

# Chinese Herbal Medicine for Depression

Subjects: Psychiatry

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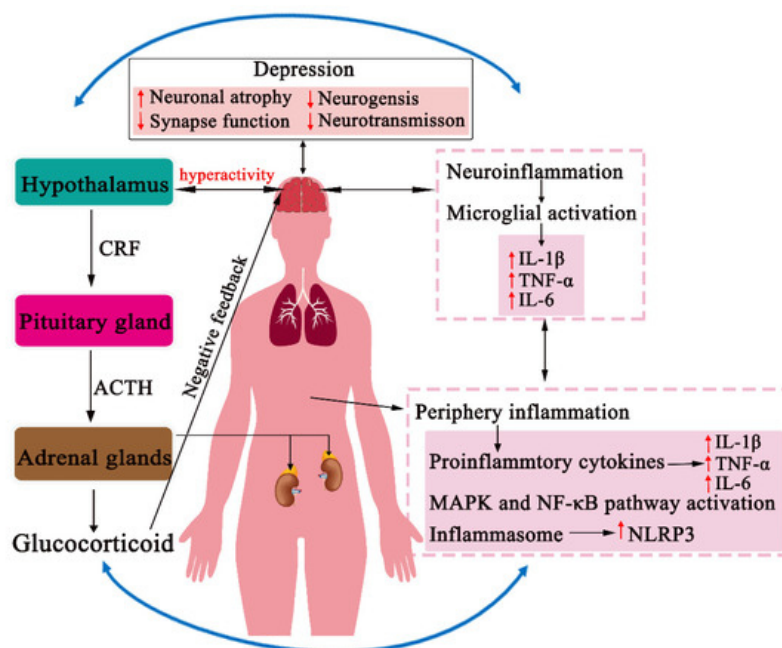
Depression is a mood disorder that causes a loss of interest and constant sadness. Central nervous system (CNS)-targeted medications alone are insufficient for the treatment of depression. Multidrug and multitarget Chinese Herbal Medicine (CHM) has great potential to assist in the development of novel medications for the systematic and effective pharmacotherapy of depression.

Keywords: Chinese herbal medicine ; depression ; neuroimmune system ; neuroendocrine system ; neuroendocrine-immune network ; neuroinflammation ; HPA axis

## 1. Introduction

Depression is a persistent and recurring mental illness, affecting more than 264 million people of all ages worldwide. It is also a major contributor to the global burden <sup>[1]</sup> and a leading cause of elevated disability <sup>[2]</sup>. Depression is clinically characterized by repeated depressive episodes, including anhedonia, insomnia, decreased speech, loss of interest and enjoyment, helplessness, and decreased energy <sup>[3]</sup>. Most researchers view depression as a multigenetic and multifactorial syndrome, which results from the complicated interplay of environmental and genetic factors and presents comorbidity with other diseases <sup>[4]</sup>.

While current antidepressant medications, such as selective monoamine reuptake inhibitors and glutamate transmission-enhanced fast-acting antidepressants, can improve mental states of depression, these drugs are far from ideal, because they have severe side effects and low rates of efficacy <sup>[5]</sup>. Growing evidence suggests that central nervous system (CNS)-targeted medications alone are insufficient, and the development of novel medications or approaches for effective and systematic depression treatment is a pressing task <sup>[4][6]</sup>. In recent decades, many divergent biological systems have been identified to be involved in the pathogenesis of depression. In particular, studies have shown that the activation of the neuroinflammatory response of the immune system and hyperactivity of the hypothalamus–pituitary–adrenal (HPA) axis of the neuroendocrine system are two critical triggers in the etiology of depression <sup>[7]</sup> (Figure 1). It should be emphasized that communication or crosstalk exists between the neuroimmune and neuroendocrine systems and that the neuroendocrine-immune network plays a vital role in the systems biology of depression <sup>[8][9]</sup>.



**Figure 1.** The neuroendocrine-immune network in the pathogenesis of depression. In response to stress, the peripheral or neuroimmune system activates the release of HPA axis hormones, whereas the stress-induced hyperactivation of the HPA axis also stimulates a proinflammatory or neuroinflammatory response. Intersystem crosstalk occurs at many levels through neural, immunological, and humoral interactions and subsequently results in the dysfunction of the central nervous system (CNS) in the pathogenesis of depression.

Preclinical studies have revealed that hyperactivity of the HPA axis can lead to the activation of the neuroinflammatory response of the immune system, whereas neuroinflammation can also modulate the activity of the HPA axis through various underlying mechanisms [4]. These findings have provided many novel pharmacological targets in either the neuroimmune or neuroendocrine system for depression treatment; however, none of these attempts have succeeded in developing new medications directed toward these systems. Because of the intersystem crosstalk, agents that target one system alone will not be effective, and an additional medication that directly acts on the other system is also required to achieve a better treatment. Therefore, an improved approach to achieve an effective depression treatment should be systems biology-orientated and simultaneously target several biological systems involved in the pathogenesis of depression.

Traditional Chinese Medicine (TCM) is a holistic medicine that has been developed in China for centuries. It emphasizes the integration of a variety of biological systems in the human body and aims to prevent or heal diseases by maintaining or restoring internal homeostasis [4]. In TCM practice, a combination of multiple herbal drugs, so-called Chinese Herbal Medicine (CHM), is often used to act on multiple pharmacological targets simultaneously [10][11]. The systems biology-based, multi-target, and multi-drug medication is particularly suitable for the treatment of multigenetic and multifactorial diseases, such as depression [12].

Numerous CHM formulas are currently used for depression treatment in TCM practice [11][13]. Clinical studies have shown that these CHM antidepressant formulas exert comparable efficacies to conventional antidepressants, but with few adverse effects [14]. In addition, preclinical studies have demonstrated that CHM antidepressant formulas exhibit antidepressant-like activities in rodent models through multiple underlying mechanisms, and the de-hyperactivation of the HPA axis and anti-inflammation are the most common actions [15][16][17]. During the past decade, preclinical studies have extensively been performed by employing the molecular or systems pharmacology approach to uncover the mechanisms of action of CHM antidepressant formulas at both the molecular and systems levels. These studies have not only remarkably improved our understanding of the molecular basis and system-wide actions of CHM antidepressant formulas, but also promoted the development of novel medications for the effective and systematic treatment of depression [4].

