Food and Chemical Toxicology 127 (2019) 81–88

Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

Immunoregulatory natural compounds in stress-induced depression: An alternative or an adjunct to conventional antidepressant therapy?

Liliya V. Vasileva[a,**], Mariya V. Ivanovska[b,c], Marianna A. Murdjeva[b,c], Kremena E. Saracheva[d], Milen I. Georgiev[a,e,*]

[a] Center of Plant Systems Biology and Biotechnology, 4000, Plovdiv, Bulgaria
[b] Department of Microbiology and Immunology, Faculty of Pharmacy, Medical University Plovdiv, 4000, Plovdiv, Bulgaria
[c] Division of Immunological Assessment of Post-traumatic Stress Disorder, Technological Center for Emergency Medicine (TCEMED), 4000, Plovdiv, Bulgaria
[d] Department of Pharmacology and Drug Toxicology, Faculty of Pharmacy, Medical University Plovdiv, 4000, Plovdiv, Bulgaria
[e] Group of Plant Cell Biotechnology and Metabolomics, The Stephan Angeloff Institute of Microbiology, Bulgarian Academy of Sciences, 139 Ruski Blvd., 4000, Plovdiv, Bulgaria

ARTICLE INFO

Keywords:
Chronic stress
Depression
Phytotherapy
Neuroinflammation
Cytokines

ABSTRACT

The interplay of chronic stress, neuroinflammation and altered immune reactivity has been shown to be important for the pathophysiology of brain disorders such as schizophrenia, depressive disorders and post-traumatic stress disorder. This immuno-inflammatory theory has been extensively studied in the past three decades leading to the formation of the integrative discipline of psychoneuroimmunology. Targeting of the central nervous system by conventional pharmacotherapeutic methods is mainly through modulation of neuroendocrine systems such as the dopaminergic, GABA-ergic, adrenergic and serotoninergic systems. In recent years an increasing number of both experimental and clinical studies have shown that antidepressants can affect the immune system by reducing the production of pro-inflammatory cytokines such as IL-1β, IL-6 and TNF-α. However, due to the serious adverse effects accompanying the chronic administration of psychoactive drugs there is a continuous need to produce novel therapeutics that are both potent and safe. The present review aims to summarize the current knowledge in the field of psychoneuroimmunology and to delineate the main interactions between stress, inflammation, immunity and the brain. Additionally, this paper explores the use of plant-derived molecules that display a strong anti-stress effect and simultaneously modulate the immune response as an alternative or adjuvant to classical antidepressant drugs.

1. Introduction

Stress accompanies human daily life in various forms and is generally defined as a state that disrupts homeostasis. Adaptation to stressful events depends on the duration and the intensity of the stressor. During acute stress, many physiological systems are activated that allow the body to survive. Acute stress prepares not only the cardiovascular, musculoskeletal and neuro-endocrine system for the "fight, flight or freeze" response under certain conditions, but also the immune system for eventual stress-induced challenges (Dhabhar, 2018). Immune cells express surface receptors for neurotransmitters generated in response to stress such as glucocorticoids and catecholamines. Clinical studies in people experiencing acute stress show its bidirectional effects on immune response which could result either in enhanced or suppressed immune function (Cohen, 2006; Dhabhar, 2018).

On the other hand, when the stress persists over long periods it leads to numerous, long-term adverse health effects (Dhabhar, 2014, 2018). Environmental factors as well as internal or external stimuli

Abbreviations: 5HT, serotonin; ACTH, adrenocorticotropic hormone; ADH, antidiuretic hormone; APCs, antigen presenting cells; BBB, blood-brain barrier; bw, body weight; CNS, central nervous system; CFS, chronic fatigue syndrome; CRH, corticotropin-releasing hormone; CSFs, colony stimulating factors; HLA-II, human leukocyte antigen class II; HPA, hypothalamic–pituitary–adrenal; Hsp72, heat-shock protein 72; IFN-γ, interferon gamma; IL, interleukin; i.p., intraperitoneally; MDD, major depressive disorder; Nrf2, nuclear factor erythroid 2-related factor 2; NPY, neuropeptide Y; PFC, prefrontal cortex; p.o., orally; PTSD, post-traumatic stress disorder; SNRIs, serotonin-noradrenaline reuptake inhibitors; SNS, sympathetic nervous system; SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants; TGF-β, transforming growth factor beta; TNF-α, tumor necrosis factor alpha; TNF-β, tumor necrosis factor beta

* Corresponding author. The Stephan Angeloff Institute of Microbiology, Bulgarian Academy of Sciences, 139 Ruski Blvd., 4000, Plovdiv, Bulgaria.;
** Corresponding author. Center of Plant Systems Biology and Biotechnology, 139 Ruski Blvd., 4000, Plovdiv, Bulgaria.
E-mail addresses: vasileva.l.vl@gmail.com (L.V. Vasileva), milengeorgiev@gbg.bg (M.I. Georgiev).

https://doi.org/10.1016/j.fct.2019.03.004
Received 27 January 2019; Received in revised form 1 March 2019; Accepted 5 March 2019
Available online 08 March 2019
0278-6915/

continuously disrupt the homeostasis. A life-threatening situation such as major physical trauma or prolonged fasting can significantly alter homeostasis and the body's attempt to restore it often takes a lot of energy and natural resources that can lead either to a new level of homeostatic state (allostasis) or be interpreted itself as stress. Chronic stress factors can eventually lead to impairments and possible dysfunctions as the ability to maintain physiological functions are impeded. Many of these stress-induced disturbances weaken the protective function of the immune system by influencing humoral and cellular factors (Dhabhar, 2014; Dhabhar et al., 2012; Padro and Sanders, 2014). Clarification of the psychological and biological mechanisms by which chronic stress weakens an organism or exacerbates chronic disease would allow the development of behavioral and pharmacological treatment strategies aimed at alleviating or eliminating the harmful effects of stress (Chrousus and Kino, 2007; Jeon and Kim, 2017; Irwin and Cole, 2011).

Psycho-emotional distress, psychosomatic disorder, mental traumas, conflicts and extreme prolonged labor in stressful conditions affect the psycho-emotional status of an individual. This can lead to symptoms that affect mood (depression, tiredness and energy loss), concentration and behavior (Lupien et al., 2018). Chronic stress often co-occurs with a chronic inflammatory state represented with increased generation of pro-inflammatory cytokines such as interleukin-1β (IL-1β), interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α), disturbed tryptophan metabolism and decreased sensitivity of the glucocorticoid receptors (Dhabhar, 2018; Jeon and Kim, 2017; Maes, 2011). For instance, people suffering from major depressive disorder (MDD) are found to have elevated IL-6 levels (Hodes et al., 2016).

Considerable research in the last decade has been concentrated on the immuno-inflammatory mechanisms as a mode of treatment for psychiatric disorders. The term psychoneuroimmunology (PNI), i.e. immunopsychiatry refers to the interdisciplinary field that studies the heterogeneous interactions between the psycho-emotional processes, the neuroendocrine system and the immune response in the human organism (Cohen, 2006; Kim and Won, 2017; Pariante, 2015, 2017). Even though there is contention as to whether immune-mediated neuroinflammation is cause or a consequence within the complex clinical picture of stress-induced brain disorders, potent and safe anti-inflammatory agents that can cross the blood-brain barrier (BBB) are nonetheless needed. For example, many antidepressants are proven to have anti-inflammatory effects (Kenis and Maes, 2002). However, due to the significant adverse reactions to conventional psychoactive drugs there is a need for a novel therapeutic approach. Natural plant products are offering potent alternatives to classical antidepressants. Though the amount of experimental data on the effect of herbal extracts or pure plant-derived molecules that counteract the consequences of chronic stress is growing, to date no review specifically explores the effect of phytotherapeutics on immune-inflammatory response in brain disorders. This paper aims to review the current knowledge in the field of immunopsychiatry regarding the interconnections between chronic stress, immune response and neuroinflammation. In addition, the present review attempts to analyze experimental and clinical data concerning herbal substances that act on immune systems as both anti-stress and anti-inflammatory agents.

