depression. *Asian journal of psychiatry*, 6(6), 473-477.

Albert, P. R., Vahid-Ansari, F., & Luckhart, C. (2014). Serotonin-prefrontal cortical circuitry in anxiety and depression phenotypes: pivotal role of pre-and post-synaptic 5-HT1A receptor expression. *Frontiers in behavioral neuroscience,* 8, 199.

Alboni, S., Van Dijk, R. M., Poggini, S., Milior, G., Perrotta, M., Drenth, T., ... & Cirulli, F. (2017). Fluoxetine effects on molecular, cellular and behavioral endophenotypes of depression are driven by the living environment. *Molecular psychiatry*, *22*(4), 552.

Alwan, S., & Bérard, A. (2019). Epidemiology of the Use of Psychotropic Drugs in Pregnant and Nursing Women. *In Perinatal Psychopharmacology* (pp. 3-16). Springer, Cham.

Arbabi, L., Baharuldin, M. T. H., Moklas, M. A. M., Fakurazi, S., & Muhammad, S. I. (2014). Antidepressant-like effects of omega-3 fatty acids in postpartum model of depression in rats. *Behavioural brain research*, *271*, 65-71.

Ay, F., Tektas, E., Mak, A., & Aktay, N. (2018). Postpartum depression and the factors affecting it: 2000-2017 study results. *Journal of Psychiatric Nursing*, 9(3),147-152.

Bai, Y., Song, L., Dai, G., Xu, M., Zhu, L., Zhang, W., ... & Ju, W. (2018). Antidepressant effects of magnolol in a mouse model of depression induced by chronic corticosterone injection. *Steroids*, *135*, 73-78.

Barnes, L. A., Barclay, L., McCaffery, K., & Aslani, P. (2019). Complementary medicine products information-seeking by pregnant and breastfeeding women in Australia. Midwifery.

Barnes, L. A., Barclay, L., McCaffery, K., & Aslani, P. (2019). Women's health literacy and the complex decision-making process to use complementary medicine products in pregnancy and lactation. *Health Expectations*.

Beydoun, M. A., Fanelli Kuczmarski, M. T., Beydoun, H. A., Hibbeln, J. R., Evans, M. K., & Zonderman, A. B. (2013). ω-3 fatty acid intakes are inversely related to elevated depressive symptoms among United States women. *The Journal of nutrition,* 143(11), 1743-1752.

Bhattacharya, A., & Jones, D. N. (2018). Emerging role of the P2× 7-NRLP3-IL1β pathway in mood disorders. *Psychoneuroendocrinology.* Vol 98, 95-100.

Bloch, M., Daly, R. C., & Rubinow, D. R. (2003). Endocrine factors in the etiology of postpartum depression. *Comprehensive psychiatry*, 44(3), 234-246.

Borsini, A., Alboni, S., Horowitz, M. A., Tojo, L. M., Cannazza, G., Su, K. P., ... & Zunszain, P. A. (2017). Rescue of IL-1β-induced reduction of human neurogenesis by omega-3 fatty acids and antidepressants. *Brain, behavior, and immunity*, 65, 230-238.

Borsonelo, E. C., Suchecki, D., & Galduróz, J. C. F. (2011). Effect of fish oil and coconut fat supplementation on depressive-type behavior and corticosterone levels of prenatally stressed male rats. *Brain research*, 1385, 144-150.

Bortolotto, V. C., Pinheiro, F. C., Araujo, S. M., Poetini, M. R., Bertolazi, B. S., de Paula, M. T., ... & Prigol, M. (2018). Chrysin reverses the depressive-like behavior induced by hypothyroidism in female mice by regulating hippocampal serotonin and dopamine. *European journal of pharmacology*, 822, 78-84.

Brummelte, S., & Galea, L. A. (2016). Postpartum depression: etiology, treatment and consequences for maternal care. *Hormones and behavior*, 77, 153-166.

Cao, K., Shen, C., Yuan, Y., Bai, S., Yang, L., Guo, L., ... & Shi, Y. (2019). SiNiSan ameliorates the depression-like behavior of maternal separation experienced rats through 5-HT1A receptor/CREB/BDNF pathway. *Frontiers in psychiatry,* 10, 160.

Carabelli, B., Delattre, A. M., Pudell, C., Mori, M. A., Suchecki, D., Machado, R. B., ... & Lima, M. M. (2015). The antidepressant-like effect of fish oil: possible role of ventral hippocampal 5-HT1A post-synaptic receptor. *Molecular neurobiology*, *52*(1), 206-215.

Carvalho, A. F., Sharma, M. S., Brunoni, A. R., Vieta, E., & Fava, G. A. (2016). The safety, tolerability and risks associated with the use of newer generation antidepressant drugs: a critical review of the literature. *Psychotherapy and psychosomatics*, 85(5), 270-288.