## References

### 2. Inflammation in the Pathogenesis of Depression

1. WHO. Depression. Available online: <https://www.who.int/news-room/fact-sheets/detail/depression> (accessed on January 30, 2020).
2. Smith first proposed that inflammation may play a crucial role in the pathogenesis of depression in 1991 [24]. Since then, the immune system has been extensively studied to explore the mechanism by which the dysfunction of immune system is associated with symptoms of depression. Accumulating evidence has demonstrated that the dysregulation of the peripheral or neuroimmune system contributes to the pathogenesis of depression (Figure 1). Clinical studies have indicated that patients suffering from depression showed significantly higher levels of proinflammatory cytokines, including interleukin-1 $\beta$ , IL-18, IL-6, TNF- $\alpha$ , IL-17, IL-23, IL-27, IL-31, IL-32, IL-33, IL-35, IL-36, IL-37, IL-38, IL-39, IL-40, IL-41, IL-42, IL-43, IL-44, IL-45, IL-46, IL-47, IL-48, IL-49, IL-50, IL-51, IL-52, IL-53, IL-54, IL-55, IL-56, IL-57, IL-58, IL-59, IL-60, IL-61, IL-62, IL-63, IL-64, IL-65, IL-66, IL-67, IL-68, IL-69, IL-70, IL-71, IL-72, IL-73, IL-74, IL-75, IL-76, IL-77, IL-78, IL-79, IL-80, IL-81, IL-82, IL-83, IL-84, IL-85, IL-86, IL-87, IL-88, IL-89, IL-90, IL-91, IL-92, IL-93, IL-94, IL-95, IL-96, IL-97, IL-98, IL-99, IL-100, IL-101, IL-102, IL-103, IL-104, IL-105, IL-106, IL-107, IL-108, IL-109, IL-110, IL-111, IL-112, IL-113, IL-114, IL-115, IL-116, IL-117, IL-118, IL-119, IL-120, IL-121, IL-122, IL-123, IL-124, IL-125, IL-126, IL-127, IL-128, IL-129, IL-130, IL-131, IL-132, IL-133, IL-134, IL-135, IL-136, IL-137, 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IL-1566, IL-1567, IL-1568, IL-1569, IL-1570, IL-1571, IL-1572, IL-1573, IL-1574, IL-1575, IL-1576, IL-1577, IL-1578, IL-1579, IL-1580, IL-1581, IL-1582, IL-1583, IL-1584, IL-1585, IL-1586, IL-1587, IL-1588, IL-1589, IL-1590, IL-1591, IL-1592, IL-1593, IL-1594, IL-1595, IL-1596, IL-1597, IL-1598, IL-1599, IL-1600, IL-1601, IL-1602, IL-1603, IL-1604, IL-1605, IL-1606, IL-1607, IL-1608, IL-1609, IL-1610, IL-1611, IL-1612, IL-1613, IL-1614, IL-1615, IL-1616, IL-1617, IL-1618, IL-1619, IL-1620, IL-1621, IL-1622, IL-1623, IL-1624, IL-1625, IL-1626, IL-1627, IL-1628, IL-1629, IL-1630, IL-1631, IL-1632, IL-1633, IL-1634, IL-1635, IL-1636, IL-1637, IL-1638, IL-1639, IL-1640, IL-1641, IL-1642, IL-1643, IL-1644, IL-1645, IL-1646, IL-1647, IL-1648, IL-1649, IL-1650, IL-1651, IL-1652, IL-1653, IL-1654, IL-1655, IL-1656, IL-1657, IL-1658, IL-1659, IL-1660, IL-1661, IL-1662, IL-1663, IL-1664, IL-1665, IL-1666, IL-1667, IL-1668, IL-1669, IL-1670, IL-1671, IL-1672, IL-1673, IL-1674, IL-1675, IL-1676, IL-1677, IL-1678, IL-1679, IL-1680, IL-1681, IL-1682, IL-1683, IL-1684, IL-1685, IL-1686, IL-1687, IL-1688, IL-1689, IL-1690, IL-1691, IL-1692, IL-1693, IL-1694, IL-1695, IL-1696, IL-1697, IL-1698, IL-1699, IL-1700, IL-1701, IL-1702, IL-1703, IL-1704, IL-1705, IL-1706, IL-1707, IL-1708, IL-1709, IL-1710, IL-1711, IL-1712, IL-1713, IL-1714, IL-1715, IL-1716, IL-1717, IL-1718, IL-1719, IL-1720, IL-1721, IL-1722, IL-1723, IL-1724, IL-1725, IL-1726, IL-1727, IL-1728, IL-1729, IL-1730, IL-1731, IL-1732, IL-1733, IL-1734, IL-1735, IL-1736, IL-1737, IL-1738, IL-1739, IL-1740, IL-1741, IL-1742, IL-1743, IL-1744, IL-1745, IL-1746, IL-1747, IL-1748, IL-1749, IL-1750, IL-1751, IL-1752, IL-1753, IL-1754, IL-1755, IL-1756, IL-1757, IL-1758, IL-1759, IL-1760, IL-1761, IL-1762, IL-1763, IL-1764, IL-1765, IL-1766, IL-1767, IL-1768, IL-1769, IL-1770, IL-1771, IL-1772, IL-1773, IL-1774, IL-1775, IL-1776, IL-1777, IL-1778, IL-1779, IL-1780, IL-1781, IL-1782, IL-1783, IL-1784, IL-1785, IL-1786, IL-1787, IL-1788, IL-1789, IL-1790, IL-1791, IL-1792, IL-1793, IL-1794, IL-1795, IL-1796, IL-1797, IL-1798, IL-1799

- associated with an alteration in the morphology and activation of microglial cells, which leads to neuroinflammation and neuronal dysfunction [19][36]. In post-mortem histological and neuroimaging studies on depressive patients, robust changes in the microglial morphology and density in the prefrontal cortex (PFC) and hippocampus have been found [37][38]. In addition, a peritoneum injection of LPS into chronic neurodegenerative mice has been shown to result in a dramatic change in the microglia phenotype, which can transform into a proinflammatory phenotype through the overexpression of proinflammatory cytokines, such as IL-1 $\beta$ , IL-6, and TNF- $\alpha$  [39][40]. Furthermore, the activation of microglia mediates depressive-like behaviors through the shaping of the dendritic architecture and synaptic connection [41][42]. Taken together, these findings have provided evidence that the dysfunction of the neuroimmune system is involved in the pathogenesis of depression. From Molecules to Systems. *Front. Pharmacol.* 2020, 11, 586, doi:10.3389/fphar.2020.00586.

