Microglia as a Potential Target for Antidepressant: A Systematic Review on Preclinical studies

by Chrismawan Ardianto

Submission date: 28-Sep-2022 02:12PM (UTC+0800)
Submission ID: 1911074896
File name: or_Antidepressant_A_Systematic_Review_on_Preclinical_studies.pdf (235.4K)
Word count: 5749
Character count: 32157

ISSN 0974-3618 (Print)
0974-360X (Online)

www.rjptonline.org

REVIEW ARTICLE

Microglia as a Potential Target for Antidepressant: A Systematic Review on Preclinical studies

Baiq Risky Wahyu Lisnasari, Chrismawan Ardianto, Junaidi Khotib*
Department of Pharmacy Practice, Faculty of Pharmacy, Universitas Airlangga, Surabaya 60115, Indonesia.
*Corresponding Author E-mail: **junaidi-k@ff.unair.ac.id**

ABSTRACT:
Depression is a heterogeneous disorder with more than one possible etiologies. Currently, studies are mostly focused on neuronal dysfunction, while the involvement of other brain cells, such as microglia, has not been widely explored. This review aimed to systematically review the studies reporting the effect of microglia inhibitors on depressive-like behavior in rodent models, to obtained a better understanding of the effectiveness of the intervention against depression. The PubMed database was explored from January 2011 to April 2021 with related keywords for full-text publications reporting antidepressant effects of microglial inhibitor in rodents. We identified 713 research publications, of which only 25 studies met the inclusion criteria and were included for analysis. Administration of antidepressant drugs/compounds that inhibit microglia was reported to be beneficial because it improved depression-like symptoms by reducing outcomes based on immobility, anhedonia, and locomotor activity. Microglia inactivation has been reported to occur through inhibition of the HMGB1/TLR4/NF-B and NLRP3/NF-κB pathways, as well as improved communication of microglia neurons through increased interaction of CX3CL1 with CX3CR1. These data indicated that the use of an agent inhibiting microglia activity is promising as a strategy in overcoming depression in humans.

KEYWORDS: Microglia, HMG/TLR pathway, Depression, Mental illness, Mental disorder.

INTRODUCTION:

Depression is the leading cause of disability worldwide and globally affects more than 264 million people of all ages[1]. The economic burden of depression is reported to be around $210.5 billion, consisting of direct costs (45%), suicide-related costs (5%), and workplace costs (50%)[2]. Depression is prevalent among elderly, females, and patient with chronic illness[3–7]. Despite its high prevalence, the mechanisms associated with the pathogenesis of depression are not fully understood and current treatments have not shown effectiveness in the majority of patients in hospital or health care settings[8,9]. Tests on the effectiveness of therapy referring to the AGT (Algorithm-guided Therapy) program showed the patient's response rate to the administration of pharmacotherapy agents (SSRI, SNRI, or TCA) was 20.7% with a remission rate of 31.0%[10]. These limitations lead to the need for the development of interventional therapies for depression so as to provide satisfactory outcomes.

Depression is a heterogeneous mental disorder, with more than one possible etiology[11,12]. Although there is ample evidence reporting on the molecular, cellular, and circuit-level mechanisms of depression, the biological mechanisms underlying this disorder are still not well understood. This may be because studies had focused on neuronal dysfunction, while the involvement of glial cells had not been widely explored[13]. Some evidence suggests microglia play an important role in the development and progression of depression[14,15]. Microglia are the main immune cells in the brain that play a role in immunosurveillance and neuroprotection through tight regulation of cytokines[15,16]. Under normal conditions, microglia are quiescent with a branched

Received on 05.07.2021 Modified on 11.11.2021
Accepted on 05.02.2022 © RJPT All right reserved
Research J. Pharm. and Tech. 2022;15(7):3317-3323.
DOI: 10.52711/0974-360X.2022.00555

morphology. Microglia will change shape into amoeboid when it detects a potentially harmful signal[17]. Microglia are categorized into 2 activation states: the M1 phenotype which is associated with the production of proinflammatory cytokines, and the M2 phenotype that expresses the cytokines to stop inflammation[18]. A number of recent evidences indicate the involvement of microglia in the pathophysiology of depression[19,20]. Synthesis of recent evidence may help to understand the extent to which inhibition of microglia activation can overcome depressive states. Thus, this study aimed to investigate the inhibitory effect of microglia activation on the improvement of depression-like behavior in rodent models.

MATERIALS AND METHODS:

Search Strategy:

PubMed database was systematically explored to identify experimental studies that tested the inhibitory effect of antidepressant in rodents. Data searching was limited to articles published from January 2011 to April 2021. We used the keywords microglia inhibitor, antidepressant, depressive-like behavior, microglia inactivation, and animal model. We used general searching keywords to find all potentially relevant articles.

We included studies reporting the effects of antidepressants which were acting by inhibiting microglia in animal models of depression, particularly mice and rats. Studies that administered antidepressants, both before and after stress induction, were included in the review. Antidepressants were classified as drugs/compounds currently prescribed for depression or drugs/compounds that were under investigation as potential antidepressant drugs. We only involved articles published in English. All studies were screened and evaluated independently by two authors (BRWL and CA). Any discrepancies in the selection process were resolved by discussion among the authors. A senior investigator (JK) was consulted to revise the selection process. Study selection flowchart is shown in figure 1.