Cassidy-Bushrow, A. E., Peters, R. M., Johnson, D. A., & Templin, T. N. (2012). Association of depressive symptoms with inflammatory biomarkers among pregnant African-American women. *Journal of reproductive immunology*, 94(2), 202-209.

Ceulemans, M., Lupattelli, A., Nordeng, H., Odalovic, M., Twigg, M., & Foulon, V. (2019). Women's Beliefs About Medicines and Adherence to Pharmacotherapy in Pregnancy: Opportunities for Community Pharmacists. *Current pharmaceutical design*, 25(5), 469-482.

Charnay, Y., & Léger, L. (2010). Brain serotonergic circuitries. *Dialogues in clinical neuroscience*, 12(4), 471.

Chen, J., Cross, W. M., Plummer, V., Lam, L., & Tang, S. (2018). A systematic review of prevalence and risk factors of postpartum depression in Chinese immigrant women. *Women and Birth*, 32(6),487-492.

Craft, R. M., Kostick, M. L., Rogers, J. A., White, C. L., & Tsutsui, K. T. (2010). Forced swim test behavior in postpartum rats. *Pharmacology Biochemistry and Behavior*, *96*(4), 402-412.

Cryan, J. F., Valentino, R. J., & Lucki, I. (2005). Assessing substrates underlying the behavioral effects of antidepressants using the modified rat forced swimming test. *Neuroscience & Biobehavioral Reviews*, 29(4-5), 547-569.

Corwin, E. J., Johnston, N., & Pugh, L. (2008). Symptoms of postpartum depression associated with elevated levels of interleukin-1 beta during the first month postpartum. *Biological research for nursing*, 10(2), 128-133.

Dang, R., Zhou, X., Tang, M., Xu, P., Gong, X., Liu, Y., ... & Jiang, P. (2018). Fish oil supplementation attenuates neuroinflammation and alleviates depressive-like behavior in rats submitted to repeated lipopolysaccharide. *European journal of nutrition*, *57*(3), 893-906.

De Boer, A. A., Monk, J. M., Liddle, D. M., Hutchinson, A. L., Power, K. A., Ma, D. W., & Robinson, L. E. (2016). Fish-oil-derived n-3 polyunsaturated fatty acids reduce NLRP3 inflammasome activity and obesity-related inflammatory cross-talk between adipocytes and CD11b+ macrophages. *The Journal of nutritional biochemistry*, 34, 61-72.

De Gomes, M. G., Souza, L. C., Goes, A. R., Del Fabbro, L., Borges Filho, C., Donato, F., ... & Boeira, S. P. (2018). Fish oil ameliorates sickness behavior induced by lipopolysaccharide in aged mice through the modulation of kynurenine pathway. *The Journal of nutritional biochemistry*, *58*, 37-48.

De Vriese, S. R., Christophe, A. B., & Maes, M. (2003). Lowered serum n-3 polyunsaturated fatty acid (PUFA) levels predict the occurrence of postpartum depression: further evidence that lowered n-PUFAs are related to major depression. *Life sciences*, 73(25), 3181-3187.

Demir, S., Atli, A., Bulut, M., İbiloğlu, A. O., Güneş, M., Kaya, M. C., ... & Sır, A. (2015). Neutrophil–lymphocyte ratio in patients with major depressive disorder undergoing no pharmacological therapy. *Neuropsychiatric disease and treatment*, *11*, 2253.

Demircan, F., Gözel, N., Kılınç, F., Ulu, R., & Atmaca, M. (2016). The impact of red blood cell distribution width and neutrophil/lymphocyte ratio on the diagnosis of major depressive disorder. *Neurology and therapy*, 5(1), 27-33.

Detke MJ, Lucki I (1996). Detection of serotonergic and noradrenergic antidepressants in the rat forced swimming test: the effects of water depth. *Behavioral Brain Research*.73:43–6.

Detke, M. J., Rickels, M., & Lucki, I. (1995). Active behaviors in the rat forced swimming test differentially produced by serotonergic and noradrenergic antidepressants. *Psychopharmacology,* 121(1), 66-72.

Diamantopoulou, A., Kalpachidou, T., Aspiotis, G., Gampierakis, I., Stylianopoulou, F., & Stamatakis, A. (2018). An early experience of mild adversity involving temporary denial of maternal contact affects the serotonergic system of adult male rats and leads to a depressive-like phenotype and inability to adapt to a chronic social stress. *Physiology & behavior*, 184, 46-54.

Ding, L. C., Gong, Q. Q., Li, S. W., Fu, X. L., Jin, Y. C., Zhang, J., ... & Sun, X. Y. (2017). Rcan2 and estradiol independently regulate body weight in female mice. *Oncotarget*, *8*(29), 48098.

Dos Santos Vaz, J., Farias, D. R., Adegboye, A. R. A., Nardi, A. E., & Kac, G. (2017). Omega-3 supplementation from pregnancy to postpartum to prevent depressive symptoms: a randomized placebo-controlled trial. *BMC pregnancy and childbirth*, *17*(1), 180.