2. Chronic stress and brain disorders

The most common psychopathologies associated with chronic stress and immuno-inflammation are depressive disorders, post-traumatic stress disorder (PTSD) and schizophrenia (Lupien et al., 2018; McEwen, 2000).

Depressive disorders are strongly correlated with acute and chronic stress (Pizzagalli, 2014; Slavich and Irwin, 2014). Increased levels of pro-inflammatory cytokines in patients with major depressive disorder could induce neurotoxicity resulting in both functional and structural brain alternations which is comprehensively reviewed by Kim and Won (2017). Inflammation and elevated immune response found in a large portion of depressive phenotypes permits the definition of a specific subtype of depressive disorder: inflammation-induced depression (Jeon and Kim, 2017; Maes, 2011; Miller and Raison, 2015).

Patients with PTSD have suppressed reactivity of the hypothalamic–pituitary–adrenal (HPA) axis, which results in elevated catecholamines and corticotropin-releasing hormone (CRH), but low circulating cortisol (Lupien et al., 2018). In addition, PTSD leads to deregulated immune response represented by elevated pro-inflammatory cytokines such as IL-6, TNF-α and IL-17 and decreased IL-4 (Wang et al., 2016).

3. Neuroinflammation and cytokines involved in stress response

Under stress, the sympathetic nervous system (SNS) is the first to be activated. This induces a rapid stress response with increased release of noradrenaline and adrenaline followed by physiological reactions such as elevated pulse and increased metabolic rate. Subsequently, as part of the delayed stress response, the activation of the HPA axis provokes the hypothalamus to secrete CRH and antidiuretic hormone (ADH) and the pituitary - adrenocorticotropic hormone (ACTH) into the systemic circulation. Approximately 10 min after the action of a stress factor, glucocorticoids are released from the adrenal gland and, 30 min later, glucocorticoid secretion reaches its peak and then decreases (Ulrich-Lai and Herman, 2009).

Apart from these main neuroendocrine mediators, there are many other parameters of the complex network involved in the body's resistance to stress. The immune cells which are circulating in the blood stream, but also distributed to certain degree in every tissue, have receptors to many neuroendocrine mediators such as ACTH, glurocorticoids, catecholamines, endogenous opiates, prolactin, melatonin, testosterone, estrogen, etc. (Besedovsky and Rey, 2007). The immune system is thus directly influenced by the varying concentrations of these neuroendocrine mediators (Glaser and Kiecolt-Glaser, 2005). Conversely, the immune cells could affect the neuroendocrine system *via* secretion of cytokines. Although the BBB excludes water-soluble substances, circulating peptides and proteins from the brain, this barrier is missing in the thermoregulatory region, *i.e.* the hypothalamic frontal optic core, which allows the penetration of cytokines from the blood into the brain. Neurons express receptors for pro-inflammatory cytokines such as IL-1β, TNF-α and IL-6 that could induce activation of the HPA axis and affect the nervous system (Wohleb et al., 2013).

Neuroinflammation or elevated microglial activity is correlated with several mental illnesses. In response to stressful stimuli, the microglia experience changes either as a result of increased number due to proliferation or *via* enrolment of monocytes from the peripheral blood. This leads to an inflammatory glial response represented as production of pro-inflammatory cytokines and expression of several cell surface antigens (Frick et al., 2013; Walker et al., 2014; Wohleb et al., 2013). The interaction between the nervous, the endocrine and the immune-inflammatory systems induced by stress is summarized in Fig. 1.

Stress exposure activates the hypothalamic-pituitary-adrenal (HPA) axis, which initiate production of corticotropin-releasing hormone (CRH) from hypothalamus to the pituitary gland. Adrenocorticotropic hormone (ACTH) secreted from the pituitary activates the adrenal glands which results in stress-induced release of glucocorticoids (GC), noradrenaline (NA) and adrenaline (A). The pituitary also produces growth hormone (GH) and prolactin. All these hormones are sensed by the immune cells. Simultaneously with the HPA axis the autonomic nervous system responds to stress resulting in activation of the sympathetic nervous system's innervation (SNSI) and the parasympathetic nervous system's innervation (PSNI). Both SNSI and PSNI produce an effect on the lymph nodes and increase immune cell trafficking to the peripheral blood. Finally, the activated immune cells produce various cytokines in response to stress, many of which could cross the brain-blood barrier (BBB) and activate the resident immune cells, *i.e.*

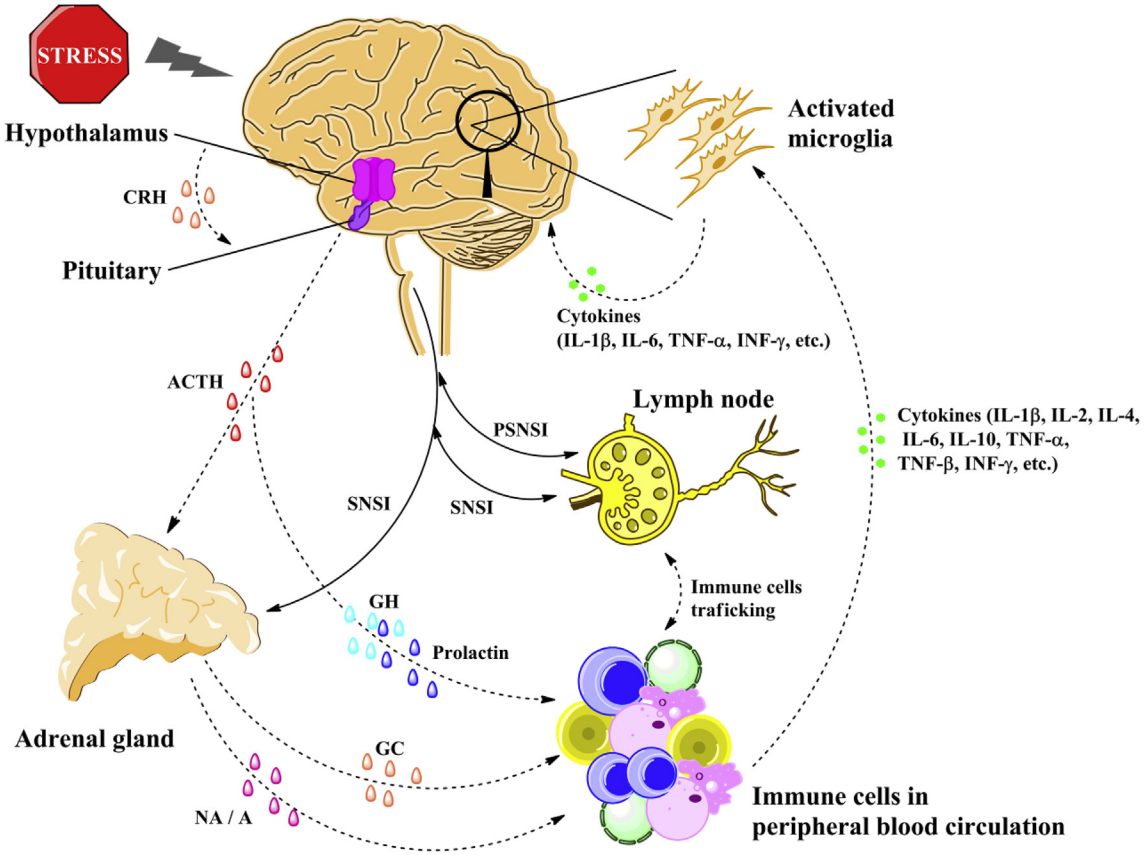

Fig. 1. Psychoneuroimmune interactions in response to stress (modified from Glaser and Kiecolt-Glaser, 2005).

microglia, to also produce cytokines and provoke neuroinflammation in the brain.