### 13. CHM Regulation of the Neuroimmune System

- Many CHM herbal constituents exert anti-inflammation activity through various underlying mechanisms of action by regulating either proinflammatory cytokines, inflammatory signaling pathways or inflammasome [43][44][45][46]. While these studies have not revealed the specific drug-target interactions of these herbal constituents with their acting proteins, they have provided the molecular basis for understanding the mechanisms of action by which CHM herbs or formulas exert antidepressant activity through the modulation of the neuroimmune system. Figure 2 shows several representative CHM ingredients in CUMS rats through improvement of insulin signaling and suppression of NLRP3 inflammasome activation in liver and brain. J. *Ethnopharmacol.* 2017, 209, 219–229, doi:10.1016/j.jep.2017.08.004.
- Other herbal constituents that possess anti-inflammation activity are also shown in Table 1. Some CHM formulas that produce antidepressant effects through the modulation of the neuroimmune system are listed in Table 2.

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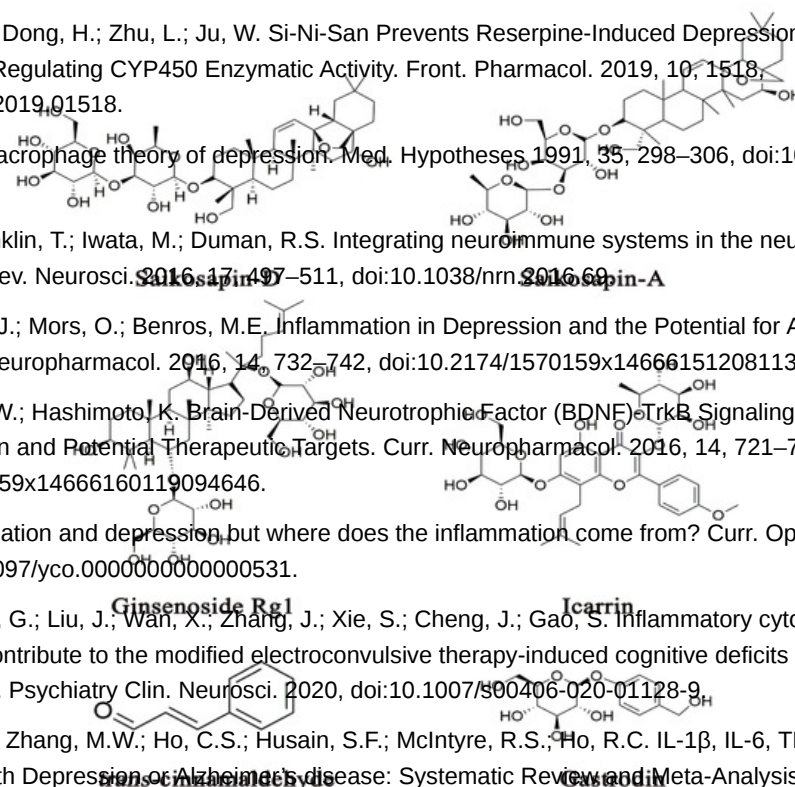
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- In addition, microglia can release proinflammatory cytokines that influence the neurobiology of depression by decreasing the number and function of astrocytes [47]. Furthermore, cytokine receptors have also been demonstrated to produce neurobiological effects on microglia activation and neuroinflammation [48].



**Figure 2** Several representative CHM constituents that have been demonstrated to exert antidepressant activity, specifically by mediating the neuroimmune system.

- Baptazar, R.C.; Di Censo, D.J.** Gasconsonin Myeloid K<sup>b</sup>-Mediated Inflammation Associated Depression Is From Saikosaponin-D, a Triterpenoidal Saponin Isolated from *Saposhnikovia Divaricata*. *J. Neurosci.* **2017**, *37*, 4268–4279. doi:10.1523/JNEUROSCI.0912-17.2017
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- Turkheimer, E.E.; Althubaity, N.; Schubert, J.; Nettis, M.A.; Cousins, O.; Dima, D.; Mondelli, V.; Bullmore, E.T.; Pariante, C.; Veronese, M. Increased serum peripheral C-reactive protein is associated with reduced brain barriers permeability of TSPO radioligands in healthy volunteers and depressed patients: Implications for inflammation and depression. *Brain Behav. Immun.* **2020**, *91*, 487–497. doi:10.1016/j.bbi.2020.10.025
- Rosenblat, J.D.; Chao, D.S.; Mansuri, R.B.; Memry, R.S. Inflamed moods: A review of the interactions between inflammation and mood disorders. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **2019**, *99*, 25–32. doi:10.1016/j.pnpbp.2019.04.003
- Chen, Y.; Chen, H.; Li, B.; Yao, Z.; Zhou, Q.; Guo, W.; Liu, Y.; Han, Y.; Wu, Y.; Liang, Y.; et al. The effect of ginseng polysaccharides on cytokine receptors, such as TollR2 and glycoprotein 130, in the hippocampus in a rat model of postpartum depression [54].



like dexamethasone (DEX) or CUMS [80][81]. Furthermore, Su et al. has suggested that NLRP3 inflammasome modulates depressive-like behaviors through the regulating activities of the MAPK, c-Jun, NF- $\kappa$ B pathways. [55]. Taken together, these studies indicate that the activation of NLRP3 inflammasome signaling is involved in the expression of depression and that inflammasome-2 serves as a potential pharmacological target in depression treatment.