Dos Santos, A. H., Vieira, M. L., de Azevedo Camin, N., Anselmo-Franci, J. A., Ceravolo, G. S., Pelosi, G. G., ... & Gerardin, D. C. C. (2016). In utero and lactational exposure to fluoxetine delays puberty onset in female rats offspring. *Reproductive Toxicology*, 62, 1-8.

Duan, K. M., Ma, J. H., Wang, S. Y., Huang, Z., Zhou, Y., & Yu, H. (2018). The role of tryptophan metabolism in postpartum depression. *Metabolic brain disease*, 33(3), 647-660.

Eckerdal, P., Georgakis, M. K., Kollia, N., Wikström, A. K., Högberg, U., & Skalkidou, A. (2018). Delineating the association between mode of delivery and postpartum depression symptoms: a longitudinal study. *Acta obstetricia et gynecologica Scandinavica*, 97(3), 301-311.

Ellulu, M. S., Khaza'ai, H., Abed, Y., Rahmat, A., Ismail, P., & Ranneh, Y. (2015). Role of fish oil in human health and possible mechanism to reduce the inflammation. *Inflammopharmacology*, 23(2-3), 79-89.

Ekinci, O., & Ekinci, A. (2017). The connections among suicidal behavior, lipid profile and low-grade inflammation in patients with major depressive disorder: a specific relationship with the neutrophil-to-lymphocyte ratio. *Nordic journal of psychiatry*, *71*(8), 574-580.

Fasching, P. A., Faschingbauer, F., Goecke, T. W., Engel, A., Häberle, L., Seifert, A., ... & Kornhuber, J. (2012). Genetic variants in the tryptophan hydroxylase 2 gene (TPH2) and depression during and after pregnancy. *Journal of Psychiatric Research*, 46(9), 1109-1117.

Fernández-Guasti, A., Olivares-Nazario, M., Reyes, R., & Martínez-Mota, L. (2017). Sex and age differences in the antidepressant-like effect of fluoxetine in the forced swim test. *Pharmacology Biochemistry and Behavior*, 152, 81-89.

Foley, E. M., Pourafshar, S., Navaei, N., Akhavan, N. S., George, K. S., & Arjmandi, B. H. (2017). The Effects of Ipriflavone, Isoflavone, and 17b-Estradiol on Body Composition in Hamster Models of Ovariectomy. *The FASEB Journal*, *31*(1 Supplement), 645-17

Freeman, M., Hibbeln, J. R., Wisner, K. L., Brumbach, B. H., Watchman, M., & Gelenberg, A. J. (2006). Randomized dose-ranging pilot trial of omega-3 fatty acids for postpartum depression. *Acta Psychiatrica Scandinavica*, *113*(1), 31-35.

Galea, L.A., Wide, J.K. & Barr, A.M. (2001). Estradiol elleviates depressive-like symptoms in a novel animal model of post-partum depression. *Behavior Brain Research Journal*. 122(1):1-9

Gao, H., Zhu, X., Xi, Y., Li, Q., Shen, Z., & Yang, Y. (2018). Anti-depressant-like effect of atractylenolide I in a mouse model of depression induced by chronic unpredictable mild stress. *Experimental and therapeutic medicine*, 15(2), 1574-1579.

Gemmel, M., Rayen, I., van Donkelaar, E., Loftus, T., Steinbusch, H. W., Kokras, N., ... & Pawluski, J. L. (2016). Gestational stress and fluoxetine treatment differentially affect plasticity, methylation and serotonin levels in the PFC and hippocampus of rat dams. *Neuroscience*, 327, 32-43.

Gentile, S., & Fusco, M. L. (2019). Antidepressants During Breastfeeding. *In Perinatal Psychopharmacology* (pp. 99-113). Springer, Cham.

Giles, G. E., Mahoney, C. R., Urry, H. L., Brunyé, T. T., Taylor, H. A., & Kanarek, R. B. (2015). Omega-3 fatty acids and stress-induced changes to mood and cognition in healthy individuals. *Pharmacology Biochemistry and Behavior*, 132, 10-19.

Godos, J., Castellano, S., Galvano, F., & Grosso, G. (2019). Linking Omega-3 Fatty Acids and Depression. In Omega Fatty Acids in Brain and Neurological Health (pp. 199-212). *Academic Press*.

Gonzales, E., Barrett, D. W., Shumake, J., Gonzalez-Lima, F., & Lane, M. A. (2015). Omega-3 fatty acids improve behavioral coping to stress in multiparous rats. *Behavioural brain research*, 279, 129-138.

Green, A. D., Barr, A. M., & Galea, L. A. (2009). Role of estradiol withdrawal in 'anhedonic'sucrose consumption: a model of postpartum depression. *Physiology & behavior*, 97(2), 259-265.

Haapakoski, R., Ebmeier, K. P., Alenius, H., & Kivimäki, M. (2016). Innate and adaptive immunity in the development of depression: an update on current knowledge and technological advances. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 66, 63-72.