The brain lacks a lymphatic system and neurons do not normally express the human leukocyte antigen class II (HLA-II) molecules required for antigen-specific immune response activation. However, it is possible to activate an immune response in the CNS under certain circumstances. Bone marrow-derived cells such as perivascular macrophages and microglia that express the HLA-II and can present antigens are part of the CNS; additionally, astrocytes and endothelial cells could play a role of antigen presenting cells (APCs) and are able to release pro-inflammatory cytokines when activated. The microglial cells synthesize and respond to cytokines such as IL-1β, IL-6, TNF-α, tumor necrosis factor beta (TNF-β), interferon gamma (IFN-γ), transforming growth factor beta (TGF-β) as well as colony stimulating factors (CSFs). The IL-1β induces astrocyte proliferation and subsequent release of other cytokines from the astrocytes. The TNF-α and TNF-β are capable of damaging the oligodendrocytes, a source of myelin in the brain. In addition, activated peripheral T-lymphocytes may penetrate the BBB and release cytokines that increase HLA-II expression in surrounding endothelial cells, further increasing the permeability of the BBB and accelerating the rate at which B-lymphocytes can penetrate into the brain (Frick et al., 2013; Walker et al., 2014). This evidence suggests that the immune system is capable of causing neuroendocrine responses and gives reason to assert that it is a peripheral receptor organ that transmits brain information about endogenous or exogenous stress stimuli (Beedovsky and Rey, 2007).

4. Psychoactive drugs and their effect on immune response in stress-induced disorders

In recent years, an increasing number of psychopharmacological studies exploited the immune-inflammatory theory of stress-induced disorders to evaluate the effect of psychoactive drugs on the immune system (Felger and Lotrich, 2013; Hiles et al., 2012). The clinical efficacy of antidepressants is related to their immunomodulatory properties (Kenis and Maes, 2002). For example, the decrease in TNF-α levels during therapy is associated with a good antidepressant response, whereas the IL-6 elevation is associated with an unsatisfactory one (Lichtblau et al., 2013).

Antidepressants, as a first-line therapy for stress-induced disorders and depressive disorders, continue to be a subject of intense study, particularly relating to their immunomodulatory effects. Apart from their main mechanism of action – the inhibition of the reuptake of certain neurotransmitters - antidepressants also produce significant reduction in pro-inflammatory cytokines such as IL-1, IL-6, TNF-α, IL-17 (Gobin et al., 2014; Hiles et al., 2012).

Considering the immunomodulatory effects of the selective serotonin reuptake inhibitors (SSRIs), special attention is paid to the role of serotonin (5HT) signaling on immune cells (Gobin et al., 2014). Not only do SSRIs have the ability to affect healthy lymphocytes, but they also influence the viability of some immune cancer cells. Given that serotonin is involved in T-cells activation, the authors propose that the anti-proliferative action of fluoxetine may be due to inhibition of 5-HT uptake in T-lymphocytes (Amit et al., 2009). Another possible mechanism for the effect on T-cells by SSRIs is suggested by Gobin et al. (2015), as they found that fluoxetine suppresses the intracellular calcium signaling.

In an *in vitro* experiment, Munzer et al. (2013) investigated the effects of citalopram, mirtazapine and escitalopram on the secretion of a panel of cytokines in activated T and B-lymphocytes. Their study found that citalopram increased the levels of IL-1β, IL-6, IL-22 and TNF-α, while escitalopram reduced the IL-17 levels. As a probable cause of the observed differences in the effect of the two SSRIs on the cytokines profile, the researchers pointed out the different stereochemical

Table 1
Examples of selected studies on the effect of antidepressants on cytokines production *in vivo* in rodent stress models.

Antidepressant drug / group	Dosage and route of administration, mg/kg bw	Period of treatment, days	Experimental stress model / animals	Effect on cytokine production	Reference
Clomipramine / TCAs	20 mg/kg bw, i.p.	21	LPS / Wistar rats	↑IL-10, ↑TGF-1β, ↓TNF-α in blood	(Kostadinov et al., 2014)
Desipramine / TCAs	10 mg/kg bw, i.p.	21	CMS / C57BL/6 mice	↑IL-10, ↓IL-1β, ↓IL-2 in spleen	(Kubera et al., 2001b)
Escitalopram / SSRIs	3 and 10 mg/kg bw, i.p.	1	LPS / C57BL/6N mice	↓TNF-α, ↓IL-10 in blood	(Dong et al., 2016)
Fluoxetine / SSRIs	10 mg/kg bw, i.p.	11	LPS / C57BL/6J mice	↓IL-1β and ↓TNF-α in spleen and hippocampus ↓IL-6, ↓IL-10 in spleen	(Duda et al., 2017)
Fluoxetine / SSRIs	42 mg/kg bw, p.o.	90, 120	CMS / SD rats	↓IL-1β, ↓IL-6, ↓TNF-α in periphery, brain	(Lu et al., 2017)
Fluoxetine/ SSRIs	3, 10 and 30 mg/kg bw, i.p.	1	LPS/ BALB mice	↑IL-10, ↓TNF-α in blood	(Ohgi et al., 2013)
Fluoxetine/ SSRIs	15 mg/kg bw, i.p.	21	CSIS/ Wistar rats	↓TNF-α in hippocampus	(Todorovic and Filipovic, 2017)
Imipramine / TCAs	15 mg/kg bw, p.o.	8	RSD / C57BL/6 mice	↓IL-6 in plasma ↔IL-1β, ↔IL-6 and ↔TNF-α in spleen ↓IL-1β, ↓IL-6 and ↓TNF-α in microglia	(Ramirez and Sheridan, 2016)
Mianserin / (TeCA)	10 mg/kg bw, i.p.	42	CMS / rats	↓TNF-α, ↓IL-6, ↓IL-10 in blood	(Manikowska et al., 2014)
Paroxetine/ SSRIs	3, 10 and 30 mg/kg bw, i.p.	1	LPS/ BALB mice	↑IL-10, ↓TNF-α in blood	(Ohgi et al., 2013)

↔, no effect; ↓, decrease; ↑, increase; bw, body weight; CSIS, chronic social isolation stress; CMS, chronic mild stress; i.p., intraperitoneally; LPS, lypopolisacharide; p.o., orally; PFC, prefrontal cortex; PNS, prenatal stress; RSD, repeated social defeat; SD, Sprague-Dawley; SDS, social defeat stress; TeCA, tetracyclic antidepressants.

structure of citalopram (a racemic mixture of R- and S-stereoisomers) compared to escitalopram (an active S-enantiomer of citalopram; Munzer et al., 2013).