52. Su, J.; Pan, Y.W.; Wang, S.Q.; Li, Y.Z.; Huang, F.; Ma, S.S. Saikosaponin d attenuated lipopolysaccharide-induced depressive-like behaviors via inhibiting microglia activation and neuroinflammation. *Int. Immunopharmacol.* **2020**, *80*, 106181. doi:10.1016/j.intimp.2019.106181.

Basella rubra, has been shown to inhibit histamine deactivation and, consequently, to attenuate inflammatory responses to various stressors. Shen, The, Wang, Si, Wang, G., Ding, R., Wang, G. S., Du, K. G., S. Q. Wei, L. P. Li, H. S. Desai, has reported that sucrose intake prior to an acute depressive-like symptom (SJM) Shao, S. The sedative and mild stressor Neurosci Lett 2018; 662: 1-5.

attenuated the expression of NF- $\kappa$ B pathway components, including TLR-4, I $\kappa$ B $\alpha$ , p65, NF- $\kappa$ B-1, and TNF- $\alpha$ , and

downregulated the expression of NLRP3, caspase-1, IL-18, and IL-18. These observations suggest that *trans*-cinnamaldehyde produces antidepressant effects through the inactivation of the NF- $\kappa$ B/NLRP3 inflammatory pathway in animal models.<sup>[23]</sup> Moreover, a recent study has suggested that cinnamaldehyde (20 or 40 mg/kg, 35 days, p.o.), a prenylated

flavonoid extracted from *Epimedium brevicornu* Maxim, exerts anti-inflammation effects and ameliorates oxidative stress-  
55. Su, W.J.; Zhang, Y.; Chen, Y.; Gong, H.; Lian, Y.J.; Peng, W.; Liu, Y.Z.; Wang, Y.X.; You, Z.L.; Feng, S.J.; et al. NLRP3  
induced brain damage by inactivating the NF- $\kappa$ B signaling and inhibiting the NLRP3-inflammasome/caspase-1/IL-1 $\beta$  axis  
gene knockout blocks NF- $\kappa$ B and MAPK signaling pathway in CUMS-induced depression mouse model. *Behav. Brain*  
in the hippocampus [83]. It would be interesting to identify their specific targeting proteins in the inflammasome complex,

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bioinformatics analysis. *Oncotarget* 2016, 7, 17410–17414. doi:10.18632/oncotarget.8202.

**Table 1:** Constituents of CHM that modulate the release of HPA axis hormones and exhibit anti-inflammatory and

antidepressant-like activities in animal models of depression. Ma, T.; Gu, S. Antidepressant-Like effects of alarmin produced by activation of TrkB receptor signaling pathways in chronic stress mice. *Behav. Brain Res.* 2015, 280, 128.

Herb	Herbal Constituent	Animal Model	Behavioral Test	Administration Dose/Time/Route or Treatment	Effects on Mediators of Inflammation	Effects on Hormones of the HPA Axis
58. Masson, J.; Emerit, M.B.; Hamon, M.; Darmon, M.	Herbal Constituent	Animal Model	Behavioral Test	Administration Dose/Time/Route or Treatment	Effects on Mediators of Inflammation	Effects on Hormones of the HPA Axis
59. Fung, V.; Banasik, M.; Leznarski, P.; Schindler, H.; Stockmeier, C.A.; Simen, A.A.; Newton, S.; Duman, R.S.	Herbal Constituent	Animal Model	Behavioral Test	Administration Dose/Time/Route or Treatment	Effects on Mediators of Inflammation	Effects on Hormones of the HPA Axis
60. Wolcemo, M.C.; Mastorakis, N.E.	Herbal Constituent	Animal Model	Behavioral Test	Administration Dose/Time/Route or Treatment	Effects on Mediators of Inflammation	Effects on Hormones of the HPA Axis
61. Chiang, J.J.; Cole, S.W.; Bower, J.E.; Irvine, M.R.; Taylor, S.E.; Arevalo, J.; Fuligni, A.	Herbal Constituent	Animal Model	Behavioral Test	Administration Dose/Time/Route or Treatment	Effects on Mediators of Inflammation	Effects on Hormones of the HPA Axis
62. Liu, W.; Jiang, H.L.; Cai, L.L.; Yan, M.; Dong, S.J.; Mao, B.	Herbal Constituent	Animal Model	Behavioral Test	Administration Dose/Time/Route or Treatment	Effects on Mediators of Inflammation	Effects on Hormones of the HPA Axis
63. Shih, R.H.; Wang, C.Y.; Yang, C.M.	Herbal Constituent	Animal Model	Behavioral Test	Administration Dose/Time/Route or Treatment	Effects on Mediators of Inflammation	Effects on Hormones of the HPA Axis
64. Lopez-Pedrajas, R.; Ramirez-Luque, D.; Muriach, B.; Sanchez-Vilarijo, M.V.; Almansa, L.; Vidal-Gil, L.; Romero, F.J.; Barcia, J.M.; Muriach, M.	Herbal Constituent	Animal Model	Behavioral Test	Administration Dose/Time/Route or Treatment	Effects on Mediators of Inflammation	Effects on Hormones of the HPA Axis
65. Kirsch, B.; Kirsch, C.	Herbal Constituent	Animal Model	Behavioral Test	Administration Dose/Time/Route or Treatment	Effects on Mediators of Inflammation	Effects on Hormones of the HPA Axis
66. Caviedes, A.; Lafourcade, C.; Soto, C.; Wyneken, U.	Herbal Constituent	Animal Model	Behavioral Test	Administration Dose/Time/Route or Treatment	Effects on Mediators of Inflammation	Effects on Hormones of the HPA Axis
67. Pradere, J.P.; Hernandez, C.; Koppe, C.; Friedman, R.A.; Luedde, T.; Schwabe, R.F.	Herbal Constituent	Animal Model	Behavioral Test	Administration Dose/Time/Route or Treatment	Effects on Mediators of Inflammation	Effects on Hormones of the HPA Axis
68. Hober, J.; Russ, H.; Ferguson, D.; Nestler, E.J.; Dunne, S.	Herbal Constituent	Animal Model	Behavioral Test	Administration Dose/Time/Route or Treatment	Effects on Mediators of Inflammation	Effects on Hormones of the HPA Axis