Hibbeln, J. R. (2002). Seafood consumption, the DHA content of mothers' milk and prevalence rates of postpartum depression: a cross-national, ecological analysis. *Journal of affective disorders*, 69(1-3), 15-29.

Hickman, D. L. (2017). Evaluation of the neutrophil: lymphocyte ratio as an indicator of chronic distress in the laboratory mouse. *Lab animal*, 46(7), 303.

Iwasa, T., Matsuzaki, T., Yano, K., & Irahara, M. (2018). The effects of ovariectomy and lifelong high-fat diet consumption on body weight, appetite, and lifespan in female rats. *Hormones and behavior*, *97*, 25-30.

Iwata, M., Ota, K. T., & Duman, R. S. (2013). The inflammasome: pathways linking psychological stress, depression, and systemic illnesses. *Brain, behavior, and immunity*, 31, 105-114.

Ji, E. S., Lee, J. M., Kim, T. W., Kim, Y. M., Kim, Y. S., & Kim, K. (2017). Treadmill exercise ameliorates depressive symptoms through increasing serotonin expression in postpartum depression rats. *Journal of exercise rehabilitation*, *13*(2), 130.

Jia, D., Heng, L. J., Yang, R. H., & Gao, G. D. (2014). Fish oil improves learning impairments of diabetic rats by blocking PI3K/AKT/nuclear factor-κB-mediated inflammatory pathways. *Neuroscience*, 258, 228-237.

Jo, W. K., Zhang, Y., Emrich, H. M., & Dietrich, D. E. (2015). Glia in the cytokine-mediated onset of depression: fine tuning the immune response. *Frontiers in cellular neuroscience*, 9, 268.

Judge, M. P., Beck, C. T., Durham, H., McKelvey, M. M., & Lammi-Keefe, C. J. (2014). Pilot trial evaluating maternal docosahexaenoic acid consumption during pregnancy: Decreased postpartum depressive symptomatology. *International Journal of Nursing Sciences*, 1(4), 339-345.

Kashani, L., Eslatmanesh, S., Saedi, N., Niroomand, N., Ebrahimi, M., Hosseinian, M., ... & Akhondzadeh, S. (2017). Comparison of saffron versus fluoxetine in treatment of mild to moderate postpartum depression: a double-blind, randomized clinical trial. *Pharmacopsychiatry*, *50*(2), 64-68

Kaseva, K., Dobewall, H., Yang, X., PulkkiRaitaki, O.,. (2019). Physical activity, sleep, and symptoms of depression in adults-testing for mediation. *Medicine and science in sports and exercise.* 51 (6), 1162-1168.

Kim, Y. K., Na, K. S., Myint, A. M., & Leonard, B. E. (2016). The role of pro-inflammatory cytokines in neuroinflammation, neurogenesis and the neuroendocrine system in major depression. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 64, 277-284.

Kosari-Nasab, M., Shokouhi, G., Azarfarin, M., Amirkhiz, M. B., Abbasi, M. M., & Salari, A. A. (2019). Serotonin 5-HT1A receptors modulate depression-related symptoms following mild traumatic brain injury in male adult mice. *Metabolic brain disease*, 34(2), 575-582.

Laino, C. H., Fonseca, C., Sterin-Speziale, N., Slobodianik, N., & Reinés, A. (2010). Potentiation of omega-3 fatty acid antidepressant-like effects with low non-antidepressant doses of fluoxetine and mirtazapine. *European journal of pharmacology*, 648(1-3), 117-126.

Leonard, B. E. (2018). Inflammation and depression: a causal or coincidental link to the pathophysiology?. *Acta neuropsychiatrica*, 30(1), 1-16.

Li, X. B., Liu, A., Yang, L., Zhang, K., Wu, Y. M., Zhao, M. G., & Liu, S. B. (2018). Antidepressant-like effects of translocator protein (18 kDa) ligand ZBD-2 in mouse models of postpartum depression. *Molecular brain*, *11*(1), 12.

Li, Y., Pehrson, A. L., Sanchez, C., & Gulinello, M. (2015, May). Effects of Antidepressants in a Rat Model of Co-Morbid Cognitive Deficits and Depression-Like Behavior Induced by Ovariectomy. In *Poster presented at the 168th Annual Meeting of the American Psychiatric Association*.

Liu, C. S., Adibfar, A., Herrmann, N., Gallagher, D., & Lanctôt, K. L. (2016). Evidence for inflammation-associated depression. In *Inflammation-Associated Depression: Evidence, Mechanisms and Implications* (pp. 3-30). Springer, Cham.

Maes, M., Song, C., & Yirmiya, R. (2012). Targeting IL-1 in depression. *Expert opinion on therapeutic targets*, 16(11), 1097-1112.

Mazza, M. G., Lucchi, S., Tringali, A. G. M., Rossetti, A., Botti, E. R., & Clerici, M. (2018). Neutrophil/lymphocyte ratio and platelet/lymphocyte ratio in mood disorders: A meta-analysis. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*. 84, 229-236.