A summary of the main findings from recent experimental studies considering the effect of antidepressants on cytokines levels are presented in Table 1. The most frequently employed experimental models of depression involve either repeated LPS stimulation or chronic stress procedures. Regardless of the model system, a stress-induced increase in the pro-inflammatory cytokines production is found in stressed compared to non-stressed animals. The elevated levels of pro-inflammatory factors such as TNF-α, IL-1β, IL-6 are decreased by antidepressant administration both peripherally and centrally (Lu et al., 2017; Ramirez and Sheridan, 2016). Interestingly, Ramirez and Sheridan (2016) reported that imipramine (15 mg/kg bw, p.o.) decreased TNF-α, IL-1β and IL-6 levels in microglial cells but did not change the levels of these cytokines in spleen. However, considering the direct anti-inflammatory activity of the antidepressant therapy, the results remain controversial. While in some of the studies - such as those reported by Kostadinov et al. (2014), Kubera et al. (2001a,b) and Ohgi et al. (2013) – an increase in anti-inflammatory factors such as IL-10 and TGF-1β is reported, in other studies by Dong et al. (2016), Duda et al. (2017) and Manikowska et al. (2014) their production is suppressed along with the production of the pro-inflammatory cytokines.

Taken together the data from the evaluated studies highlights the negative regulatory effect of antidepressants on the immuno-inflammatory reactions, represented as decreased pro-inflammatory cytokines production. These promising experimental findings warrant transition to clinical studies in depressed patients that aim to confirm the connection between the effectiveness of the therapy and the cytokines profile of the patient. However, clinical trials evaluating the effect of antidepressant therapy on the production of cytokines are insufficient. For example, in a double-blind, placebo-controlled study after 6-weeks of sertraline administration (SSRI), at a dose of 50 mg per day, Brunoni et al. (2014) did not observe significant changes in TNF-α levels despite clinical improvement. There is also evidence for fluoxetine inhibition of IFN-γ and an increase in IL-10 production in blood from depressed patients. Given the complexity of the immune response in humans, the diverse subtypes of depressive disorders and the highly variable efficacy of antidepressant treatment the inconsistent results reported on cytokines levels in depressed patients are expected. The mechanisms of the immunomodulation of antidepressants should be further clarified in experimental settings in order to permit more precisely designed clinical studies in patients.

5. Plant extracts and their bioactive molecules with effect on immune-inflammatory response in stress-induced disorders

Natural products and, more specifically, medicinal plant species have been utilized for centuries in the treatment and management of various pathological conditions (Georgiev, 2014). Stress-induced disorders are characterized by changes in the CNS that involve a plethora of molecular pathways, suggesting that the therapy against such multifactorial conditions should target more than one neuroendocrine system. Plant extracts comprise complex mixtures of usually more than one bioactive molecule and so the conventional pharmacological concept of “one drug – one receptor – one disease” is not easily applicable to explain their mode of action. In general, phytotherapeutics that are known to act on the CNS are classified into several categories according to their main action on the brain: antidepressant, sedative, nootropic, tonic and adaptogenic. Ethnopharmacologically among the most extensively studied plants for their psychotropic action are *Hypericum perforatum* L., *Valeriana officinalis* L., *Passiflora incarnata* L., *Crocus sativus* L., *Curcuma longa* L., *Rhodiola rosea* L., *Coffea arabica* L., and *Cannabis sativa* L. (Panossian et al., 2018; Sarris et al., 2011; Shafiee et al., 2017).

Plant extracts that non-specifically increase an organism's resistance

to stress *via* modulation of the two main stress control systems in the body namely the HPA axis and the SNS, are termed adaptogens (Panossian et al., 2009). Studies on their mechanism of action have shown enhancement of the production of neuropeptide Y (NPY) and heat-shock protein 72 (Hsp72), which promotes relaxation and increases neuronal plasticity and adaptability (Panossian and Wikman, 2010; Panossian et al., 2012).

Plant adaptogens alleviate the negative effects on health from prolonged exposure to stress, and this is at least in part a result of immunomodulation. Our previous studies found that treatment of stressed rats with extracts from *Rhodiola rosea* L. and *Curcuma longa* L. as well as their respective marker substances, salidroside and curcumin, attenuate the production of both IL-6 and TNF-α levels in brain tissue and in serum (Vasileva et al., 2017, 2018). Salidroside has been previously reported to inhibit the pro-inflammatory cytokines' production in depression models (Yang et al., 2014; Zhu et al., 2015).

Special attention has been generated by the antidepressant potential of curcumin – the active compound of *Curcuma longa* L. – which is a strong natural antioxidant with potent inhibiting activity against pro-inflammatory factors. Fot this reason, it has been implemented within the therapy for osteoarthritis, inflammatory bowel disease, certain types of cancer (*e.g.* colorectal carcinoma) and other diseases (Salehi et al., 2019). In recent years, extensive studies revealed the profound activity of curcumin on depressive and stress-induced disorders, especially regarding the accompanying immune-inflammatory dysregulations, both in experimental and clinical settings (Jiang et al., 2013; Kaufmann et al., 2016; Lopresti et al., 2014; Vasileva et al., 2018). However, despite the diverse range of beneficial activities designated to this natural compounds there are also some controversies about its mechanisms of action. One is the extensively discussed bioavailability of curcumin (Aggarwal et al., 2013). Another recently reported problem is that it could give interference in some biological screening assays leading to false-positive results (Baell and Nissink, 2018).

Zhang et al. (2017b) aimed to examine the antidepressant-like effect of sulforaphane a potent natural antioxidant and nuclear factor erythroid 2–related factor 2 (Nrf2) activator derived from plants of the Brassicaceae family. Interestingly, the authors reported that pretreatment with sulforaphane (30 mg/kg bw, p.o.) resulted in a strong reduction of the immobilization time on forced swim test and a decrease of the production of the pro-inflammatory cytokine TNF-α but had no effect on the levels of the anti-inflammatory IL-10 (Zhang et al., 2017b). In similar experimental set-up, Jiang et al. (2017) provided evidences that proanthocyanidins (80 mg/kg bw, p.o.) from *Vitis vinifera* L. dose-dependently decreased the LPS-induced neuroinflammation *via* inhibition of the NF-κB pathway in the hippocampus of depressed mice. The authors reported decreased levels of IL-1β, IL-6 and TNF-α in brain tissue as a result of the proanthocyanidin administration (Jiang et al., 2017). Further, Liu et al. (2014) reported that treatment with extract from *Hemerocallis citrina* (130 mg/kg bw, p.o.) produces an antidepressant-like effect in chronically stressed rats and suggested that this effect could be mediated through inhibition of neuroinflammation represented by decreased levels of IL-1β, IL-6 and TNF-α in the prefrontal cortex (PFC) in rats (Liu et al., 2014).

Natural compounds such as bilobalide, ginsenoside, rosmarinic acid, salvianolic acid and hesperidin are exploited for their strong anti-inflammatory effects in studies of different models of brain illnesses (Sui et al., 2019; Yu et al., 2019). Some of the plant-derived natural substances that have gained focus for their effect on cytokines and neuroinflammation in experimental models of stress and depression are shown in Table 2. Promising behavioral outcomes, along with attenuation of inflammatory mediators, are shown for the herbal molecules in these studies. In some cases, the decrease in the stress-induced production of TNF-α, IL-1β and IL-6 in brain tissue was comparable to that of a positive control, indicative of possible common modes of action between the studied phytochemicals and conventional antidepressants such as fluoxetine (Cheng et al., 2018; Vasileva et al., 2017;

Table 2
Examples of selected studies of natural compounds with antidepressant-like effect on cytokines production *in vivo* in rodent stress models.

