The impact of nutrition on neuroinflammation in vitro and in vivo
Kurtys, Ewelina Anna

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Chapter 3

Anti-inflammatory effects of rice bran components

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Abstract

Neuroinflammation has been implicated in the pathology of various psychiatric and neurodegenerative disorders. Accumulating evidence suggests that food components can modulate inflammatory processes and therefore it is hypothesized that such nutrients exhibit therapeutic efficacy against these brain diseases.

Rice bran is often discarded as a waste product, although it contains a wide range of potentially useful substances. Several rice bran components have been described to possess anti-inflammatory properties. This review summarizes the evidence supporting a modulatory effect of rice bran components on neuroinflammation. In vitro studies with these rice bran components on immune cells and in vivo studies on nutritional intervention in animal models of central and peripheral inflammation are discussed in the context of the potential use of rice bran components for prevention and treatment of brain diseases in which neuroinflammation is involved.
1. Introduction

Neuroinflammation is a natural response of the central nervous system (CNS) to alterations in the environment and disturbances in homeostasis, for example due to invasion of pathogens or neuronal damage. Astrocytes and microglia are two important cell types in the CNS that are responsible for the maintenance of homeostasis. Astrocytes are necessary for the trophic support of neurons and microglia are the main immune cells in the brain and therefore are also called brain macrophages [1]. During neuroinflammation, activated astrocytes and microglia produce a wide range of inflammatory mediators, such as cytokines, chemokines, reactive oxygen and nitrogen species (ROS and NOS) [1,2]. These proinflammatory mediators help to destroy invading pathogens, to clear cell debris and to repair damaged cells. However, when neuroinflammation becomes persistent and excessive, it may also have a detrimental effect on brain functions [1]. Evidence suggests that pro-inflammatory mediators, especially when chronically produced, are involved in the development of brain diseases. Chronic neuroinflammation has been observed in many psychiatric and neurodegenerative diseases, including schizophrenia [3], depression [4], Parkinson’s disease and Alzheimer’s disease [5–7]. It is currently is even believed that peripheral inflammation can trigger brain diseases, such as Parkinson’s diseases, Alzheimer’s disease [7–9], depression [10–12] and cognitive decline [13,14], via induction of neuroinflammation.

Neuroinflammation appears to be an important factor in the etiology of brain diseases and in disease progression. Therefore, neuroinflammation may present a promising target for new treatment approaches against these diseases [15]. Since epidemiological studies demonstrated that our diet can have an impact on incidence of brain diseases in for which pathology neuroinflammation is involved [16,17], there is a lot of interest in the investigation of specific nutrients that may be responsible for this effect and therefore could be good candidates for future nutrition-based therapies.
2. Rice bran components

Rice is the major component of the diet for a large part of the human population and provides more than 20% of the calories consumed by humans worldwide. Rice bran, the outer layer of a whole brown rice kernel, consists of aleurone and pericarp. It is often considered as a by-product of rice processing and is discarded as waste or used as animal food. However, rice bran contains high amounts of useful nutrients, including proteins, fats, dietary fibers, minerals, anti-oxidants and phytochemicals [18,19]. Recent studies have shown that rice bran components like phytosteryl pherulates and isoprenoids can exert anti-inflammatory effects, either acting directly on the immune cells [20] or affecting inflammation indirectly via modulation of gut microbiota [21]. These results may open the road towards the design of an (adjuvant) therapeutic intervention with specific rice bran components for brain disorders, for which effective treatment is currently not available. This review therefore surveys the anti-inflammatory properties of several rice bran components in the context of potential intervention for brain diseases associated with neuroinflammation.

2.1 Phytosteryl pherulates and ferulic acid

2.1.1 Phytosteryl pherulates

Mode of action

Gamma oryzanol (γ-OZ) is a secondary plant metabolite from bran layers of grains and is a mixture of at least 10 ferulic acid esters of phytosterols. γ-OZ is rich in anti-oxidants and lipid lowering compounds [22–24]. Its ROS-scavenging properties have been extensively investigated in vitro on lipids [24], tissue homogenates [25] and LPS-stimulated macrophages [26]. The anti-inflammatory properties of γ-OZ have been demonstrated in LPS-stimulated vascular endothelial cells (model for atherosclerosis) where it inhibited the expression of adhesion molecules through inhibition of NF-κB [27]. Interestingly, a recent in vivo study demonstrated that the permeation of the γ-OZ components through the gut is very low, suggesting that the effects of γ-OZ are probably indirect [28].
Peripheral inflammation

In vivo, the anti-inflammatory properties of γ-OZ have been demonstrated in DSS-induced colitis. Oral administration of γ-OZ inhibited inflammation in mice with DSS-induced colitis and thus prevented disease progression [29]. The anti-inflammatory and lipid-lowering properties of γ-OZ have also been demonstrated in metabolic syndrome models, such as high fat and high fructose diet-induced metabolic syndrome in rats [30], high fat diet in rats [22] and in Zucker rats [23]. Despite promising data from animal studies suggesting anti-inflammatory properties of γ-OZ in the gut, potential effects on neuroinflammation, brain function and behavior have not been shown yet.