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77. Walsh, J.G.; Muruve, D.A.; Power, C. Inflammasomes in the CNS. *Nat. Rev. Neurosci.* 2014, 15, 84–97, doi:10.1038/nrn3530. ↓ TNF-α, IL-6, IL-1β signaling pathway in PFC
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81. Zhang, Y.; Liu, L.; Peng, Y.L.; Liu, Y.Z.; Wu, T.Y.; Shen, X.L.; Zhou, J.R.; Sun, D.Y.; Huang, A.; Wang, X.; et al. Involvement of inflammasome activation in lipopolysaccharide-induced mice depressive-like behaviors. *CNS Neurosci. Ther.* 2014, 20, 119–124, doi:10.1111/cns.12170. ↓ TNF-α, IL-6, IL-1β in the brain
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84. (Wu) An, B.; Jacob, S. A simple practice guide for dose conversion between animals and human. *J. Basic Clin. Pharm.* 2016, 7, 27–31, doi:10.4103/0976-0105.177703. ↓ CRH, CORT, ACTH in serum
85. Teasdale, M.F. Early-Life Stress and HPA-axis dysregulation: a developmental perspective. *Epilepsy Behav.* 2014, 38, 148–159, doi:10.1016/j.yebeh.2013.10.020. ↓ CRH, CORT in serum
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**Table 2.** CHM formulas traditionally used in TCM for the treatment of depression, which exhibit anti-inflammatory activity and modulate the release of HPA axis hormones.

CHM Formula	Plant Name/Formula Combination	Dose	Animal Model	Behavioral Test	Administration of Treatment	Effects on Mediators of Inflammation	Effects on Hormones of the HPA Axis
118	<i>Bupleurum chinense</i> DC., <i>Osmanthus fragrans</i> var. <i>aurantiacus</i> Makino, <i>Paeonia officinalis</i> L., <i>Scilla glauca</i> Bunge, <i>Shi Jiao Gou</i> (Xiao Yao San)	2 times/day	PSD rats	TST, FST, OFT, SPT	2.5, 12.5, 25 g/kg, 1 week	IL-6 in serum, TNF-α in hippocampus and cortex	ND
119	<i>Bupleurum chinense</i> DC., <i>Osmanthus fragrans</i> var. <i>aurantiacus</i> Makino, <i>Paeonia officinalis</i> L., <i>Scilla glauca</i> Bunge, <i>Shi Jiao Gou</i> (Xiao Yao San)	2 times/day	PSD rats	TST, FST, OFT, SPT	2.5, 12.5, 25 g/kg, 1 week	IL-6 in serum, TNF-α in hippocampus and cortex	ND
120	<i>Bupleurum chinense</i> DC., <i>Osmanthus fragrans</i> var. <i>aurantiacus</i> Makino, <i>Paeonia officinalis</i> L., <i>Scilla glauca</i> Bunge, <i>Shi Jiao Gou</i> (Xiao Yao San)	2 times/day	PSD rats	TST, FST, OFT, SPT	2.5, 12.5, 25 g/kg, 1 week	IL-6 in serum, TNF-α in hippocampus and cortex	ND
121	<i>Bupleurum chinense</i> DC., <i>Osmanthus fragrans</i> var. <i>aurantiacus</i> Makino, <i>Paeonia officinalis</i> L., <i>Scilla glauca</i> Bunge, <i>Shi Jiao Gou</i> (Xiao Yao San)	2 times/day	PSD rats	TST, FST, OFT, SPT	2.5, 12.5, 25 g/kg, 1 week	IL-6 in serum, TNF-α in hippocampus and cortex	ND
122	<i>Bupleurum chinense</i> DC., <i>Osmanthus fragrans</i> var. <i>aurantiacus</i> Makino, <i>Paeonia officinalis</i> L., <i>Scilla glauca</i> Bunge, <i>Shi Jiao Gou</i> (Xiao Yao San)	2 times/day	PSD rats	TST, FST, OFT, SPT	2.5, 12.5, 25 g/kg, 1 week	IL-6 in serum, TNF-α in hippocampus and cortex	ND
123	<i>Bupleurum chinense</i> DC., <i>Osmanthus fragrans</i> var. <i>aurantiacus</i> Makino, <i>Paeonia officinalis</i> L., <i>Scilla glauca</i> Bunge, <i>Shi Jiao Gou</i> (Xiao Yao San)	2 times/day	PSD rats	TST, FST, OFT, SPT	2.5, 12.5, 25 g/kg, 1 week	IL-6 in serum, TNF-α in hippocampus and cortex	ND
124	<i>Bupleurum chinense</i> DC., <i>Osmanthus fragrans</i> var. <i>aurantiacus</i> Makino, <i>Paeonia officinalis</i> L., <i>Scilla glauca</i> Bunge, <i>Shi Jiao Gou</i> (Xiao Yao San)	2 times/day	PSD rats	TST, FST, OFT, SPT	2.5, 12.5, 25 g/kg, 1 week	IL-6 in serum, TNF-α in hippocampus and cortex	ND
125	<i>Bupleurum chinense</i> DC., <i>Osmanthus fragrans</i> var. <i>aurantiacus</i> Makino, <i>Paeonia officinalis</i> L., <i>Scilla glauca</i> Bunge, <i>Shi Jiao Gou</i> (Xiao Yao San)	2 times/day	PSD rats	TST, FST, OFT, SPT	2.5, 12.5, 25 g/kg, 1 week	IL-6 in serum, TNF-α in hippocampus and cortex	ND
126	<i>Bupleurum chinense</i> DC., <i>Osmanthus fragrans</i> var. <i>aurantiacus</i> Makino, <i>Paeonia officinalis</i> L., <i>Scilla glauca</i> Bunge, <i>Shi Jiao Gou</i> (Xiao Yao San)	2 times/day	PSD rats	TST, FST, OFT, SPT	2.5, 12.5, 25 g/kg, 1 week	IL-6 in serum, TNF-α in hippocampus and cortex	ND
127	<i>Bupleurum chinense</i> DC., <i>Osmanthus fragrans</i> var. <i>aurantiacus</i> Makino, <i>Paeonia officinalis</i> L., <i>Scilla glauca</i> Bunge, <i>Shi Jiao Gou</i> (Xiao Yao San)	2 times/day	PSD rats	TST, FST, OFT, SPT	2.5, 12.5, 25 g/kg, 1 week	IL-6 in serum, TNF-α in hippocampus and cortex	ND
128	<i>Bupleurum chinense</i> DC., <i>Osmanthus fragrans</i> var. <i>aurantiacus</i> Makino, <i>Paeonia officinalis</i> L., <i>Scilla glauca</i> Bunge, <i>Shi Jiao Gou</i> (Xiao Yao San)	2 times/day	PSD rats	TST, FST, OFT, SPT	2.5, 12.5, 25 g/kg, 1 week	IL-6 in serum, TNF-α in hippocampus and cortex	ND
129	<i>Bupleurum chinense</i> DC., <i>Osmanthus fragrans</i> var. <i>aurantiacus</i> Makino, <i>Paeonia officinalis</i> L., <i>Scilla glauca</i> Bunge, <i>Shi Jiao Gou</i> (Xiao Yao San)	2 times/day	PSD rats	TST, FST, OFT, SPT	2.5, 12.5, 25 g/kg, 1 week	IL-6 in serum, TNF-α in hippocampus and cortex	ND
130	<i>Bupleurum chinense</i> DC., <i>Osmanthus fragrans</i> var. <i>aurantiacus</i> Makino, <i>Paeonia officinalis</i> L., <i>Scilla glauca</i> Bunge, <i>Shi Jiao Gou</i> (Xiao Yao San)	2 times/day	PSD rats	TST, FST, OFT, SPT	2.5, 12.5, 25 g/kg, 1 week	IL-6 in serum, TNF-α in hippocampus and cortex	ND
131	<i>Bupleurum chinense</i> DC., <i>Osmanthus fragrans</i> var. <i>aurantiacus</i> Makino, <i>Paeonia officinalis</i> L., <i>Scilla glauca</i> Bunge, <i>Shi Jiao Gou</i> (Xiao Yao San)	2 times/day	PSD rats	TST, FST, OFT, SPT	2.5, 12.5, 25 g/kg, 1 week	IL-6 in serum, TNF-α in hippocampus and cortex	ND