Risk of Bias Assessment:

Risk of bias assessment was carried out based on risk of bias instrument the Systematic Review Center for Laboratory Animal Experimentation (SYRCLE) (Hooijmans et al., 2014). This instrument is based on the Cochrane Collaboration RoB Tool, which is based on the aspect of bias that plays an important role in animal studies. The aim is to uniformly assess methodological quality in the field of animal research. SYRCLE's risk bias of tools consists of 10 items with 6 types of bias, ie. selection bias, performance bias, detection bias, attrition bias, reporting bias, and other potential biases. The ten items were organized into sub-items in the form of questions that supported the answers “yes”, “no”, and “unclear answer”. A score of “yes” indicated a low risk of bias, “no” indicated a high risk of bias, and “unclear” indicated an unknown risk of bias.

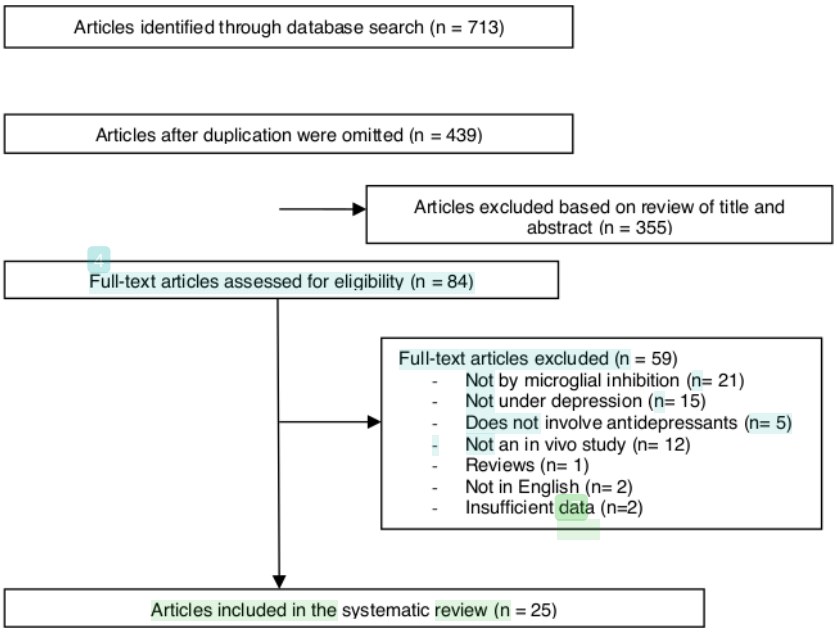

Fig 1. Flowchart of selecting articles in the study

Table 1. The main of article characteristic and outcomes of the study

Authors	Species	Gender	Induction model	Drugs Administered	Behavior Test	Results
Xu, et al.[21]	C57BL/6 Mice	Male	CUMS dan LPS	GW3965	SPT: sucrose intake ↑; TST: immobility ↓; EPM: anxiety ↔	Inhibiting M1 microglia polarization and NF-κB phosphorylation.
Cheng, et al.[22]	ICR Mice	Male	LPS	Paeoniflorin	SPT: sucrose intake ↑; FST: immobility ↓	Activating FGF-2/FGFR1 signaling
Feng et al.[23]	C57BL/6J Mice	Male	LPS	Phenol glycoside extract from *Fructus Ligustri Lucidi*	SPT: sucrose intake ↑; TST: immobility ↓; FST: immobility ↓; OFT: locomotor activity ↑	Inhibiting TLR4/MyD88 and TLR4/NLRP3 pathways
Zhang et al.[24]	C57BL/6J Mice	Male	LPS	Asperosaponin VI	OFT: time in center ↑; FST: immobility ↓	Inhibiting TLR4/NF-κB signaling pathway
Su et al.[25]	ICR Mice	Male	LPS	Saikosaponin-d	SPT: sucrose intake ↑; TST: immobility ↓; FST: immobility ↓; OFT: ↔	Regulating HMGB1/TLR4/NF-κB signaling pathway
Guo et al.[26]	Sprague Dawley Rats	Male	CUMS	Fingolimod	SPT: sucrose intake ↑; FST: immobility ↓; OFT: locomotor activity ↑	Shifting microglia polarization to M2 phenotype
Zhou et al.[27]	Sprague Dawley Rats	Male	*Chronic water immersion restraint stress*	Apelin-13	SPT: sucrose intake ↑; TST: immobility ↓; FST: immobility ↓; OFT: locomotor activity ↑	Inhibiting M1 microglia polarization, presumably via the inhibition of STAT3/NLRP3 pathway
Habib et al.[28]	Wistar Rats	Male	CMS	Lithium	SPT: sucrose intake ↑; FST: immobility ↓; OFT: locomotor activity ↑	Increasing hippocampal Wnt/β-catenin signaling pathway expression
Mao et al.[29]	Kunming Mice	Male	*Chronic water immersion restraint stress*	Caffeine	SPT: sucrose intake ↑; TST: immobility ↓; FST: immobility ↓	Inhibiting A2AR/MEK/ERK/NF-κB signaling pathway
Xu et al.[30]	C57BL/6J Mice	Male	CUMS	Arctigenin	SPT: sucrose intake ↑; TST: immobility ↓; FST: immobility ↓; OFT: locomotor activity ↑	Inhibiting HMGB1/TLR4/NF-κB signaling pathway
Chen et al.[31]	ICR Mice	Male	LPS	Esculin	SPT: sucrose intake ↑; TST: immobility ↓; FST: immobility ↓; OFT: locomotor activity ↑	Inhibiting CCR5-regulated TLR4/NF-κB signaling pathway, leading to increased microglial M2 polarization
Feng et al.[32]	C57BL/6 Mice	Male	CMS	Mefenamic acid, celecoxib	SPT: sucrose intake ↑; FST: immobility ↓	Inhibiting ERK1/2 and P38 MAPK activation
Han et al.[33]	C57BL/6 Mice	Male	*Maternal separation*	Minocycline	SPT: sucrose intake ↑; FST: immobility ↓; OFT: ↔	Suppressing morphological and phenotypic changes of microglial M2
Wang et al.[34]	Balb/c Mice	Male	CUMS	Minocycline	SPT: sucrose intake ↑; TST: immobility ↓; Barned maze: cognitive↑	Inhibiting HMGB1 release
Zhang et al.[35]	Sprague Dawley Rats	Betina	CUMS	Minocycline	SPT: sucrose intake ↑; FST: immobility ↓; EPM: anxiety ↓	Suppressing M1 response and restoring GFAP and BDNF levels
Zheng et al.[36]	C57BL/6 Mice	Male	IFN-α	Minocycline	TST: immobility ↓; FST: immobility ↓	Preserving NSCs, neuronal progenitors, and new neurons, thereby enhancing neurogenesis
Wang et al.[37]	Sprague Dawley Rats	Male	*Early-life social isolation*	Minocycline	SPT: sucrose intake ↑; FST: immobility ↓	Downregulating H3K9me2 expression and restoring NR1, GluR1, and GluR2 expression
He et al.[38]	C57BL/6 Mice	Male	LPS	Paricalcitol	SPT: sucrose intake ↑; TST: immobility ↓; FST: immobility ↓	Restoring microglia to a ramified form with normal soma size, suppressing NF-B activation and NLRP3 and caspase-1 overexpression
Ito et al.[39]	C57BL/6 Mice	Male	*Chronic social defeat stress*	Kososan, a Japanese traditional herbal medicine	Social avoidance test: interaction ↑	Enhancing anti-inflammatory phenotype and inhibiting the increase of microglial proinflammatory phenotype
Vega-Rivera et al.[40]	Balb/c Mice	Male	CMS	Melatonin	SPT: sucrose intake ↑; FST: immobility ↓	Increasing CX3CL1/CX3CR1 signaling pathway, keeping the