2.1.2 Ferulic acid

Mode of action

One of the most extensively studied component of γ-OZ is ferulic acid (FA), a phenolic derivative of cinnamic acid. FA is present in rice bran and several other plants, such as whole grain, citrus fruit, banana, beet root, cabbage, spinach and broccoli [31]. FA can also be isolated from arabinoxylans, fibers present in the plant cell wall, which are also emerging as promising anti-inflammatory compounds [32]. Studies on animal models of diseases in which inflammation is involved have demonstrated neuroprotective and anti-oxidative effects of FA. In the middle cerebral artery occlusion model of stroke in rats, administration of FA decreased the infarct volume. This neuroprotective effect of FA was mediated by activation of Akt signaling pathway, which plays a critical role in cell survival signaling and restoring the anti-oxidant proteins peroxiredoxin-2 and thioredoxin [33,34]. Further studies on the same model have demonstrated that FA administration leads to inhibition of the activation of microglia, macrophages, oxidative stress and apoptosis markers [35]. Likewise, FA showed neuroprotective properties in aged rats by inhibiting cytokine release and upregulating the MEK/ERK½ survival pathway in the hippocampus [36].

Peripheral inflammation

Several peripheral inflammation models were used to investigate the ability of FA to modulate disease progression. In a model of high-fat diet-induced oxidative stress in mice, FA alone or in combination with atorvastatin ameliorated oxidative stress
and thus protected the liver by reducing lipid peroxidation, normalizing the hepatic lipid profile and elevating hepatic antioxidant enzymes [37]. In a model of streptozotocine-induced diabetes in rats, FA also decreased oxidative stress, the release of pro-inflammatory cytokines and apoptosis of pancreatic beta cells and consequently the normalization of blood glucose levels [31].

**Neuroinflammation and behavior**

Evidence also suggests a role of FA in the CNS, which could be due to the modulation of neuroinflammation. In a model of gamma radiation-induced neuroinflammation in mice, FA exhibited a neuroprotective and anti-neuroinflammatory effect by increasing antioxidant enzymes (SOD, CAT) and by partly reducing the levels of pro-inflammatory markers, such as NF-κB, COX-2, iNOS, TNFα and IL-6 [38]. An anti-depressant effect of FA was shown in several preclinical investigations. Screening assays for new antidepressants with the tail suspension test and the forced swim test in mice showed that acute administration of FA has an anti-depressant effect through modulation of the serotoninergic system. Moreover, sub-effective doses of FA demonstrated synergistic anti-depressant effects with serotonergic drugs used in the clinic for the treatment of depression (fluoxetine, paroxetine and sertraline) [39]. Other studies demonstrated the involvement of anti-oxidative modulation in the anti-depressant effects of FA in stress-induced depressive-like behavior. Amelioration of behavioral abnormalities was accompanied with a decrease in stress-induced anti-oxidative enzymes (SOD, CAT, GSH) [40]. Similar anti-depressant effects were shown in a reserpine-induced pain and a depressive-like behavior model in mice, in which FA partly reversed behavioral abnormalities, increased the nociceptive threshold and decreased the inflammatory and apoptosis markers, NF-κB and caspase 3 in the prefrontal cortex [41]. Behavior improvement and anti-inflammatory effects due to the FA administration was also demonstrated in animal models of neurodegenerative diseases. For example, in a transgenic model of Alzheimer’s disease, FA attenuated behavioral abnormalities and diseases-related pathology, including the proinflammatory markers [42]. In chemically-induced Parkinson’s disease models, FA attenuated behavioral abnormalities, suppressed neuroinflammation and had a neuroprotective effect [43][43,44].
Summarizing, these data from preclinical studies indicate that FA can have beneficial effects on neuroinflammation, inflammation-related behavior and disease progression. Therefore, this rice bran component might be considered as potential candidates for further clinical investigation. Unfortunately, clinical studies with FA are lacking so far.