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then activates the pituitary to synthesize and release adrenocorticotrophic hormone (ACTH). ACTH further activates the adrenal cortex to release glucocorticoid (corticosterone (CORT) or cortisol), which, in turn, regulates the HPA axis through a negative feedback loop at multiple levels: directly on elements of the axis and indirectly through the PFC, amygdala, and hippocampus (Figure 1). Studies have demonstrated that hyperactivity of the HPA axis reduces synaptic function.

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On the other hand, preclinical studies have demonstrated that many CHM herbal constituents or formulas can  
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#### 4.1. CRF Antagonists

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known as the Huang-Qin-Hua-Shi decoction (1 mL/100 g, 3 weeks, i.g.), has also been shown to block the high-temperature- and high-humidity-stress-induced upregulation of hypothalamus GR mRNA expression in rats, which is similar to the action of the GR antagonist, mifepristone [124].

## 5. CHM Effects on the Neuroendocrine-Immune Network

As mentioned above, either the neuroimmune or neuroendocrine system plays a pivotal role in the pathogenesis of depression, but neither of these individual systems is fully responsible for the pathogenesis of depression. Indeed, clinical studies have demonstrated that abnormal neuroinflammatory responses of the immune system and dysfunction of the HPA axis commonly co-occur in depressive patients [125]. In addition, preclinical evidence has suggested that crosstalk exists between two biological systems through neural, endocrinal, and immunological interactions in the pathogenesis of depression (Figure 1).

Stress activates the HPA axis and sympathetic nervous system, resulting in neuroendocrinal and immunological changes, which, in turn, promote detrimental neuroinflammatory reactions [125][126][127][128][129]. Glucocorticoid immunomodulatory action is a key interaction between the HPA axis and neuroimmune system, which allows for coping with any situation that could challenge homeostasis in the pathogenesis of depression [130][131]. Specifically, glucocorticoids exert immunomodulatory effects, primarily through GR-mediated inflammatory factors, including NF- $\kappa$ B and activator protein-1 [132][133][134]. Meanwhile, proinflammatory cytokines can also regulate the HPA axis by disturbing the GR function mediated by inflammatory signaling components, such as p38MAPK, NF- $\kappa$ B, and cyclooxygenase-2 (COX2) [8][47]. All MAPKs are potential targets of the anti-inflammatory actions of glucocorticoids through the inhibition of their phosphorylation, whereas proinflammatory cytokines induce the abnormal activation of MAPK signaling, which results in the alternation of GR phosphorylation and activity [8]. Furthermore, a chronic blockade of GR reverses GR dysfunction and decreases depressive-like behaviors induced by LPS [135][136].

Additionally, the activity of the HPA axis is also regulated by proinflammatory cytokines, such as IL-6, IL-1 $\beta$ , and TNF- $\alpha$ , which can easily cross BBB and exert their effects through various cytokine receptors [9]. In Li's study, elevated CORT levels were observed in the plasma and hippocampus after the administration of LPS [137]. It has also been indicated that an intraperitoneal injection of IL-1 administered to rats activated the HPA axis by increasing the ACTH and corticosterone levels in plasma [138]. On the other hand, it has been demonstrated that the levels of TNF- $\alpha$  and IL-6 were upregulated by an intraperitoneal injection of CRF [139]. It is noteworthy that neuroinflammation in stress-induced animal models can be attenuated by the CRF<sub>1</sub> antagonist, SSR125543 [140]. These findings have suggested that the release of CORT, ACTH, and CRF can be induced by proinflammatory cytokines and, conversely, proinflammatory cytokines can also be regulated by the modulation of HPA axis hormones.