Plant-derived compound	Positive control for antidepressant action	Dosage and route of administration, mg/kg bw	Period of treatment, days	Experimental stress model / animals	Effect on cytokine production	Reference
Apigenin	Fluoxetine (20 mg/kg bw, i.p.)	25 and 50 mg/kg bw, i.p.	7	LPS / IRC mice	↓IL-1β and ↓TNF-α in PFC	(Li et al., 2015)
Berberine	Fluoxetine (20 mg/kg bw, p.o.)	50 and 100 mg/kg bw, i.p.	28	CUMS / IRC mice	↓IL-1β, ↓IL-6 and ↓TNF-α in hippocampus	(Liu et al., 2017)
Curcumin	-	40 mg/kg bw, p.o.	40	CMS / Wistar rats	↓IL-1β, ↓IL-6 and ↓TNF-α in PFC	(Fan et al., 2018)
Curcumin	Fluoxetine (2.5 mg/kg bw, p.o.)	20 mg/kg bw, p.o.	8	CMS / Wistar rats	↓IL-6 and ↓TNF-α in serum ↓TNF-α in brain	(Vasileva et al., 2018)
Quercetin	-	20, 40 and 80 mg/kg bw, p.o.	14	OBX / Wistar rats	↓IL-6 and ↓TNF-α in cortex and hippocampus	(Rinwa and Kumar, 2013)
Icariin	Fluoxetine (10 mg/kg bw, p.o.)	20 and 40 mg/kg bw, p.o.	35	CMS/ SD rats	↓IL-1β and ↓TNF-α in hippocampus	(Liu et al., 2015)
Magnolol	Fluoxetine (20 mg/kg bw, p.o.)	20 and 40 mg/kg bw, p.o.	28	CMS/ Kunming mice	↓IL-1β, ↓IL-6 and ↓TNF-α in PFC	(Cheng et al., 2018)
Naringenin	-	10, 25 and 50 mg/kg bw, i.p.	14	SDS/ Swiss mice	↓IL-1β and ↓TNF-α in brain tissue	(Umukoro et al., 2018)
Resveratrol	-	10 and 30 mg/kg bw, i.p.	12	SDS / SD rats	↓IL-1β, ↓IL-2, ↑IL-4, ↓IL-6, ↔IL-10, ↓IL-13 and ↓TNF-α in brain tissue	(Finnell et al., 2017)
Salidroside	Fluoxetine (2.5 mg/kg bw, p.o.)	5 mg/kg bw, p.o.	8	CMS / Wistar rats	↓IL-6 and ↓TNF-α in serum ↓TNF-α in brain	(Vasileva et al., 2018)
Salvianolic acid	Imipramine (10 mg/kg bw, i.p.)	20 mg/kg bw, i.p.	21	CMS / C57BL/6 mice	↓IL-1β, ↑IL-4, ↓IL-6, ↔IL-10, ↓TNF-α, ↓IFN-γ, ↔TGF-β in microglia	(Zhang et al., 2017a)
Senegenin	Fluoxetine (20 mg/kg bw, p.o.)	8 mg/kg bw, p.o.	21	CUMS / IRC mice	↓IL-1β and ↓TNF-α in hippocampus	(Li et al., 2017)
Sesamin	-	50 mg/kg bw, p.o.	48	CUMS / CD-1 mice	↓IL-1β and ↓TNF-α in brain tissue	(Zhao et al., 2018)

-, none; ↔, no effect; ↓, decrease; ↑, increase; bw, body weight; CMS, chronic mild stress; CUMS, chronic unpredictable mild stress; i.p., intraperitoneally; p.o., orally; PFC, prefrontal cortex; RSD, repeated social defeat; SD, Sprague-Dawley; SDS, social defeat stress.

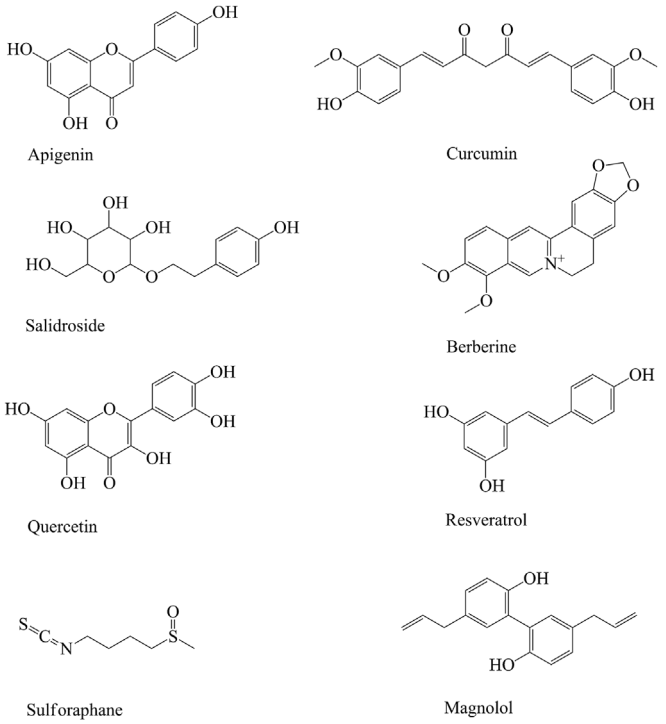

Fig. 2. Chemical structures of selected natural compounds with potential antidepressant-like effects.

Zhang et al., 2017a). Other studies that lack a positive control are worth repeating, as the reported results showed a pronounced anti-inflammatory effect for substances such as naringenin, resveratrol, sesamin and quercetin in brain tissue (Rinwa and Kumar, 2013; Umukoro et al., 2018; Zhao et al., 2018). Selected examples of the plant-derived molecules with promising antidepressant-like potential are presented with their chemical structures in Fig. 2. Regarding the structure-activity relationship among the most commonly known to act on the brain are the polyphenolic compounds. As this interesting and challenging topic that is out of the scope of the current review, we recommend recent publication in the field (Bakoyiannis et al., 2019; Sagandykova et al., 2018).

Even though plant-derived compounds are generally considered to have a lower potential for toxic effects on health than chemically synthetized molecules, it is still advisable to take the necessary care and evaluate the respective toxicology risk. Another uncertainty is the relevance of the doses used in experimental methods. Allometric scaling should be considered when experimental doses are translated between animal species and humans (Nair and Jacob, 2016). In most of the discussed studies the chosen experimental doses are comparable to human doses. However, there are some examples - such as the use of berberine in doses of 50 and 100 mg/kg bw, i.p. in mice - that could doubtfully be applied as respective human doses in clinical settings (Liu et al., 2017). Moreover, the administration of berberine in doses over 50 mg/kg bw, i.p. has been reported to produce toxic effects in mice (Kheir et al., 2010; Kukula-Koch et al., 2017).

The data gathered experimentally on the antidepressant and immunomodulating effect of plant extracts and natural compounds derived from them is substantial. The efficacy of the studied phytochemicals is often comparable to that of conventional antidepressants which suggests that the natural molecules could be used as an adjuvant, if not as a replacement, in the therapy of depressive disorders. An interesting hypothesis, worthy of being explored is the use of plant-derived compounds together with conventional pharmaceuticals. The idea of hybrid combinations is tested predominantly in chemotherapy (Seo et al., 2018; Wagner and Efferth, 2017). Most cytostatic drugs are known to impair normal cells along with eliminating cancer cells. Seo et al. (2018) found that addition of plant extracts to a fixed combination of cytostatics alleviated the negative effects from the chemotherapy on neuroglial cells. Further detailed studies are required to confirm and develop the idea of effective hybrid combinations between synthetic drugs and natural compounds (Wagner and Efferth, 2017). Hypothetically such hybrid combinations could be tested in the therapy of various medicinal conditions as well as in stress-induced disorders. The use of conventional antidepressants is usually prolonged and accompanied with serious systemic adverse effects including weight gain, sexual dysfunctions, sleep disturbances, addiction, withdrawal syndrome and suicidal ideations. Investigation into combinations of synthetic antidepressants and plant molecules with promising anti-stress and anti-inflammatory effects could result in viable hybrid combinations with improved efficacy and/or safety in the chronic therapy of depressive disorders. Moreover, such studies should implement "-omics" techniques such as metabolomics, pharmacogenomics and proteomics to clarify the detailed mechanism of interaction between the components included (Chen et al., 2018; Sahoo and Brijesh, 2019).