						microglia in resting phenotype
Weng et al.[41]	ICR Mice	Male	LPS	Macranthol	SPT: sucrose intake ↑; FST: immobility ↓	Inhibiting the increase of Cd11b expression
Yamawaki et al.[42]	C57BL/6 Mice	Male	LPS	Sodium butyrate	FST: immobility ↓, OFT: ↔	Epigenetic regulation by downgrading the expression of the Efcab1 gene
Zhang et al.[43]	C57BL/6 Mice	Male	CMS	Salvianolic acid	SPT: sucrose intake ↑; TST: immobility ↓; FST: immobility ↓; OFT: ↔	Inhibiting microglial M1 polarization and activating microglial M2
Zhang et al.[44]	C57BL/6 Mice	Male	CMS	Salvianolic acid	TST: immobility ↓; FST: immobility ↓; OFT: ↔	Reducing the percentage of cleaved caspase-3
Zhao et al.[45]	C57BL/6 Mice	Male	CMS	Pioglitazone	TST: immobility ↓; FST: immobility ↓; OFT: locomotor activity ↑	Suppressing the expression of microglial M1 marker

Abbreviations: LPS: Lipopolysaccharide, CUMS: Chronic Unpredictable Mild Stress, SPT: Sucrose Preference Test, FST: Forced Swim Test, TST: Tail Suspension Test, OFT: Open Field Test, EPM: Elevated Plus Maze, ↑ represent a statistically significant increase in measured behavior, ↓ represent decrease, and ↔ represent unchanged behavior.

Table 2. Assessment of the bias risk of the study

Studies	Selection bias 1	Selection bias 2	Selection bias 3	Performance bias 1	Performance bias 2	Detection bias 1	Detection bias 2	Attrition bias	Reporting bias	Other potential bias
Xu, et al	Yes	Yes	Unclear	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes
Cheng, et al	Yes	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Yes
Feng et al	Yes	Yes	Unclear	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes
Zhang et al	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Yes
Su et al	Unclear	Yes	Unclear	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes
Guo et al	No	No	Unclear	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes
Zhou et al	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Yes
Habib et al	Yes	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Yes
Mao et al	Yes	Yes	Unclear	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes
Xu et al	Yes	Yes	Unclear	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes
Chen et al	Yes	Yes	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes
Feng et al	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Yes
Han et al	Yes	Yes	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes
Wang et al	Yes	Yes	Unclear	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes
Zhang et al	Unclear	Yes	Unclear	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes
Zheng et al	Unclear	Yes	Unclear	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes
Wang et al	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes
He et al	Unclear	Yes	Unclear	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes
Ito et al	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes
Vega-Rivera et al	Yes	Yes	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes
Weng et al	Yes	Yes	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes
Yesmawaki et al	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes
Zhang et al	Yes	Yes	Unclear	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes
Zhang et al	No	No	Unclear	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes
Zhao et al	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes

RESULTS AND DISCUSSION:

Characteristics of Included Studies:

Twenty-five articles were included in the review after inclusion and exclusion criteria were applied. Five studies (20%) used rats as experimental animals and the other 20(80%) studies used mice. The induction models used were CUMS (44%), LPS injection (36%), TNF-α injection (4%), chronic social defeat stress (4%), maternal separation (4%), early-life social isolation (4%), and chronic water immersion restraint stress (8%). Twenty-three studies (92%) tested immobilization-based depressive-like behavior with forced swim test and/or tail-suspension test, 19 studies (76%) tested anhedonia-based depressive-like behavior with the sucrose preference test, 12 studies (48%) tested locomotor activity with open field test, and 1 study (4%) tested social interaction with social avoidance test. The treatments (drugs or antidepressant-like compounds) administered were GW3965 (liver X receptor agonist) (4%), paeoniflorin (4%), phenol glycoside extract from *Fructus Ligustri lucidi* (4%), asperosaponin VI (4%), saikosaponin- d (4%), fingolimod (4%), applein-13 (4%), lithium (4%), caffeine (4%), arctigenin (4%), esculin (4%), mefenamic acid (4%) , celecoxib (4%), minocycline (20%), paricalcitol (4%), kososan (4%), melatonin (4%), macranthol (4%), sodium butyrate (4%), salvianolic acid (8%), and pioglitazone (4%). The main characteristics and outcomes of the included studies are listed in Table 1. In general, the studies identified in this review support the evidence that

inhibition of microglia improves depressive-like behavior in experimental animals. Although the reports were heterogeneous, all studies (n=25, 100%) demonstrated that microglia inhibitors were effective in suppressing depression-like behavior and stress-induced changes in biological markers.

Assessment of the risk of bias of the included studies is shown in Table 2. Of the 25 studies, 23 studies reported randomization at the time of grouping of the experimental animals. However, there were no studies that mentioned the randomization method applied and the allocation sequence during the randomization process. In 8% of the studies, the baseline characteristics between control and experimental groups were different from the start of the experiment. There were no studies reporting efforts made to reduce performance bias. Blinding of outcome asessors was reported in 80% of the studies. There were no studies reporting randomized outcome assessments. The included studies had a low risk for attrition bias, reporting bias, and other potential biases. Overall, most sources of potential bias should be assessed as risk of unclear bias, resulting from poor reporting.

Available studies on the inhibitory effect of microglia activation on depressive states were heterogeneous and consist mostly of low-quality studies. The compounds administered varied widely among the studies selected for the final analysis, and so did the dose and duration of treatment, as well as the method of administration. Most of the studies used male experimental animals, so the effect of sex differences on outcomes was not considered in this analysis. The majority of selected studies found significant positive effects of antidepressant-like drugs/compounds on the observed measures, ranging from decreased neuroinflammatory markers, increased neurogenesis, and improved depression-like behavior on a number of behavioral tests.

Effect of Microglial Inhibitor on Depressive Behavior:

Microglia inhibitors have been shown to improve depressive-like behavior based on immobilization, anhedonia, and locomotor activity. Testing of new substances with desperate behavior tests, such as the forced swim test and tail suspension test, allows a simple assessment of their potential antidepressant activity by measuring their effect on immobilization[46–48]. The duration and latency of immobility reflect decreased mood in rodents that are selectively sensitive to antidepressant therapy[47,49,50]. The sucrose preference test was used to assess anhedonia loss of interest or pleasure behavior. Symptoms of anhedonia or decreased mood are criteria that must exist for the diagnosis of major depressive disorder[51]. Anhedonia has been associated with a poorer disease prognosis and less optimal response to treatment[52]. The impact of anhedonia on quality of life and functional outcome in MDD makes it a very important target for antidepressant therapy. The open field test was used to measure locomotion and anxiety behavior, in which variables such as overall activity in the open field, time in center, and distance traveled were evaluated for 5 minutes[53,54].

Mechanism of action of Microglial Inhibitor:

One of the classic activation results of the innate immune system is the induction of the proinflammatory phase, which is characterized by the production and release of proinflammatory cytokines, such as tumor necrosis factor-1 (TNF-1), interleukin-6 (IL-6), interleukin-1β (IL-1β), proteases (matrix metalloproteinase-9), superoxide anion, nitric oxide (NO) and reactive oxygen-nitrogen species (N2O3, NO2)[55]. This systematic review provides evidence indicating that microglia inhibitors may represent an effective treatment option for depressive conditions. Several studies included in this review attempted to identify the pathways by which microglia inhibitory agents acted on the nervous system. The role of TLR4/NF-κB pathway was emphasized in 4 studies because of its role in regulating microglia polarization[25,30,31,34]. TLR-4, a microglia-expressed first-line molecule to initiate the innate immune response, mediates the release of proinflammatory mediators via the NF-κB pathway[56,57]. Inhibition of the TLR4/NF-κB pathway causes a decrease in TNF-α and IL-1β levels, thereby preventing the conversion of microglia to M1 phenotype[24,30]. Inhibition of microglia will then cause a decrease in the release of HMGB1 (high mobility group box-1), damage associated molecular pattern (DAMP), an alarmin protein that may trigger a proinflammatory immune response through the activation of the TLR4/NF-κB pathway[25,30,34].

The involvement of NLRP3 was reported in 3 studies (23, 27, 38). Activated NF-κB induces the transcription of NLRP3 (NOD-, LRR- and domain-containing pyrin 3), a cytosolic innate immune signaling receptor[38]. NLRP3 is a post-transcriptional regulator of IL-1β protein. Activation of NLRP3, one of which by TLR4, will cause caspase-1-mediated proteolysis of the IL-1β family[23,27].

Neurons can regulate and/or maintain microglial activation status by releasing factors that influence basal microglial properties, which are thought to maintain homeostatic conditions in healthy brains[58,59]. Microglial cell activation is associated with decreased neuronal CX3CL1 (fractalkine) interactions with its receptor, CX3CR1, which is expressed by microglia[40]. Decreased CX3CL1 signaling and attenuation of crosstalk between neurons and microglia, affect transmission efficiency in adult brain synapses[60].

CONCLUSION:

The use of an agent inhibiting the activity of microglia may suppress the development of depressive-like behavior in experimental animals. This mechanism can be translated and further developed as a promising strategy in overcoming depression in humans.