Mazza, M. G., Tringali, A. G. M., Rossetti, A., Botti, R. E., & Clerici, M. (2019). Cross-sectional study of neutrophil-lymphocyte, platelet-lymphocyte and monocyte-lymphocyte ratios in mood disorders. *General hospital psychiatry*, 58, 7-12.

Maurer, D. M., Raymond, T. J., & Davis, B. N. (2018). Depression: Screening and Diagnosis. *American family physician*, *98*(8), 508-515.

Meng, G., Wang, L., Wang, X., Chi, V. T. Q., Zhang, Q., Liu, L., ... & Zhang, S. (2019). Association between neutrophil to lymphocyte ratio and depressive symptoms among Chinese adults: A population study from the TCLSIH cohort study. *Psychoneuroendocrinology*, 103, 76-82.

Ming, L. I., & Shinn-Yi, C. H. O. U. (2016). Modeling postpartum depression in rats: theoretic and methodological issues. *Zoological Research*, *37*(4), 229.

Mosienko, V., Beis, D., Pasqualetti, M., Waider, J., Matthes, S., Qadri, F., ... & Alenina, N. (2015). Life without brain serotonin: reevaluation of serotonin function with mice deficient in brain serotonin synthesis. *Behavioural brain research*, 277, 78-88.

Moses-Kolko, E. L., Wisner, K. L., Price, J. C., Berga, S. L., Drevets, W. C., Hanusa, B. H., ... & Meltzer, C. C. (2008). Serotonin 1A receptor reductions in postpartum depression: a positron emission tomography study. *Fertility and sterility*, 89(3), 685-692.

Naderi, V., Khaksari, M., Abbasi, R., & Maghool, F. (2015). Estrogen provides neuroprotection against brain edema and blood brain barrier disruption through both estrogen receptors α and β following traumatic brain injury. *Iranian journal of basic medical sciences*, 18(2), 138.

Navarre, B. M., Laggart, J. D., & Craft, R. M. (2010). Anhedonia in postpartum rats. *Physiology & behavior*, 99(1), 59-66.

Nishi, D., Su, K. P., Usuda, K., Chang, J. P. C., Hamazaki, K., Ishima, T., ... & Tanigaki, S. (2019). Plasma estradiol levels and antidepressant effects of omega-3 fatty acids in pregnant women. *Brain, behavior, and immunity*. https://doi.org/10.1016/j.bbi.2019.02.014

Osman, N. N., & Bahri, A. I. (2019). Impact of Altered Hormonal and Neurochemical Levels on Depression Symptoms in Women During Pregnancy and Postpartum Period. *Journal of Biochemical Technology*, 10(1).

Özyurt, G., & Binici, N. C. (2018). Increased neutrophil-lymphocyte ratios in depressive adolescents is correlated with the severity of depression. *Psychiatry research*, *268*, 426-431.

Palumbo, G., Mirabella, F., & Gigantesco, A. (2017). Positive screening and risk factors for postpartum depression. *European Psychiatry*, 42, 77-85.

Parletta, N., Zarnowiecki, D., Cho, J., Wilson, A., Bogomolova, S., Villani, A., ... & Segal, L. (2019). A Mediterranean-style dietary intervention supplemented with fish oil improves diet quality and mental health in people with depression: A randomized controlled trial (HELFIMED). *Nutritional neuroscience*, 22(7), 474-487.

Pařízek, A., Mikešová, M., Jirák, R., Hill, M., Koucký, M., Pašková, A., ... & Dušková, M. (2014). Steroid hormones in the development of postpartum depression. *Physiology Research*, 63(Suppl 2), S277-S282.

Pawluski, J. L., Lonstein, J. S., & Fleming, A. S. (2017). The neurobiology of postpartum anxiety and depression. *Trends in Neurosciences*, 40(2), 106-120.

Pawluski, J. L., Rayen, I., Niessen, N. A., Kristensen, S., van Donkelaar, E. L., Balthazart, J., ... & Charlier, T. D. (2012). Developmental fluoxetine exposure differentially alters central and peripheral measures of the HPA system in adolescent male and female offspring. *Neuroscience*, 220, 131-141.

Payne, J. L., & Maguire, J. (2018). Pathophysiological mechanisms implicated in postpartum depression. *Frontiers in neuroendocrinology*. 52,165-180.

Petit-Demouliere, B., Chenu, F., & Bourin, M. (2005). Forced swimming test in mice: a review of antidepressant activity. *Psychopharmacology*, *177*(3), 245-255.

Porsolt, R. D., Le Pichon, M., & Jalfre, M. L. (1977). Depression: a new animal model sensitive to antidepressant treatments. *Nature*, 266(5604), 730.

Porsolt RD, Anton G, Blavet N, Jalfre M. (1978). Behavioural despair in rats: a new model sensitive to antidepressant treatments. *European Journal of Pharmacology*. 47:379–91.