6. Conclusions

In the past three decades, the field of psychoneuroimmunology has witnessed tremendous progress. The role of chronic stress and immune-inflammation as risk factors for brain disorders such as MDD or PTSD is unquestioned. Understanding the cytokine profiles of stress-induced psychopathologies would aid not only the early diagnosis of stress-induced brain disorders but will eventually be of great importance in both the choice of proper therapy and the development of novel treatments. Many experimental and clinical studies have confirmed that the antidepressant effect of the SSRIs is mediated partly *via* immunomodulation. Plant-derived molecules with antidepressant-like effect are of great scientific interest as many of these phytotherapeutics show properties comparable to that of conventional antidepressants. Furthermore, natural compounds with significant anti-inflammatory effects warrant further investigation regarding their use in hybrid combinations with synthetic psychoactive drugs.

Conflicts of interest

The authors declare that the present work is not a subject of any potential conflict of interest.

Acknowledgments

This project for establishment of CPSBB has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement № PlantaSYST – SGA/CSA: 739582 – under FPA: 664620. The authors are grateful to Dr. Rafe Lyall a Postdoctoral Researcher at the Department of Bioinformatics and Mathematical Modeling of the CPSBB for proofreading and linguistic editing of the manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2019.03.004.

References

Aggarwal, B.B., Gupta, S.C., Sung, B., 2013. Curcumin: an orally bioavailable blocker of TNF and other pro-inflammatory biomarkers. Br. J. Pharmacol. 169, 1672–1692.
Amit, B.H., Gil-Ad, I., Taler, M., Zolokov, A., Weizman, A., 2009. Proapoptotic and chemosensitizing effects of selective serotonin reuptake inhibitors on T cell lymphoma/leukemia (Jurkat) in vitro. Eur. Neuropsychopharmacol. 19, 726–734.
Baell, J.B., Nissink, J.W.M., 2018. Seven year itch: pan-assay interference compounds (PAINS) in 2017 - utility and limitations. ACS Chem. Biol. 13, 36–44.