LIMITATIONS:

The main limitation of this systematic review was the heterogeneity and quality of the included studies. Species, designs and intervention protocols in preclinical studies often vary between studies. Analysis of the risk of bias showed poor reporting of important methodological details in most studies. Consequently, the risk of bias for each individual study was assessed as unclear risk of bias, which suggested that the effect of the treatment observed may be overestimated.

CONFLICT OF INTEREST:

The authors declare no conflict of interest.

REFERENCES:

1. James SL, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 354 Diseases and Injuries for 195 countries and territories, 1990-2017: A systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2018; 392(10159):1789–858. Available from: https://doi.org/10.1016/S0140-6736(18)32279-7.
2. Greenberg PE, Fournier AA, Sisitsky T, Pike CT, Kessler RC. The economic burden of adults with major depressive disorder in the United States (2005 and 2010). J Clin Psychiatry. 2015; 76(2):155–62. Available from: https://doi.org/10.4088/JCP.14m09298.
3. Sangroyangla, Temjentula, Imchen T, Longkumer T, Vizayieno, Murry K. Prevalence of Depression and the associated risk factors among the Elderly. Asian J Nurs Educ Res. 2019; 9(4):552. Available from: https://doi.org/10.5958/2349-2996.2019.00119.8.
4. Sonia Devi, Suman, Dr. Santosh Gurjar. a Comparative Study To Assess the Level of Depression Between Elderly Living At Old Age Home and Living With Families in Haryana. EPRA Int J Multidiscip Res. 2020; 2(March):102–6. doi: 10.36713/epra5119.
5. Joshi R, Hugo V. A Study to Assess the Level of Depression among Old Age People in Selected Villages in Mehsana District , Gujarat. Int J Nurs Educ Res. 2014; 2(December):379–80. ISSN: 2347–8640
6. Kumar D. Comorbid Depression in Inflammatory Bowel Disease. Asian J Res Pharm Sci. 2020; 10(1):35. doi: 10.5958/2231-5659.2020.00008.9.
7. Vijayalakshmi K. Assessment of Depression among Cancer Patients. Asian J Nurs Educ Res. 2018; 8(1):11. doi: 10.5958/2349-2996.2018.00004.6.
8. Patel M, Patel C, Patel D, Anand I, Patel C. A Review on Novel Strategies for Pharmacotherapy of Depression. Res J Pharmacol Pharmacodyn. 2010; 2(2):153-159–159. ISSN: 0975-4407.
9. Bhagat V, Bin Symbak N, Husain R, Mat KC. The role of selective serotonin reuptake inhibitors and cognitive behavioral therapy in preventing relapse of major depressive disorder. Res J Pharm Technol. 2019; 12(8):3818–24. doi: 10.5958/0974-360X.2019.00654.1.
10. Kan K, Feenstra TL, de Vries SO, Visser E, Schoevers RA, Jörg F. The clinical effectiveness of an algorithm-guided treatment program for depression in specialized mental healthcare: A comparison with efficacy trials. J Affect Disord [Internet]. 2020; 275(September 2019):216–23. Available from: https://doi.org/10.1016/j.jad.2020.07.010
11. Deng S long, Chen J guo, Wang F. Microglia: A Central Player in Depression. Curr Med Sci. 2020; 40(3):391–400. doi: 10.1007/s11596-020-2193-1.
12. Brites D, Fernandes A. Neuroinflammation and depression: Microglia activation, extracellular microvesicles and microRNA dysregulation. Front Cell Neurosci. 2015; 9(DEC):1–20. doi 10.3389/fncel.2015.00476.
13. Yirmiya R, Rimmerman N, Reshef R. Depression as a Microglial Disease. Trends Neurosci. 2015; 38(10):637–58. doi: 10.1016/j.tins.2015.08.001.
14. Jia X, Gao Z, Hu H. Microglia in depression: current perspectives. Sci China Life Sci. 2020; 64(6):911–25. doi: 10.1007/s11427-020-1815-6.
15. Zhang L, Zhang J, You Z. Switching of the Microglial Activation Phenotype Is a Possible Treatment for Depression Disorder. Front Cell Neurosci. 2018; 12(October):1–13. doi: 10.3389/fncel.2018.00306.
16. Singhal G, Baune BT. Microglia: An interface between the loss of neuroplasticity and depression. Front Cell Neurosci. 2017; 11(September):1–16. doi: 10.3389/fncel.2017.00270.
17. Jurga AM, Paleczna M, Kuter KZ. Overview of General and Discriminating Markers of Differential Microglia Phenotypes. Front Cell Neurosci. 2020; 14(August):1–18. doi: 10.3389/fncel.2020.00198.
18. Stein DJ, Vasconcelos MF, Albrechet-souza L, Ceresér KMM, de Almeida RMM. Microglial Over-Activation by Social Defeat Stress Contributes to Anxiety-. Front Behav Neurosci. 2017; 11(207):1–10. doi: 10.3389/fnbeh.2017.00207.
19. Hinwood M, Morandini J, Day TA, Walker FR. Evidence that Microglia Mediate the Neurobiological Effects of Chronic Psychological Stress on the Medial Prefrontal Cortex. Cereb Cortex. 2011; 22:1442–54. doi: 10.1093/cercor/bhr229.
20. Wang YL, Han QQ, Gong WQ, Pan DH, Wang LZ, Hu W, et al. Microglial activation mediates chronic mild stress-induced depressive- and anxiety-like behavior in adult rats. J Neuroinflammation. 2018; 15(1):1–14. doi: 10.1186/s12974-018-1054-3.
21. Xu X, Xiao X, Yan Y, Zhang T. Activation of liver X receptors prevents emotional and cognitive dysfunction by suppressing microglial M1-polarization and restoring synaptic plasticity in the hippocampus of mice. Brain Behav Immun [Internet]. 2021; 94(February):111–24. Available from: https://doi.org/10.1016/j.bbi.2021.02.026
22. Cheng J, Chen M, Wan HQ, Chen XQ, Li CF, Zhu JX, et al. Paeoniflorin exerts antidepressant-like effects through enhancing neuronal FGF-2 by microglial inactivation. J Ethnopharmacol [Internet]. 2021; 274(February):114046. Available from: https://doi.org/10.1016/j.jep.2021.114046
23. Feng R, He MC, Li Q, Liang XQ, Tang DZ, Zhang JL, et al. Phenol glycosides extract of Fructus Ligustri Lucidi attenuated depressive-like behaviors by suppressing neuroinflammation in hypothalamus of mice. Phyther Res. 2020; 34(12):3273–86. doi: 10.1002/ptr.6777.
24. Zhang J, Yi S, Li Y, Xiao C, Liu C, Jiang W, et al. The antidepressant effects of asperosaponin VI are mediated by the suppression of microglial activation and reduction of TLR4/NF-κB induced IDO expression. Psychopharmacology (Berl). 2020. doi: 10.1101/2020.03.15.992529.
25. Su J, Pan YW, Wang SQ, Li XZ, Huang F, Ma SP. Saikosaponin-d attenuated lipopolysaccharide-induced depressive-like behaviors via inhibiting microglia activation and neuroinflammation. Int Immunopharmacol [Internet]. 2020; 80(December 2019):106181. Available from: https://doi.org/10.1016/j.intimp.2019.106181
26. Guo Y, Gan X, Zhou H, Zhou H, Pu S, Long X, et al. Fingolimod suppressed the chronic unpredictable mild stress-induced depressive-like behaviors via affecting microglial and NLRP3 inflammasome activation. Life Sci [Internet]. 2020; 263(July):118582. Available from: https://doi.org/10.1016/j.lfs.2020.118582
27. Zhou S, Chen S, Xie W, Guo X, Zhao J. Microglia polarization of hippocampus is involved in the mechanism of Apelin-13 ameliorating chronic water immersion restraint stress-induced depression-like behavior in rats. Neuropeptides [Internet]. 2020; 81(January):102006. Available from: https://doi.org/10.1016/j.npep.2020.102006
28. Habib MZ, Ebeid MA, el Faramawy Y, Saad SST, El Magdoub HM, Attia AA, et al. Effects of lithium on cytokine neuro-inflammatory mediators, Wnt/β-catenin signaling and microglial activation in the hippocampus of chronic mild stress-exposed rats [Internet]. Vol. 399, Toxicology and Applied Pharmacology. Elsevier Inc; 2020. 115073 p. Available from: https://doi.org/10.1016/j.taap.2020.115073
29. Mao ZF, Ouyang SH, Zhang QY, Wu YP, Wang GE, Tu LF, et al. New insights into the effects of caffeine on adult hippocampal neurogenesis in stressed mice: Inhibition of CORT-induced microglia activation. FASEB J. 2020; 34(8):10998–1014. doi: 10.1096/fj.202000146RR
30. Xu X, Piao HN, Aosai F, Zeng XY, Cheng JH, Cui YX, et al. Arctigenin protects against depression by inhibiting microglial