The HPA axis has been shown to be involved in microglial activation. Both CRF receptors and GR are abundantly distributed in microglial cells [141][142][143], and CRF stimulates release of TNF- $\alpha$  in cultured microglial cells [144]. High levels of glucocorticoids have been shown to participate in both proinflammatory cytokine production and the sensitization of microglial cells [6][145]. In addition, glucocorticoids induce microglial proliferation in restraint stress-induced mice [145]. However, due to a lack of correlation between the HPA axis and immune measures, the specific function of the HPA axis in microglial physiology and the mechanism by which chronic cytokine exposure influences the HPA axis function remains to be uncovered [146][147]. Overall, these studies have indicated that the reciprocal regulation between the HPA axis and neuroimmune system represents a common feature in the pathogenesis of depression.

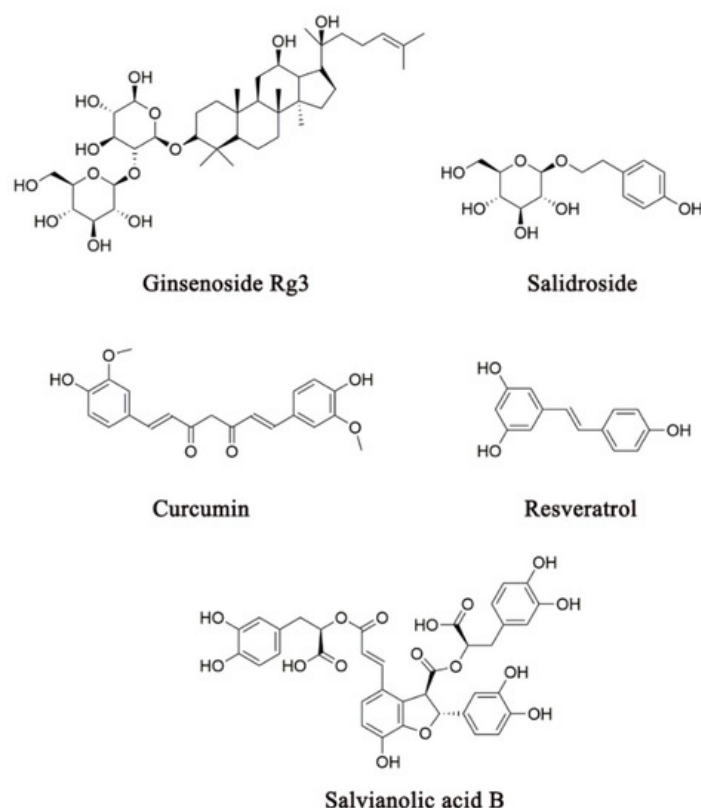
It has often been reported that a CHM herbal constituent exhibits multiple effects in the pathogenesis of depression [148][149][150]. Several representative CHM constituents that have been shown to exert multiple actions on the neuroendocrine-immune network are shown in Figure 4. Ginsenoside Rg3 (20 or 40 mg/kg, 3 days, i.g.) was isolated from *Panax ginseng* C.A. Meyer has been shown to effectively suppress LPS-induced neuroinflammation by reducing the proinflammatory cytokines (IL-1 $\beta$ , IL-6, and TNF- $\alpha$ ), NF- $\kappa$ B signal pathway, and microglial activation in the brain [107]. It has also been reported that Rg3 (20 or 40 mg/kg, 14 days, i.g.) attenuated the hyperactivation of the HPA axis by reducing CRH, CORT, and ACTH in CUS rats [108]. Furthermore, it has been shown that total ginsenosides (200 mg/kg, 7 days, i.g.) significantly decrease serum CORT levels, increase GR mRNA expression, and reduce IL-1 $\beta$ , IL-6, TNF- $\alpha$ , and IDO in the hippocampus of LPS mice or CUMS rats [104][105].

Curcumin, a diarylheptanoid from *Curcuma longa* L., is another example of CHM constituents that possess multiple actions on the neuroendocrine-immune network. Xu et al. showed that curcumin (5 or 10 mg/kg, 21 days, p.o.) produces antidepressant activity by suppressing the aberrant activation of the HPA axis caused by an elevated serum CORT level



and GR mRNA expression in CUS rats [116]. Interestingly, a recent study has shown that curcumin (100 mg/kg, 4 weeks, i.g.) significantly reduces the mRNA expression of proinflammatory cytokines, including IL-1 $\beta$ , IL-6, and TNF- $\alpha$ , and suppresses the activation of NF- $\kappa$ B signaling and the NLRP3 inflammasome in CUMS rats [115].

The phenomenon that one CHM constituent exerts multiple actions on several biological systems has been understood poorly because of the lack of experimental evidence to define its pharmacological profiles and specific interactions with its targeting proteins [12]. It is most likely the case that crosstalk exists between these biological systems or that one CHM constituent acts non-selectively on multiple targets [12]. This makes it difficult to understand the mechanisms of action of CHM constituents at the molecular level. Thus, more in-depth studies are required to uncover the specific interactions between these CHM constituents and their targeting proteins. Nevertheless, multi-target actions of these CHM constituents provide the scientific basis for interpreting their system-wide mechanisms of action.



**Figure 4.** Several representative CHM constituents that have been shown to produce antidepressant effects through their actions on the neuroendocrine-immune network.

In addition to these CHM constituents, many CHM antidepressant formulas have been shown to possess multiple underlying mechanisms of action, particularly on the HPA axis and neuroimmune system (Table 2). This is shown in the studies on Kai-Xin-San (KXS), an empirical antidepressant formula, which consists of *Panax ginseng* C.A. Meyer, *Poria cocos* (Schw.) Wolf, *Polygala tenuifolia* Willd, and *Acorus tatarinowii* Schott [151]. A chronic administration of KXS (338 or 676 mg/kg, 3 weeks, i.g.) has been shown to produce antidepressant-like activity in CUMS-induced animal models through the reduction of COX-2, IL-2, IL-6, and TNF- $\alpha$  expression levels and increase in IFN- $\gamma$  and IL-10 production [152]. Notably, in other studies, KXS (0.9 or 2.7 g/kg, 5 weeks, i.g.) has also been reported to modulate the activity of the HPA axis by reversing the elevated ACTH level in CMS-induced mice [153]. Taken together, these studies indicate that the underlying mechanisms of KXS, as an antidepressant formula, include its actions on the neuroendocrine-immune network.