Porsolt RD. Animal model of depression. *Biomedicine*. 1979;30:139–40.

Prabhu, S., George, L. S., Shyamala, G., & Hebbar, S. (2019). Prevalence and Associated risk Factors of Postnatal Depression in South Asian region—A Systematic review. *Indian Journal of Public Health Research & Development*, 10(5), 329-333.

Pudell, C., Vicente, B. A., Delattre, A. M., Carabelli, B., Mori, M. A., Suchecki, D., ... & Lima, M. M. (2014). Fish oil improves anxiety-like, depressive-like and cognitive behaviors in olfactory bulbectomised rats. *European Journal of Neuroscience*, 39(2), 266-274.

O'hara, M. W., & McCabe, J. E. (2013). Postpartum depression: current status and future directions. *Annual review of clinical psychology*, 9, 379-407.

Overgaard, A., Lieblich, S. E., Richardson, R., Galea, L. A., & Frokjaer, V. G. (2017). Paroxetine blunts the corticosterone response to swim-induced stress and increases depressive-like behavior in a rat model of postpartum depression. *Psychoneuroendocrinology*. 89,223-228.

ÖZTüRK, A. H. M. E. T., Şahan, E., MIRçIK, A. B., Deveci, E., Yilmaz, O., & Kirpinar, I. (2019). Mean platelet volume and neutrophil to lymphocyte ratio decrease in patients with depression with antidepressant treatment. *Archives of Clinical Psychiatry (São Paulo)*, *46*(1), 9-13.

Ramirez, J.L., Drudi,L.M., & Grenon, S.M. (2018). Review of biologic and behavioral risk factors linking depression and peripheral artery disease. *Vascular Medicine*, 23(5),478-488.

Rechenberg, K. (2016). Nutritional interventions in clinical depression. *Clinical Psychological Science*, *4*(1), 144-162.

Redivo, D. D., Schreiber, A. K., Adami, E. R., Ribeiro, D. E., Joca, S. R., Zanoveli, J. M., & Cunha, J. M. (2016). Effect of omega-3 polyunsaturated fatty acid treatment over mechanical allodynia and depressive-like behavior associated with experimental diabetes. *Behavioural brain research*, 298, 57-64.

Rein, M., & Allen, N., (2018). Preventing Postpartum Depression in Women Living in the United States: An Integrative Literature Review. 9.

Ross LE., Evans Sellers EM., Romach MK. (2003). Measurement issues in postpartum depression part 1: Anxiety as a feature of postpartum depression. *Arch Women Mental Health Journal*.6:51-57.

Saccone, G., Saccone, I., & Berghella, V. (2016). Omega-3 long-chain polyunsaturated fatty acids and fish oil supplementation during pregnancy: which evidence?. *The Journal of Maternal-Fetal & Neonatal Medicine*, 29(15), 2389-2397.

Salari, A. A., Fatehi-Gharehlar, L., Motayagheni, N., & Homberg, J. R. (2016). Fluoxetine normalizes the effects of prenatal maternal stress on depression-and anxiety-like behaviors in mouse dams and male offspring. *Behavioural brain research*, 311, 354-367.

Schiller, C. E., O'Hara, M. W., Rubinow, D. R., & Johnson, A. K. (2013). Estradiol modulates anhedonia and behavioral despair in rats and negative affect in a subgroup of women at high risk for postpartum depression. *Physiology & behavior*, 119, 137-144.

Shi, Z., Ren, H., Huang, Z., Peng, Y., He, B., Yao, X., ... & Su, H. (2017). Fish oil prevents lipopolysaccharide-induced depressive-like behavior by inhibiting neuroinflammation. *Molecular neurobiology*, 54(9), 7327-7334.

Shih, R. H., Wang, C. Y., & Yang, C. M. (2015). NF-kappaB signaling pathways in neurological inflammation: a mini review. *Frontiers in molecular neuroscience*, *8*, 77.

Schiller, C. E., O'Hara, M. W., Rubinow, D. R., & Johnson, A. K. (2013). Estradiol modulates anhedonia and behavioral despair in rats and negative affect in a subgroup of women at high risk for postpartum depression. *Physiology & behavior*, 119, 137-144.

Shorey, S., Ing, C. C. Y., Ng, E. D., Huak, C. Y., San, W. T. W., & Seng, C. Y. (2018). Prevalence and incidence of postpartum depression among healthy mothers: a systematic review and meta-analysis. *Journal of psychiatric research*. 104, 235-248

Shukkoor, A., Saleem, M., Baharuldin, M. T. H. B., Jais, M., Manan, A., Moklas, M., ... & Basir, R. (2017). Antidepressant-Like Effect of Lipid Extract of Channa striatus in Postpartum Model of Depression in Rats. *Evidence-Based Complementary and Alternative Medicine*, *2017*, 1469209.