activation and neuroinflammation via HMGB1/TLR4/NF-κB and TNF-α/TNFR1/NF-κB pathways. Vol. 177, British Journal of Pharmacology. 2020. 5224–5245 p. doi: 10.1111/bph.15261.
31. Chen T, Zheng M, Li Y, Liu S, He L. The role of CCR5 in the protective effect of Esculin on lipopolysaccharide-induced depressive symptom in mice. J Affect Disord [Internet]. 2020; 277(March):755–64. Available from: https://doi.org/10.1016/j.jad.2020.08.065
32. Feng X, Fan Y, Chung CY. Mefenamic acid can attenuate depressive symptoms by suppressing microglia activation induced upon chronic stress. Brain Res [Internet]. 2020; 1740(October 2019):146846. Available from: https://doi.org/10.1016/j.brainres.2020.146846
33. Han Y, Zhang L, Wang Q, Zhang D, Zhao Q, Zhang J, et al. Minocycline inhibits microglial activation and alleviates depressive-like behaviors in male adolescent mice subjected to maternal separation. Psychoneuroendocrinology [Internet]. 2019; 107(April):37–45. Available from: https://doi.org/10.1016/j.psyneuen.2019.04.021
34. Wang B, Huang X, Pan X, Zhang T, Hou C, Su WJ, et al. Minocycline prevents the depressive-like behavior through inhibiting the release of HMGB1 from microglia and neurons. Brain Behav Immun [Internet]. 2020; 88:132–43. Available from: https://doi.org/10.1016/j.bbi.2020.06.019
35. Zhang C, Zhang YP, Li YY, Liu BP, Wang HY, Li KW, et al. Minocycline ameliorates depressive behaviors and neuro-immune dysfunction induced by chronic unpredictable mild stress in the rat. Behav Brain Res. 2019; 356:348–57. doi: 10.1016/j.bbr.2018.07.001
36. Zheng LS, Kaneko N, Sawamoto K. Minocycline treatment ameliorates interferon-alpha-induced neurogenic defects and depression-like behaviors in mice. Front Cell Neurosci. 2015; 9(JAN):1–10. doi: 10.3389/fncel.2015.00005
37. Wang HT, Huang FL, Hu ZL, Zhang WJ, Qiao XQ, Huang YQ, et al. Early-Life Social Isolation-Induced Depressive-Like Behavior in Rats Results in Microglial Activation and Neuronal Histone Methylation that Are Mitigated by Minocycline. Neurotox Res [Internet]. 2017; 31(4):505–20. Available from: http://dx.doi.org/10.1007/s12640-016-9696-3
38. He M chao, Shi Z, Sha N nan, Chen N, Peng S yu, Liao D fang, et al. Paricalcitol alleviates lipopolysaccharide-induced depressive-like behavior by suppressing hypothalamic microglia activation and neuroinflammation. Biochem Pharmacol [Internet]. 2019; 163(January):1–8. Available from: https://doi.org/10.1016/j.bcp.2019.01.021
39. Ito N, Hirose E, Ishida T, Hori A, Nagai T, Kobayashi Y, et al. Kososan, a Kampo medicine, prevents a social avoidance behavior and attenuates neuroinflammation in socially defeated mice. J Neuroinflammation. 2017; 14(1):1–15. doi: 10.1186/s12974-017-0876-8
40. Vega-Rivera NM, Ortiz-López L, Granados-Juárez A, Estrada-Camarena EM, Ramírez-Rodríguez GB. Melatonin Reverses the Depression-associated Behaviour and Regulates Microglia, Fractalkine Expression and Neurogenesis in Adult Mice Exposed to Chronic Mild Stress. Neuroscience. 2020; 440:316–36. doi: 10.1016/j.neuroscience.2020.05.014
41. Weng L, Dong S, Wang S, Yi L, Geng D. Macranthol attenuates lipopolysaccharide-induced depressive-like behaviors by inhibiting neuroinflammation in prefrontal cortex. Physiol Behav [Internet]. 2019; 204(September 2018):33–40. Available from: https://doi.org/10.1016/j.physbeh.2019.02.010
42. Yamawaki Y, Yoshioka N, Nozaki K, Ito H, Oda K, Harada K, et al. Sodium butyrate abolishes lipopolysaccharide-induced depression-like behaviors and hippocampal microglial activation in mice. Brain Res [Internet]. 2018; 1680:13–38. Available from: https://doi.org/10.1016/j.brainres.2017.12.004
43. Zhang J, Xie X, Tang M, Zhang J, Zhang B, Zhao Q, et al. Salvianolic acid B promotes microglial M2-polarization and rescues neurogenesis in stress-exposed mice. Brain Behav Immun [Internet]. 2017; 66:111–24. Available from: http://dx.doi.org/10.1016/j.bbi.2017.07.012