In comparison with single CHM herbal constituents, the multidrug feature of a CHM antidepressant formula confers its pharmacological actions on multiple targets toward diverse pathological systems. The antidepressant actions of KXS are triggered by its numerous bioactive constituents within the formula. For instance, ginsenosides Rg1, Rg3, Rh1, Rh3, Rb1, Rk1, and Rf from *Panax ginseng* C.A. Meyer have been demonstrated to exhibit dual actions against neuroinflammation and hyperactivation of the HPA axis [106][108][154][155][156][157][158][159][160][161][162][163], while 3,6'-disinapoyl sucrose and the oligosaccharide esters-enriched fraction, YZ50, from *Polygala tenuifolia* Willd have been shown to possess bioactivity that de-hyperactivates the HPA axis [164][165][166]. Additionally, poricoic acid A, isolated from *Poria cocos* (Schw.) Wolf, has been reported to produce anti-inflammatory effects by inhibiting prostaglandin E<sub>2</sub> and NO production through a decrease in COX-2 and iNOS expression, respectively [167].  $\beta$ -Asarone, a major bioactive constituent of *Acorus tatarinowii* Schott, has also been demonstrated to be an anti-inflammation agent, as it downregulates TNF- $\alpha$ , IL-1 $\beta$ , and IL-6 expression [168].



Multiple actions of these constituents in KXS toward multiple biological systems, such as the neuroendocrine-immune network, represent an excellent example of CHM antidepressant formulas in the systematic treatment of depression. Likewise, many other CHM antidepressant formulas have been shown to possess multiple mechanisms of action on diverse biological systems, particularly the neuroendocrine-immune network, in the pathogenesis of depression ([Table 2](#)).

Dysfunction of the neuroimmune or neuroendocrine system results in profound effects on the CNS through the neuroendocrine-immune network. To uncover the system-wide mechanism of action of KXS, a study has been conducted to assess the protein expression in serum samples of depressive patients, before or after Shen-Zhi-Ling (a proprietary tablet formulated from KXS) treatment (3.2 g/day, 8 weeks, i.g.), using quantitative proteomic analysis <sup>[169]</sup>. Of a total of 878 serum proteins, the abnormal expression of 12 proteins in depressive patients could be reversed by treatment with KXS. Functional analysis further revealed that these proteins are implicated in platelet activation, immune regulation, and lipid metabolism. Moreover, a quantitative proteomic study has also been performed to evaluate the hippocampal proteins of CMS-induced rats in response to KXS administration (0.6 g/kg, 14 days, i.g.) <sup>[170]</sup>. This study identified 33 hippocampal proteins that are associated with KXS treatment. Protein–protein interaction network analysis showed that these proteins can be classified into several categories that participate in glutamate signaling, synaptic plasticity, the metabolic process, the cell survival process, and the BDNF, mTORC1, and cAMP pathways. These studies indicated that KXS exhibits antidepressant actions through targeting numerous proteins across multiple biological systems, providing a network or systems pharmacology approach to understanding the mechanism of action of KXS at the systems level.

## **6. Discussion**

Numerous empirical CHM antidepressant formulas are often used in clinical practice for the treatment of depression ([Table 2](#)). To elucidate the mechanism of action by which a CHM formula exhibits antidepressant-like activity through the modulation of multiple biological factors across divergent systems is an important research direction. Two major pharmacological approaches are commonly employed in the analysis of the mechanism of action of a CHM formula on the biological factors in the pathogenesis of depression. One is the molecular approach, which uses single bioactive constituents from an herb used in a CHM antidepressant formula to explore their specific actions on potential pharmacological targets. The studies that employ the molecular approach have provided a scientific basis for revealing the mechanism of action of a CHM antidepressant herb or formula at the molecular level ([Figure 2](#), [Figure 3](#) and [Figure 4](#) and [Table 1](#)). Because the constituent complexity and drug–drug interactions of an entire formula often prevent the molecular mechanism of action from being uncovered, the molecular approach plays a critical role in our understanding of the drug–target interactions in depression treatment. However, the effects of single molecular constituents cannot exactly reflect the action of a CHM composite formula, which contains numerous bioactive constituents that are proposed to simultaneously act on diverse pharmacological targets across biological systems. Hence, it is necessary to integrate the mechanism of action from the molecular level into the systems level in order to understand the role of CHM in depression treatment.

Another approach is the systems pharmacology approach, which involves uncovering the system-wide mechanism of action of an entire CHM antidepressant formula. Systems pharmacology studies drugs, drug targets, and drug effects at the systems level and reveals all responses to the pharmacological actions of drugs across various biological systems <sup>[171]</sup>. The systems pharmacology approach has recently been applied in studies of CHM antidepressant formulas and shown to be a powerful tool for understanding the system-wide mechanism of action ([Table 2](#) and [Section 5](#)). It aims to create a network of the biological factors within a specific system or across diverse systems in response to the pharmacological actions of an entire CHM formula. Several advanced analysis techniques, including DNA or RNA microarray <sup>[172][173][174][175][176]</sup> and quantitative proteomics <sup>[177]</sup>, have been used to identify the potential targeting proteins that are associated with a typical CHM formula. While systems pharmacology-based studies provide a holistic point of view on the pharmacological actions of a given CHM formula, they cannot provide detailed information on molecular drug–target interactions. In addition, the targeting protein candidates resulting from the system pharmacology-based analysis still require further validation by the molecular approaches. While these two approaches are commonly used in preclinical studies, neither can provide a holographic picture of the mechanism of action of a CHM formula in the treatment of depression. Therefore, it is vital to integrate the two approaches into the study of CHM in order to understand the mechanism of action of a CHM antidepressant formula in its entirety.

In summary, the neuroimmune or neuroendocrine system not only exhibit profound effects on the CNS, but also reciprocally regulate one another through the neuroendocrine-immune network. Thus, the effective approach to the treatment of depression induced by the dysfunction of the neuroendocrine-immune network should concurrently target multiple pathological factors across these biological systems. Preclinical studies have demonstrated that the holistic, multidrug, and multitarget CHM represents an excellent example of systems medicine in the treatment of depression.