Siscovick, D. S., Barringer, T. A., Fretts, A. M., Wu, J. H., Lichtenstein, A. H., Costello, R. B., ... & Appel, L. J. (2017). Omega-3 polyunsaturated fatty acid (fish oil) supplementation and the prevention of clinical cardiovascular disease: a science advisory from the American Heart Association. *Circulation*, 135(15), e867-e884.

Staal, L., & Olivier, J. D. (2019). Influences of Maternal Vulnerability and Antidepressant Treatment during Pregnancy on the Developing Offspring. In Antidepressants-Preclinical, Clinical and Translational Aspects. 10.5772/*intechopen*.83761

Steck, N., Cooper, C., & Orgeta, V., (2018). Investigation of possible risk factors for depression in Alzheimer's disease: A systematic review of the evidence. *Journal of affective disorders*, 236,149-156.

Stewart, D. E., & Vigod, S. (2016). Postpartum depression. *New England Journal of Medicine*, 375(22), 2177-2186.

Stoffel, E.C & Craft, R.M. (2004). Ovarian hormone withdrawal-induced "depression" in female rats. *Physiology & Behavior*. 83(3):505-13

Su, K.P., et al., 2015. Omega-3 polyunsaturated fatty acids in prevention of mood and anxiety disorders. *Clin. Psychopharmacol. Neurosci. Off. Sci. J. Korean Coll. Neuropsychopharmacol.* 13, 129–137.

Suda, S., Segi-Nishida, E., Newton, S. S., & Duman, R. S. (2008). A postpartum model in rat: behavioral and gene expression changes induced by ovarian steroid deprivation. *Biological psychiatry*, 64(4), 311-319.

Szewczyk B., Kotarska K., Siwek A., Olech L., Kuter K., (2017). Antidepressant activity of zinc: Further evidence for the involvement of serotonergic system. *Pharmacological Reports*. 69.456-461.

Szewczyk, B., Poleszak, E., Wlaź, P., Wróbel, A., Blicharska, E., Cichy, A., ... & Brański, P. (2009). The involvement of serotonergic system in the antidepressant effect of zinc in the forced swim test. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 33(2), 323-329.

Tanbouly, N., El Sayed, A. M., Ali, Z. Y., Abdel Wahab, S., El Gayed, S. H., Ezzat, S. M., ... & Abdel-Sattar, E. (2017). Antidepressant-Like Effect of Selected Egyptian Cultivars of Flaxseed Oil on a Rodent Model of Postpartum Depression. *Evidence-Based Complementary and Alternative Medicine*, 2017, 6405789.

Tang, SEG., M. M., Lin, W. J., Pan, Y. Q., & Li, Y. C. (2018). Fibroblast growth factor 2 modulates hippocampal microglia activation in a neuroinflammation induced model of depression. *Frontiers in Cellular Neuroscience*, 12, 255.

Thawkar, B. S., & Kaur, G. (2019). Inhibitors of NF-κB and P2X7/NLRP3/Caspase 1 pathway in microglia: Novel therapeutic opportunities in neuroinflammation induced early-stage Alzheimer's disease. *Journal of neuroimmunology*, 326, 62-74.

Trujillo J, Vieira MC., Lepsch J., Rebelo F., Poston L., Pasupathy D., Kac G. (2018). A systematic review of the associations between maternal nutrition biomarkers and depression and/or anxiety during pregnancy and postpartum. *Journal of Affective Disorders*.185-203.

Toffoli, L. V., Rodrigues Jr, G. M., Oliveira, J. F., Silva, A. S., Moreira, E. G., Pelosi, G. G., & Gomes, M. V. (2014). Maternal exposure to fluoxetine during gestation and lactation affects the DNA methylation programming of rat's offspring: modulation by folic acid supplementation. *Behavioural brain research*, 265, 142-147.

Turner, C. M., Arulkumaran, N., Singer, M., Unwin, R. J., & Tam, F. W. (2014). Is the inflammasome a potential therapeutic target in renal disease?. *BMC nephrology*, 15(1), 21.

Upthegrove, R., Abu-Akel, A., Chisholm, K., Lin, A., Zahid, S., Pelton, M., & Wood, S.J. (2018). Autism and psychosis: clinical implications for depression and suicide . *Schizophrenia research*, 195,80-85.

Vahid-Ansari, F., Daigle, M., Manzini, M. C., Tanaka, K. F., Hen, R., Geddes, S. D., ... & Albert, P. R. (2017). Abrogated freud-1/Cc2d1a repression of 5-HT1A autoreceptors induces fluoxetine-resistant anxiety/depression-like behavior. *Journal of neuroscience*, 37(49), 11967-11978.

Veen, C., Myint, A. M., Burgerhout, K. M., Schwarz, M. J., Schütze, G., Kushner, S. A., ... & Bergink, V. (2016). Tryptophan pathway alterations in the postpartum period and in acute postpartum psychosis and depression. *Journal of affective disorders*, 189, 298-305.