44. Zhang JQ, Wu XH, Feng Y, Xie XF, Fan YH, Yan S, et al. Salvianolic acid B ameliorates depressive-like behaviors in chronic mild stress-treated mice: Involvement of the neuroinflammatory pathway. Acta Pharmacol Sin [Internet]. 2016; 37(9):1141–53. Available from: http://dx.doi.org/10.1038/aps.2016.63
45. Zhao Q, Wu X, Yan S, Xie X, Fan Y, Zhang J, et al. The antidepressant-like effects of pioglitazone in a chronic mild stress mouse model are associated with PPARγ-mediated alteration of microglial activation phenotypes. J Neuroinflammation [Internet]. 2016; 13(1):1–17. Available from: http://dx.doi.org/10.1186/s12974-016-0728-y
46. Pollak DD, Rey CE, Monje FJ. Rodent models in depression research: Classical strategies and new directions. Ann Med. 2010; 42(4):252–64. doi: 10.3109/07853891003769957
47. Anggreini P, Ardianto C, Rahmadi M, Khotib J. Quercetin attenuates acute predator stress exposure-evoked innate fear and behavioral perturbation. J Basic Clin Physiol Pharmacol. 2020; 30(6):1–7. doi: 10.1515/jbcpp-2019-0242
48. Velraj M, Vijayalakshmi A, Jayakumari S. Antidepressant-Like Effects of the Ethanolic Extract of Albizzia lebbeck (Linn) Leaves in Animal Models of Depression. Res J Pharmacogn Phytochem. 2010; 2(1):30–3. ISSN: 0975- 2331.
49. Lakshmi JA, Satyavthi D. Evaluation of Anti Depressant and MAO Inhibitory Activity of Rhodiola rhodantha rhizome methanolic extract . Res J Pharm Technol. 2015; 8(3):310. doi: 10.5958/0974-360x.2015.00051.7
50. Mahmudah R, Hasanuddin S, Saleh A, Yuliastri WO, Isrul M. Antidepressant activity and identification of chemical compounds extract mustard leaves (Brassica juncea l.). Res J Pharm Technol. 2019; 12(7):3223–7. doi: 10.5958/0974-360X.2019.00542.0
51. Fruyt J De. Anhedonia in Depressive Disorder : A Narrative Review. Psychopathology. 2020; 53:274–81. doi: 10.1159/000508773
52. Buckner JD, Joiner TE, Pettit JW, Lewinsohn PM, Schmidt NB. Implications of the DSM ' s emphasis on sadness and anhedonia in major depressive disorder. Psychiatry Res. 2008; 159:25–30. doi: 10.1016/j.psychres.2007.05.010
53. Schmidt M V, Planck M. Anxiety- and depression-like behavior in mice lacking the CD157/BST1 gene, a risk factor for Parkinson's disease. Front Behav Neurosci. 2014; 8(April):1–18. doi: 10.3389/fnbeh.2014.00133
54. Gomathi S, Shanmuga Sundaram R, Vijayabaskaran M, Kannan C, Sambathkumar R. Pedalium murex linn leaves against LPS-induced oxidative stress, anxiety and depression behavioural alterations in rats. Res J Pharm Technol. 2017; 10(5):1333–8. doi: 10.5958/0974-360X.2017.00236.0.
55. Colton CA, Wilcock DM. Assessing Activation States in Microglia. CNS Neurol Disord - Drug Targets. 2010; 9(2):174–91. doi: 10.2174/187152710791012053
56. Yao L, Kan EM, Lu J, Hao A, Dheen ST, Kaur C, et al. Toll-like receptor 4 mediates microglial activation and production of inflammatory mediators in neonatal rat brain following hypoxia: Role of TLR4 in hypoxic microglia. J Neuroinflammation. 2013; 10:1–21. doi: 10.1186/1742-2094-10-23
57. Wang H, Song X, Li M, Wang X, Tao Y, Xiya X, et al. The role of TLR4/NF-κB signaling pathway in activated microglia of rats with chronic high intraocular pressure and vitro scratch injury-induced microglia. Int Immunopharmacol [Internet]. 2020; 83(March):106395. Available from: https://doi.org/10.1016/j.intimp.2020.106395
58. Eyo UB, Wu LJ. Bidirectional microglia-neuron communication in the healthy brain. Neural Plast. 2013; 2013. doi: 10.1155/2013/456857
59. Paolicelli RC, Bisht K, Tremblay MÈ. Fractalkine regulation of microglial physiology and consequences on the brain and behavior. Front Cell Neurosci. 2014; 8(MAY):1–10. doi: 10.3389/fncel.2014.00129
60. Szepesi Z, Manouchehrian O, Bachiller S, Deierborg T. Bidirectional Microglia–Neuron Communication in Health and Disease. Front Cell Neurosci. 2018; 12(September):1–26. doi: 10.3389/fncel.2018.00323