2.2 Isoprenoids

Isoprenoids (terpenoids) are secondary metabolites of the mevalonate pathway, in which cholesterol and isoprenoid lipids are produced. Isoprenoids are involved in maintaining endotoxin tolerance. Some autoimmune diseases are caused by mutations of enzymes in the mevalonate pathway. Isoprenoids, such as geranylgeraniol (GGOH), farnesol (FOH) and geraniol (GOH), are produced endogenously, but are also consumed via our diet, as they are present in several fruits, vegetables and grains, including rice [45].

2.2.1 Geranylgeraniol

*Mode of action*

GGOH is believed to play an important role in regulation of inflammatory responses. Recent studies have shown that sufficient production of GGOH is necessary to prevent chronic inflammation due to repetitive exposure to a pro-inflammatory stimulus (endotoxin tolerance). An in vitro study demonstrated that chemical blocking of the mevalonate pathway caused mitochondrial dysfunction and apoptosis in LPS-stimulated murine monocytes. The effect of inhibition of the mevalonate pathway was reversed by treatment with GGOH [46]. In macrophage-derived RAW cells, chemical suppression of mevalonate pathway caused an excessive proinflammatory response, which could be reversed by the exogenous administration of GGOH. Similar beneficial effects of GGOH were demonstrated on human monocytes from patients with an impaired mevalonate pathway [47]. Also in peritoneal macrophages repeatedly stimulated *in vitro* with LPS, insufficient GGOH production, caused by inhibition of 3-hydroxy-3-methyl-glutaryl-CoA reductase, led to the excessive proinflammatory response [48].

*Peripheral inflammation*

The findings from *in vitro* models have been confirmed in animals. In a mouse model of mevalonate pathway dysfunction, administration of GGOH reduced the
levels of inflammatory markers, serum amyloid-A and peritoneal exudate cells [49]. In rats intraperitoneally injected with LPS, dietary supplementation with GGOH reduced the plasma levels of inflammatory cytokines, attenuated the activation of the pro-inflammatory transcription factor NF-κB in the liver and prevented liver damage [50].

Studies on the effect of GGOH on neuroinflammation and brain function are currently lacking.

2.2.2 Farnesol

Peripheral inflammation

FOH was described to possess anti-inflammatory and anti-oxidative properties and to exert beneficial effects on lung injury [51], metabolic disorders [52], colitis [53] and allergic reactions [54]. In chemically-induced colitis in rats, FOH decreased colonic mucosal damage by decreasing ROS, inflammation and apoptosis, stimulating anti-oxidative enzymes and reducing colitis-related mucosal edema [53]. However, the anti-inflammatory effects of FOH are not always beneficial for human health. FOH produced by Candida albicans is involved in quorum sensing. Thus, FOH can suppress the Th1 response in favor of an anti-inflammatory Th2 response and thus promote fungal growth and exacerbation of infection [55].

Neuroinflammation

Recent studies point towards beneficial effects of FOH on the CNS, as FOH was suggested to be a modulator of neuroinflammation and pain. In a mouse model of acrylamide-induced neurotoxicity, FOH supplementation caused behavioral improvement (measured with gait performance, neuromuscular function and fine motor coordination) and attenuation of inflammation as measured with astrocytes and microglia staining in cortex, hippocampus and striatum [56]. Neroli oil containing FOH was demonstrated to have central and peripheral nociceptive effects in both rats and mice [57].

Although the available data suggest promising properties of isoprenoids on inflammation and brain function, more studies in inflammation-related brain diseases models are needed to determine the potential usefulness of isoprenoids as modulator of neuroinflammation in clinical investigations.
3. Nutrients combinations: the most effective way?

As follows from the above, several rice bran components are able to attenuate inflammatory processes, not only in the gastrointestinal tract, but possibly also in the brain. Dietary interventions with specific food components with potent anti-inflammatory properties, such as rice bran components, may therefore be explored as new therapeutic strategies against brain diseases. Yet, it can be expected that each individual component is less effective than pharmaceutical drugs that are specially designed to inhibit inflammation. However, food components can interact with different pathways involved in the inflammatory process and therefore a combination of several nutrients acting on convergent pathways may increase the efficacy of dietary interventions. The first step to test possible synergistic or additive anti-inflammatory effects of specific food components are in vitro experiments on activated immune cells. So far, no studies have been published, in which the anti-inflammatory properties of combinations of rice bran components have been investigated. However, several studies have investigated combinations of other nutrients on LPS-activated microglia or macrophages. For example, the combination eicosapentaenoic acid and resveratrol showed higher potency to inhibit LPS-induced NO release and proinflammatory genes expression than each individual nutrients [58]. Likewise, a combination of flavonoids synergistically inhibited the release of NO, TNFα and PGE2 [59], whereas additive and synergistic effects of vitamin D combined with the plant extract β-sitosterol on the release of NO, TNF-α, IFN-γ, IL-6, IL-10 and MCP-1 and on the activation of NF-κB were observed in murine J774A.1 macrophage cells stimulated with LPS [60].