Vieira, M. L., Hamada, R. Y., Gonzaga, N. I., Bacchi, A. D., Barbieri, M., Moreira, E. G., ... & Gerardin, D. C. C. (2013). Could maternal exposure to the antidepressants fluoxetine and St. John's Wort induce long-term reproductive effects on male rats?. *Reproductive Toxicology*, 35, 102-107.

Vines, A., Delattre, A. M., Lima, M. M., Rodrigues, L. S., Suchecki, D., Machado, R. B., ... & Ferraz, A. C. (2012). The role of 5-HT1A receptors in fish oil-mediated increased BDNF expression in the rat hippocampus and cortex: a possible antidepressant mechanism. *Neuropharmacology*, 62(1), 184-191.

Weaver, S., Fricke, H., & Hernandez, L. (2017). Administration of Fluoxetine or a Small Molecule TPH1 Inhibitor Affects Litter Size, Pup Mortality, and Milk Yield During Murine Pregnancy and Lactation. *The FASEB Journal*, 31(1_supplement), 457-5.

Whitaker-Azmitia, P. M. (2001). Serotonin and brain development: role in human developmental diseases. *Brain research bulletin*, 56(5), 479-485.

Whitney, D.G., Shapiro, D.N., Peterson, M.D., & Warschausky, S.A. (2019). Factors associated with depression and anxiety in children with intellectual disabilities. *Journal of intellectual disability research*, 63(5),408-417.

World Health Organization (WHO), 2017. Depression and Other Common Mental
Disorders. (WHO reference number: WHO/MSD/MER/2017.2).

XIE, R., XIE, H., Krewski, D., & HE, G. (2018). Plasma concentrations of neurotransmitters and postpartum depression. *Zhong nan da xue xue bao. Yi xue ban= Journal of Central South University. Medical sciences*, *43*(3), 274.

Xu, Y., Sheng, H., Tang, Z., Lu, J., & Ni, X. (2015). Inflammation and increased IDO in hippocampus contribute to depression-like behavior induced by estrogen deficiency. *Behavioural brain research*, 288, 71-78.

Xu, Y., Sheng, H., Bao, Q., Wang, Y., Lu, J., & Ni, X. (2016). NLRP3 inflammasome activation mediates estrogen deficiency-induced depression-and anxiety-like behavior and hippocampal inflammation in mice. *Brain, behavior, and immunity*, 56, 175-186.

Xue, J., Li, H., Deng, X., Ma, Z., Fu, Q., & Ma, S. (2015). L-Menthone confers antidepressant-like effects in an unpredictable chronic mild stress mouse model via NLRP3 inflammasome-mediated inflammatory cytokines and central neurotransmitters. *Pharmacology Biochemistry and Behavior*, 134, 42-48.

Yalagala, P. C., Sugasini, D., Dasarathi, S., Pahan, K., & Subbaiah, P. V. (2019). Dietary lysophosphatidylcholine-EPA enriches both EPA and DHA in the brain: potential treatment for depression. *Journal of lipid research*, 60(3), 566-578.

Yildiz, G., Senturk, M. B., Yildiz, P., Cakmak, Y., Budak, M. S., & Cakar, E. (2017). Serum serotonin, leptin, and adiponectin changes in women with postpartum depression: controlled study. *Archives of gynecology and obstetrics*, 295(4), 853-858.

Yousef, N., & Kouser, S. (2018). Role Of Ecosapentaeconic Acid (Epa) And Decosahexaenoic Acid (Dha) As Add-On Treatment Of Major Depressive Disorder (MDD). *Indeprendant Journal of Allied Health Sciences*, 04(01-07):247-253

Yusuff, A. S. M., Tang, L., Binns, C. W., & Lee, A. H. (2015). Prevalence and risk factors for postnatal depression in Sabah, Malaysia: a cohort study. *Women and Birth*, 28(1), 25-29.

Yuvaci, H. U., Yazici, E., Yazici, A. B., & Cevrioglu, S. (2019). How often do women use non-drug treatment methods for psyschiatric symptoms during pregnancy and postpartum periods?. *Mental illness*, 11(1),7988.

Zhang, Y., Liu, L., Liu, Y. Z., Shen, X. L., Wu, T. Y., Zhang, T., ... & Jiang, C. L. (2015). NLRP3 inflammasome mediates chronic mild stress-induced depression in mice via neuroinflammation. *International Journal of Neuropsychopharmacology*, *18*(8), 006.

Zhang, L., Previn, R., Lu, L., Liao, R. F., Jin, Y., & Wang, R. K. (2018). Crocin, a natural product attenuates lipopolysaccharide-induced anxiety and depressive-like behaviors through suppressing NF-kB and NLRP3 signaling pathway. *Brain research bulletin*, 142, 352-359.

Zullino, S., & Simoncini, T. (2018). Impact of selective serotonin reuptake inhibitors (SSRIs) during pregnancy and lactation: a focus on short and long-term vascular effects. *Vascular pharmacology*, 108, 74-76.