Microglia as a Potential Target for Antidepressant: A Systematic Review on Preclinical studies

ORIGINALITY REPORT

7%	5%	5%	0%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	www.nature.com Internet Source	1%
2	Hai Jiang, Liu Yang, Ajiao Hou, Jiaxu Zhang et al. "Botany, traditional uses, phytochemistry, analytical methods, processing, pharmacology and pharmacokinetics of Bupleuri Radix: A systematic review", Biomedicine & Pharmacotherapy, 2020 Publication	1%
3	Ming-chao He, Zhe Shi, Nan-nan Sha, Nan Chen et al. "Paricalcitol alleviates lipopolysaccharide-induced depressive-like behavior by suppressing hypothalamic microglia activation and neuroinflammation", Biochemical Pharmacology, 2019 Publication	1%
4	digital.library.adelaide.edu.au Internet Source	1%
5	Qingbo Lu, Fangfang Wu, Jiao Jiao, Le Xue, Ruize Song, Yachen Shi, Yan Kong, Jianfei Sun,	1%

	Ning Gu, Ming-Hu Han, Zhijun Zhang. "Selective activation of ABCA1/ApoA1 signalling in the V1 by magnetoelectric stimulation ameliorates depression via regulation of synaptic plasticity", iScience, 2022 Publication	
6	coek.info Internet Source	<1 %
7	link.springer.com Internet Source	<1 %
8	Petros Galanis, Aglaia Katsiroumpa, Irene Vraka, Olga Siskou, Olympia Konstantakopoulou, Theodoros Katsoulas, Daphne Kaitelidou. "Relationship between social support and resilience among nurses: a systematic review", Cold Spring Harbor Laboratory, 2022 Publication	<1 %
9	www.jove.com Internet Source	<1 %
10	idus.us.es Internet Source	<1 %
11	www.researchgate.net Internet Source	<1 %

12	María Fernanda Serna-Rodríguez, Sofía Bernal-Vega, José Alfonso Ontiveros-Sánchez de la Barquera, Alberto Camacho-Morales et al. "The role of damage associated molecular pattern molecules (DAMPs) and permeability of the blood-brain barrier in depression and neuroinflammation", Journal of Neuroimmunology, 2022 Publication	<1 %
13	Powell, David R., Jason P. Gay, Nathaniel Wilganowski, Deon Doree, Katerina V. Savelieva, Thomas H. Lanthorn, Robert Read, Peter Vogel, Gwenn M. Hansen, Robert Brommage, Zhi-Ming Ding, Urvi Desai, and Brian Zambrowicz. "Diacylglycerol Lipase α Knockout Mice Demonstrate Metabolic and Behavioral Phenotypes Similar to Those of Cannabinoid Receptor 1 Knockout Mice", Frontiers in Endocrinology, 2015. Publication	<1 %
14	Yousef Tizabi. "Duality of Antidepressants and Neuroprotectants", Neurotoxicity Research, 2015 Publication	<1 %
15	journals.physiology.org Internet Source	<1 %
16	repub.eur.nl Internet Source	<1 %

17	theses.gla.ac.uk Internet Source	<1%
18	worldwidescience.org Internet Source	<1%
19	www.dovepress.com Internet Source	<1%
20	Bin Lv, Naiting Shen, Zhangrong Cheng, Yuhang Chen, Hua Ding, Jishan Yuan, Kangchen Zhao, Yukun Zhang. "Strategies for Biomaterial-Based Spinal Cord Injury Repair via the TLR4-NF-κB Signaling Pathway", Frontiers in Bioengineering and Biotechnology, 2022 Publication	<1%

Exclude quotes	Off	Exclude matches	Off
Exclude bibliography	On		

Microglia as a Potential Target for Antidepressant: A Systematic Review on Preclinical studies

GRADEMARK REPORT

FINAL GRADE

/0

GENERAL COMMENTS

Instructor

PAGE 1

PAGE 2

PAGE 3

PAGE 4

PAGE 5

PAGE 6

PAGE 7