The concept of combined food components has also been investigated in vivo. For example, a combination of vegetable components, containing polyphenols and amino acids has been shown to improve spatial memory and modulate inflammation in aged rats [61]. A similar approach could be applied to the combinations of the rice bran components discussed in this review.

In vitro studies on single components may help to reveal the specific pathways that rice bran components may affect. This information can be used to design studies with multiple nutrient combinations acting on different pathways in order to induce possible synergistic effects of these nutrients. Multi-nutrient dietary supplementation targeting inflammation is an interesting concept for safe
interventions in humans, given the low toxicity of common food supplements [62]. However, this compelling approach first needs to be tested in animal models of diseases associated with neuroinflammation.

4. Concluding remarks

Rice bran components are emerging as potential anti-inflammatory agents. Some of them have been demonstrated to act on peripheral and central inflammation (figure 1). Although some promising results have been obtained in vitro and in vivo (table 1 and 2), rice bran components still need to be further investigated in animal models and subsequently in clinical trials in order to evaluate their potency to prevent or cure brain diseases via modulation of neuroinflammation. To achieve adequate efficacy, rice bran components may need to be combined with other anti-inflammatory nutrients.

Better knowledge on nutritional intervention strategies can also contribute to the development of lifestyle recommendations concerning healthy nutritional behavior, which could be beneficial for general public.

Conflict of interest This study is part of the BrainMenu project and was financially supported by the STW-Danone Partnership Program. J.M. Verkuyl and L.M. Broersen are employees of Nutricia Research and therefore declare potential conflicts of interest. All other authors report no financial interest or potential conflicts of interest.

Figures and tables

Table 1 The effects of nutrients on inflammation in cell models, divided according to the cell type used.(on the next page)
<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Cell type</th>
<th>Main outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indigestible oligosaccharides</strong></td>
<td>Peripheral blood mononuclear cells [33]</td>
<td>↓ TNFα, ↓ IL-10, ↑ Cell viability</td>
</tr>
<tr>
<td><strong>Gamma oryzanol</strong></td>
<td>Tissue homogenates [53]</td>
<td>↓ Brain protein and lipid peroxidation, ↓ NF-κB, ↓ NF-κB, ↓ adhesion molecule expression</td>
</tr>
<tr>
<td></td>
<td>Macrophages [54]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vascular endothelial cells [55]</td>
<td></td>
</tr>
<tr>
<td><strong>Ferulic acid</strong></td>
<td>Microglia [69]</td>
<td>↓ NF-κB, ↓ Glyoxal cytotoxicity, ↓ Methylglyoxal cytotoxicity, ↓ ROS</td>
</tr>
<tr>
<td></td>
<td>Hepatocytes [89]</td>
<td>Improved mitochondrial membrane potential</td>
</tr>
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<td></td>
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</tr>
<tr>
<td><strong>Geranylgeraniol</strong></td>
<td>Murine monocytes [72]</td>
<td>↓ Programmed cell death, ↓ Proinflammatory cytokines (IL-1α, IL-1β, IL-6, IL-12, TNFα, granulocyte-macrophage colony-stimulating factor)</td>
</tr>
<tr>
<td></td>
<td>Human monocytes [73]</td>
<td>↓ NO, ↓ Proinflammatory cytokines (IL-1β, TNFα), ↓ Malt-1 (NF-κB-activating protein)</td>
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<tr>
<td></td>
<td>Murine peritoneal macrophages [74]</td>
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<tr>
<td><strong>Farnesol</strong></td>
<td>Murine splenocytes [80]</td>
<td>Did not change IL-10/IL-2 cytokine secretion ratios, potential to improve Th2-skewed allergic disease (Th2 inflammation may induce allergic disease)</td>
</tr>
</tbody>
</table>
Table 2 The effects of nutrients on inflammation and brain functions in animals and humans, divided according to the model used. Abbreviations: BDNF - brain derived neurotrophic factor, cPLA2 – calcium-dependent cytosolic phospholipase A2, CSF – cerebrospinal fluid, DMH - 1,2-dimethylhydrazine, FST - forced swim test, DSS – dextran sodium sulfate, MCAO - middle cerebral artery occlusion, MPTP - 1-methyl-4 phenyl-1, 2, 3, 6-tetrahydropyridine, PBMCs – peripheral blood mononuclear cells, TNBS - 2,4,6-trinitrobenzene sulfonic acid, TS - tail suspension test (on the next pages).
## Review on rice bran components