Bakoyiannis, I., Daskalopoulou, A., Pergialiotis, V., Perrea, D., 2019. Phytochemicals and cognitive health: are flavonoids doing the trick? Biomed. Pharmacother. 109, 1488–1497.
Besedovsky, H.O., Rey, A.D., 2007. Physiology of psychoneuroimmunology: a personal view. Brain Behav. Immun. 21, 34–44.
Brunoni, A.R., Machado-Vieira, R., Zarate, C.A., Valiengo, L., Vieira, E.L., Bensenor, I.M., Lotufo, P.A., Gattaz, W.F., Teixeira, A.L., 2014. Cytokines plasma levels during antidepressant treatment with sertraline and transcranial direct current stimulation (tDCS): results from a factorial, randomized, controlled trial. Psychopharmacology 231, 1315–1323.
Chen, L., Teng, H., Xie, Z., Cao, H., Cheang, W.S., Skalicka-Wozniak, K., Georgiev, I.M., Xiao, J., 2018. Modifications of dietary flavonoids towards improved bioactivity: an update on structure–activity relationship. Crit. Rev. Food Sci. Nutr. 58, 513–527.
Cheng, J., Dong, S., Yi, L., Geng, D., Liu, Q., 2018. Magnolol abrogates chronic mild stress-induced depressive-like behaviors by inhibiting neuroinflammation and oxidative stress in the prefrontal cortex of mice. Int. Immunopharmacol. 59, 61–67.
Chrousos, G.P., Kino, T., 2007. Glucocorticoid action networks and complex psychiatric and/or somatic disorders. Stress 10, 213–219.
Cohen, N., 2006. The uses and abuses of psychoneuroimmunology: a global overview. Brain Behav. Immun. 20, 99–112.
Dhabhar, F.S., Malarkey, W.B., Neri, E., McEwen, B.S., 2012. Stress-induced redistribution of immune cells—from barracks to boulevards to battlefields: a tale of three hormones – curt Richter Award Winner. Psychoneuroendocrinology 37, 1345–1368.
Dhabhar, F.S., 2014. Effects of stress on immune function: the good, the bad, and the beautiful. Immunol. Res. 58, 193–210.
Dhabhar, F.S., 2018. The short-term stress response - mother nature's mechanism for enhancing protection and performance under conditions of threat, challenge, and opportunity. Front. Neuroendocrinol. 49, 175–192.
Dong, C., Zhang, J.C., Yao, W., Ren, Q., Yang, C., Ma, M., Han, M., Saito, R., Hashimoto, K., 2016. Effects of escitalopram, R-citalopram, and reboxetine on serum levels of tumor necrosis factor-α, interleukin-10, and depression-like behavior in mice after lipopolysaccharide administration. Pharmacol. Biochem. Behav. 144, 7–12.
Duda, W., Kubera, M., Kreiner, G., Curzytek, K., Detka, J., Glombik, K., Slusarczyk, J., Basta-Kaim, A., Budziszewska, B., Lason, W., Regulska, M., Leskiewicz, M., Roman, A., Zelek-Molik, A., Nalepa, I., 2017. Suppression of pro-inflammatory cytokine expression and lack of anti-depressant-like effect of fluoxetine in lipopolysaccharide-treated old female mice. Int. Immunopharmacol. 48, 35–42.
Fan, C., Song, Q., Wang, P., Li, Y., Yang, M., Liu, B., Yu, S.Y., 2018. Curcumin protects against chronic stress-induced dysregulation of neuroplasticity and depression-like behaviors via suppressing IL-1β pathway in rats. Neuroscience 392, 92–106.
Felger, J.C., Lotrich, F.E., 2013. Inflammatory cytokines in depression: neurobiological mechanisms and therapeutic implications. Neuroscience 246, 199–229.
Finnell, J.E., Lombard, C.M., Melson, M.N., Singh, N.P., Nagarkatti, M., Nagarkatti, P., Fadel, J.R., Wood, C.S., Wood, S.K., 2017. The protective effects of resveratrol on social stress-induced cytokine release and depressive-like behavior. Brain Behav. Immun. 59, 147–157.
Frick, L.R., Williams, K., Pittenger, C., 2013. Microglial dysregulation in psychiatric disease. Clin. Dev. Immunol. 2013, 608654.
Georgiev, M.I., 2014. Natural products utilization. Phytochemistry Rev. 13, 339–341.
Glaser, R., Kiecolt-Glaser, J.K., 2005. Stress-induced immune dysfunction: implications for health. Nat. Rev. Immunol. 5, 243–251.
Gobin, V., De Bock, M., Broeckx, B.J., Kiselinova, M., De Spiegelaere, W., Vanderkerckhove, L., Van Steendam, K., Leybaert, L., Deforce, D., 2015. Fluoxetine suppresses calcium signaling in human T lymphocytes through depletion of intracellular calcium stores. Cell Calcium 58, 254–263.
Gobin, V., Steendam, K. Van, Denys, D., Deforce, D., 2014. Selective serotonin reuptake inhibitors as a novel class of immunosuppressants. Int. Immunopharmacol. 20, 148–156.
Hiles, S.A., Baker, A.L., de Malmanche, T., Attia, J., 2012. Interleukin-6, C-reactive protein and interleukin-10 after antidepressant treatment in people with depression: a meta-analysis. Psychol. Med. 42, 2015–2026.
Hodes, G.E., Menard, C., Russo, S.J., 2016. Integrating interleukin-6 into depression diagnosis and treatment. Neurobiol. Stress 4, 15–22.
Irwin, M., Cole, S.W., 2011. Reciprocal regulation of the neural and innate immune systems. Nat. Rev. Immunol. 11, 625–632.
Jeon, S.W., Kim, Y.K., 2017. Inflammation-induced depression: its pathophysiology and therapeutic implications. J. Neuroimmunol. 313, 92–98.
Jiang, H., Wang, Z., Wang, Y., Xie, K., Zhang, Q., Luan, Q., Chen, W., Liu, D., 2013. Antidepressant-like effects of curcumin in chronic mild stress of rats: involvement of its anti-inflammatory action. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 47, 33–39.
Jiang, X., Liu, J., Lin, Q., Mao, K., Tian, F., Jing, C., Wang, C., Ding, L., Pang, C., 2017. Proanthocyanidin prevents lipopolysaccharide-induced depressive-like behavior in mice via neuroinflammatory pathway. Brain Res. Bull. 135, 40–46.
Kaufmann, F.N., Gazal, M., Bastos, C.R., Kaster, M.P., Ghisleni, G., 2016. Curcumin in depressive disorders: an overview of potential mechanisms, preclinical and clinical findings. Eur. J. Pharmacol. 784, 192–198.
Kenis, G., Maes, M., 2002. Effects of antidepressants on the production of cytokines. Int. J. Neuropsychopharmacol. 5, 401–412.
Kheir, M.M., Wang, Y., Hua, L., Hu, J., Li, L., Lei, F., Du, L., 2010. Acute toxicity of berberine and its correlation with the blood concentration in mice. Food Chem. Toxicol. 48, 1105–1110.
Kim, Y.K., Won, E., 2017. The Influence of stress on neuroinflammation and alternations in brain structure and function in major depressive disorder. Behav. Brain Res. 329, 6–11.
Kostadinov, I., Delev, D., Petrova, A., Stanimirova, I., Draganova, K., Kostadinova, I., Murdjeva, M., 2014. Study on anti-inflammatory and immunomodulatory effects of clomipramine in carrageenan- and lipopolysaccharide-induced rat models of inflammation. Biotechnol. Biotechnol. Equip. 28, 552–558.
Kubera, M., Lin, A., Kenis, G.R.L., Bosmans, E., van Bockstaele, D., Maes, M., 2001a. Anti-inflammatory effects of antidepressants through suppression of the interferon-gamma/interleukin-10 production ratio. J. Clin. Psychopharmacol. 21, 199–206.
Kubera, M., Maes, M., Holan, V., Basta-Kaim, A., Roman, A., Shani, J., 2001b. Prolonged desipramine treatment increases the production of interleukin-10, an anti-inflammatory cytokine, in C57BL/6 mice subjected to the chronic mild stress model of depression. J. Affect. Disord. 63, 171–178.
Kukula-Koch, W., Kruk-Slomka, M., SDtepnik, K., Szalak, R., Biala, G., 2017. The evaluation of pro-cognitive and antiamnestic properties of berberine and magnoflorine isolated from barberry species by centrifugal partition chromatography (CPC), in relation to QSAR modelling. Int. J. Mol. Sci. 18, 2511.
Li, H., Lin, S., Qin, T., Li, H., Ma, Z., Ma, S., 2017. Senegenin exerts anti-depression effect in mice induced by chronic un-predictable mild stress via inhibition of NF-κB regulating NLRP3 signal pathway. Int. Immunopharmacol. 53, 24–32.
Li, R., Zhao, D., Qu, R., Fu, Q., Ma, S., 2015. The effects of apigenin on lipopolysaccharide-induced depressive-like behavior in mice. Neurosci. Lett. 594, 17–22.
Lichtblau, N., Schmidt, F.M., Schumann, R., Kirkby, K.C., Himmerich, H., 2013. Cytokines as biomarkers in depressive disorder: current standing and prospects. Int. Rev. Psychiatry 25, 592–603.
Liu, B., Xu, C., Wu, X., Liu, F., Du, Y., Sun, J., Tao, J., Dong, J., 2015. Icariin exerts an antidepressant effect in an unpredictable chronic mild stress model of depression in rats and is associated with the regulation of hippocampal neuroinflammation. Neuroscience 294, 193–205.
Liu, X.L., Luo, L., Liu, B.B., Li, J., Geng, D., Liu, Q., Yu, L.T., 2014. Ethanol extracts from *Hemerocallis citrina* attenuate the upregulation of proinflammatory cytokines and indoleamine 2,3-dioxygenase in rats. J. Ethnopharmacol. 153, 484–490.
Liu, Y.M., Niu, L., Wang, L.L., Bai, L., Fang, X.Y., Li, Y.C., Yi, L.T., 2017. Berberine attenuates depressive-like behaviors by suppressing neuro-inflammation in stressed mice. Brain Res. Bull. 134, 220–227.
Lopresti, A.L., Maes, M., Maker, G.L., Hood, S.D., Drummond, P.D., 2014. Curcumin for the treatment of major depression: a randomised, double-blind, placebo controlled study. J. Affect. Disord. 167, 368–375.
Lu, Y., Ho, C.S., Liu, X., Chua, A.N., Wang, W., McIntyre, R.S., Ho, R.C., 2017. Chronic administration of fluoxetine and pro-inflammatory cytokine change in a rat model of depression. PLoS One 12 e0186700.
Lupien, S.J., Juster, R.P., Raymond, C., Marin, M.F., 2018. The effects of chronic stress on the human brain: from neurotoxicity, to vulnerability, to opportunity. Front. Neuroendocrinol. 49, 91–105.
Maes, M., 2011. Depression is an inflammatory disease, but cell-mediated immune activation is the key component of depression. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 35, 664–675.
Manikowska, K., Mikolajczyk, M., Mikolajczak, P.L., Bobkiewicz-Kozlowska, T., 2014. The influence of mianserin on TNF-α, IL-6 and IL-10 serum levels in rats under chronic mild stress. Pharmacol. Rep. 66, 22–27.
McEwen, B.S., 2000. Effects of adverse experiences for brain structure and function. Biol. Psychiatry 48, 721–731.
Miller, A.H., Raison, C.L., 2015. The role of inflammation in depression: from evolutionary imperative to modern treatment target. Nat. Rev. Immunol. 16, 22–34.
Munzer, A., Sack, U., Mergl, R., Schonnherr, J., Petersein, C., Bartsch, S., Kirkby, K.C., Bauer, K., Himmerich, H., 2013. Impact of antidepressants on cytokine production of depressed patients in vitro. Toxins 5, 222–240.
Nair, A.B., Jacob, S., 2016. A simple practice guide for dose conversion between animals and human. J. Basic Clin. Pharm. 7, 27–31.
Ohgi, Y., Futamura, T., Kikuchi, T., Hashimoto, K., 2013. Effects of antidepressants on alternations in serum cytokines and depressive-like behavior in mice after lipopolysaccharide administration. Pharmacol. Biochem. Behav. 103, 853–859.
Padro, C.J., Sanders, V.M., 2014. Neuroendocrine regulation of inflammation. Semin. Immunol. 26, 357–368.
Panossian, A., Seo, E.J., Efferth, T., 2018. Novel molecular mechanisms for the adaptogenic effects of herbal extracts on isolated brain cells using systems biology. Phytomedicine 50, 257–284.
Panossian, A., Wikman, G., 2010. Effects of adaptogens on the central nervous system and the molecular mechanisms associated with their stress-protective activity. Pharmaceuticals 3, 188–224.
Panossian, A., Wikman, G., Kaur, P., Asea, A., 2009. Adaptogens exert a stress-protective effect by modulation of expression of molecular chaperones. Phytomedicine 16, 617–622.
Panossian, A., Wikman, G., Kaur, P., Asea, A., 2012. Adaptogens stimulate neuropeptid Y and Hsp72 expression and release in neuroglia cells. Front. Neurosci. 6, 1–12.
Pariante, C.M., 2015. Psychoneuroimmunology or immunopsychiatry? Lancet Psychiatry 2, 197–199.
Pariante, C.M., 2017. Why are depressed patients inflamed? A reflection on 20 years of research on depression, glucocorticoid resistance and inflammation. Eur. Neuropsychopharmacol. 27, 554–559.
Pizzagalli, D.A., 2014. Depression, stress, and anhedonia: toward a synthesis and integrated model. Annu. Rev. Clin. Psychol. 10, 393–423.
Ramirez, K., Sheridan, J.F., 2016. Antidepressant imipramine diminishes stress-induced inflammation in the periphery and central nervous system and related anxiety- and depressive- like behaviors. Brain Behav. Immun. 57, 293–303.
Rinwa, P., Kumar, A., 2013. Quercetin suppress microglial neuroinflammatory response and induce antide pressent-like effect in olfactory bulbectomized rats. Neuroscience 255, 86–98.
Sagandykova, G.N., Pomastowski, P.P., Kaliszan, R., Buszewski, B., 2018. Modern