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Disease/animal model</th>
<th>Peripheral inflammation</th>
<th>Brain inflammation and behavior</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gamma oryzanol</strong></td>
<td>Colitis (DSS, mice) [55]</td>
<td>↓ Inflammation</td>
<td>↓ Neuroinflammation [IL-1β release, p38/activation]</td>
</tr>
<tr>
<td></td>
<td>High fat high fructose diet-induced metabolic syndrome (rats) [58], high fat diet (rats) [50], Zucker rats [51]</td>
<td>↓ Disease progression</td>
<td>↑ MEK/ERK1/2 survival pathway in hippocampus (↓ apoptosis)</td>
</tr>
<tr>
<td></td>
<td>Ferulic acid Aged rats [63]</td>
<td>↓ Inflammation</td>
<td>↓ Neuroinflammation</td>
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<tr>
<td></td>
<td>Alzheimer's disease (transgenic mice) [68]</td>
<td></td>
<td>↓ Bradykinesia</td>
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<tr>
<td></td>
<td>Parkinson's disease (MPTP, rats) [69], (rotenone, rats) [70]</td>
<td></td>
<td>↓ Oxidative stress (↑ glutathione, ↓ lipid peroxidation)</td>
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<tr>
<td></td>
<td>Acylamide-induced stress model (rats) [82]</td>
<td></td>
<td>↓ Microglia activation</td>
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<td></td>
<td>High fat diet-induced oxidative stress (mice) [64]</td>
<td>↓ Oxidative stress</td>
<td>↓ Astrocyte activation</td>
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<td></td>
<td>Gamma radiation-induced inflammation (mice) [43]</td>
<td>↓ Inflammation</td>
<td>↓ Proinflammatory markers (IL-1β, TNFα, NO)</td>
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<tr>
<td></td>
<td>Streptozotocine-induced diabetes (rats) [59]</td>
<td>↓ Oxidative stress</td>
<td>↓ Behavioral abnormalities (improvement in gait performance, neuromuscular function and fine motor coordination)</td>
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<tr>
<td>Stroke (MCAO, rats) [60, 62]</td>
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<td>↓ Brain damage</td>
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<td></td>
<td>Depressive-like behavior (TS, FST, mice) [65, 66], (reserpine, mice) [67]</td>
<td></td>
<td>↓ Neuroinflammation</td>
</tr>
<tr>
<td></td>
<td><strong>Geranylgeraniol</strong> Model of mevalonate pathway dysfunction (mice) [75]</td>
<td>↓ Inflammation</td>
<td>↓ Apoptosis</td>
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<tr>
<td></td>
<td>LPS-induced challenge (rats) [76]</td>
<td>↓ Serum amyloid A</td>
<td>↑ Neuroprotectants (peroxiredoxin-2, thioredoxin)</td>
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<td></td>
<td></td>
<td>↓ Peritoneal exudate cells</td>
<td>↑ Anti-depressant (synergistic with serotonergic drugs)</td>
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<td></td>
<td>↓ Inflammation</td>
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<td></td>
<td>Farnesol Colitis (DMH, rats) [79]</td>
<td>↓ Inflammation</td>
<td></td>
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<tr>
<td></td>
<td>Ovalbumin-sensitized mice [90]</td>
<td>↓ Apoptosis</td>
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<td></td>
<td>Acylamide-induced neurotoxicity [82]</td>
<td>↓ Mucosal edema</td>
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<td>↓ TH-2 skewed</td>
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<td>↓ Allergic reaction</td>
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<td>↓ Inflammation</td>
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<td>Behavioral improvement</td>
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**Figure 1** A schematic overview of the potential role of nutrients described in this review on the regulation of neuroinflammation.

<table>
<thead>
<tr>
<th>Phytosterol pherulates Isoprenoids</th>
<th>CNS</th>
<th>Neuroinflammation</th>
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<tbody>
<tr>
<td></td>
<td>-</td>
<td>- Activation of microglia and astrocytes</td>
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<td>- Cytokine release</td>
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<td>- Neurotoxicity</td>
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<td>Peripheral tissues</td>
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<td>Pathology of brain disease</td>
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<td>Immune cells</td>
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<td></td>
<td>-</td>
<td>Gut and gut microbiota</td>
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</table>

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[35] Cheng CY, Su SY, Tang NY, Ho TY, Chiang SY, Hsieh CL. Ferulic acid provides


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