analytical methods for consideration on natural biological activity. Trends Anal. Chem. 109, 198–213.
Sahoo, S., Brijesh, S., 2019. Pharmacogenomic assessment of herbal drugs in affective disorders. Biomed. Pharmacother. 109, 1148–1162.
Salehi, B., Stojanovic-Radic, Z., Matejic, J., Sharifi-Rad, M., Kumar, N.J.A., Martins, N., Shafiri-Rad, J., 2019. The therapeutic potential of curcumin: a reviews of clinical trials. Eur. J. Med. Chem. 163, 527–545.
Sarris, J., Panossian, A., Schweitzer, I., Stough, C., Scholey, A., 2011. Herbal medicine for depression, anxiety and insomnia: a review of psychopharmacology and clinical evidence. Eur. Neuropsychopharmacol. 21, 841–860.
Seo, E.J., Klauck, S.M., Efferth, T., Panossian, A., 2018. Adaptogens in chemobrain (Part I): plant extracts attenuate cancer chemotherapy-induced cognitive impairment - transcriptome-wide microarray profiles of neuroglia cells. Phytomedicine 55, 80–91.
Shafiee, M., Arekhi, S., Omranzadeh, A., Sahebkar, A., 2017. Saffron in the treatment of depression, anxiety and other mental disorders: current evidence and potential mechanisms of action. J. Affect. Disord. 227, 330–337.
Slavich, G.M., Irwin, M.R., 2014. From stress to inflammation and major depressive disorder: a social signal transduction theory of depression. Psychol. Bull. 140, 774–815.
Sui, R.X., Miao, Q., Wang, J., Wang, Q., Song, L.J., Yu, J.W., Cao, L., Xiao, W., Xiao, B.G., Ma, C.G., 2019. Protective and therapeutic role of bilobalide in cuprozine-induced demyelination. Int. Immunopharmacol. 66, 69–81.
Todorovic, N., Filipovic, D., 2017. The antidepressant- and anxiolytic-like effects of fluoxetine and clozapine in chronically isolated rats involve inhibition of hippocampal TNF-α. Pharmacol. Biochem. Behav. 163, 57–65.
Ulrich-Lai, Y.M., Herman, J.P., 2009. Neural regulation of endocrine and autonomic stress responses. Nat. Rev. Neurosci. 10, 397–409.
Umukoro, S., Kalejaye, H.A., Ben-Azu, B., Ajayi, A.M., 2018. Naringenin attenuates behavioral derangements induced by social defeat stress in mice via inhibition of acetylcholinesterase activity, oxidative stress and release of pro-inflammatory cytokines. Biomed. Pharmacother. 105, 714–723.
Vasileva, L.V., Saracheva, K.E., Ivanovska, M.V., Petrova, A.P., Sucouglu, E., Murdjeva, M.A., Getova-Spasova, D.P., 2017. Beneficial effect of chronic treatment with extracts from *Rhodiola rosea* L. and *Curcuma longa* L. on the immunoreactivity of animals subjected to a chronic mild stress model. Folia Med. 59, 95–104.
Vasileva, L.V., Saracheva, K.E., Ivanovska, M.V., Petrova, A.P., Marchev, A.S., Georgiev, M.I., Murdjeva, M.A., Getova, D.P., 2018. Antidepressant-like effect of salidroside and curcumin on the immunoreactivity of rats subjected to a chronic mild stress model. Food Chem. Toxicol. 121, 604–611.
Wagner, H., Efferth, T., 2017. Introduction: novel hybrid combinations containing synthetic or antibiotic drugs with plant-derived phenolic or terpenoid compounds. Phytomedicine 37, 1–3.
Walker, F.R., Beynon, S.B., Jones, K.A., Zhao, Z., Kongsui, R., Cairns, M., Nilsson, M., 2014. Dynamic structural remodelling of microglia in health and disease: a review of the models, the signals and the mechanisms. Brain Behav. Immun. 37, 1–14.
Wang, Z., Mandel, H., Levingston, C.A., Young, M.R., 2016. An exploratory approach demonstrating immune skewing and a loss of coordination among cytokines in plasma and saliva of Veterans with combat-related PTSD. Hum. Immunol. 77, 652–657.
Wohleb, E.S., Powell, N.D., Godbout, J.P., Sheridan, J.F., 2013. Stress-induced recruitment of bone marrow-derived monocytes to the brain promotes anxiety-like behavior. J. Neurosci. 33, 13820–13833.
Yang, S.J., Yu, H.Y., Kang, D.Y., Ma, Z.Q., Qu, R., Fu, Q., Ma, S.P., 2014. Antidepressant-like effects of salidroside on olfactory bulbectomy-induced pro-inflammatory cytokine production and hyperactivity of HPA axis in rats. Pharmacol. Biochem. Behav. 124, 451–457.
Yu, S., Liu, M., Hu, K., 2019. Natural products: potential therapeutic agents in multiple sclerosis. Int. Immunopharmacol. 67, 87–97.
Zhang, J., Xie, X., Tang, M., Zhang, J., Zhang, B., Zhao, Q., Han, Y., Yan, W., Peng, C., You, Z., 2017a. Salvianolic acid B promotes microglial M2-polarization and rescues neurogenesis in stress-exposed mice. Brain Behav. Immun. 66, 111–124.
Zhang, J., Yao, W., Dong, C., Yang, C., Ren, Q., Ma, M., Han, M., Wu, J., Ushida, Y., Suganuma, H., Hashimoto, K., 2017b. Prophylactic effects of sulforaphane on depression-like behavior and dendritic changes in mice after inflammation. J. Nutr. Biochem. 39, 134–144.
Zhao, Y., Wang, Q., Jia, M., Fu, S., Pan, J., Chu, C., Liu, X., Liu, X., Liu, Z., 2018. (+)-Sesamin attenuates chronic unpredictable mild stress-induced depressive-like behaviors and memory deficits via suppression of neuroinflammation. J. Nutr. Biochem. 64, 61–71.
Zhu, L., Wei, T., Gao, J., Chang, X., He, H., Miao, M., Yan, T., 2015. Salidroside attenuates lipopolysaccharide (LPS) induced serum cytokines and depressive-like behavior in mice. Neurosci. Lett. 606, 1–6.