Review
Unearthing the Potential Therapeutic Effects of Oxyresveratrol Based on Intrinsic Links between Pharmacological Effects: Implications for the Gut–Liver–Brain Axis

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Abstract: Oxyresveratrol is a stilbene compound with a simple chemical structure and various therapeutic potentials. This study summarized and analyzed the multiple pharmacological effects and mechanisms of oxyresveratrol, identifying its prominent performance in neuroprotection, hepatoprotection, and anti-inflammatory activities in the intestines. By integrating the pharmacological effects of oxyresveratrol with insights from the network pharmacology and molecular docking of its interactions with targets linked to gut–liver–brain axis disorders, it has been shown that oxyresveratrol may hold promise for the treatment of gut–liver–brain axis-related disorders. The synergistic effect between various mechanisms has inspired further research and the development of oxyresveratrol’s application value.

Keywords: oxyresveratrol; stilbene compounds; molecular docking; gut–liver–brain axis; synergistic effect

1. Introduction
Oxyresveratrol (4-[E)-2-(3,5-dihydroxyphenyl)ethenyl]benzene-1,3-diol), a small-molecule stilbene compound, is known for its diverse pharmacological activities. Its chemical structure is depicted in Figure 1A. Oxyresveratrol is naturally present in gymnosperm plants of the Gynaceae family and has been identified in various species of angiosperms, including 6 species of plants, 9 species of monocots, and 38 species of dicots [1]. Plants known to contain oxyresveratrol include Artocarpus lakoocha Roxb., Smilax poria, Veratrum nigrum L., Gnetum montanum Markgr., Mori Cortex, and Ramulus Mori [2,3]. Stilbene compounds are a type of plant secondary metabolite, and their synthetic pathway relies on the key enzyme stilbene synthase. Some scholars believe that resveratrol (Figure 1B) and similar compounds, such as pinoresinol (Figure 1C) and piceatannol (Figure 1D), are precursors for all stilbene derivatives, including oxyresveratrol. However, more specific experimental evidence is needed to support this claim [1].

Oxyresveratrol and resveratrol have similar structures. Oxyresveratrol exhibits a higher vital clearance ability and tissue permeability than resveratrol [4,5]. According to the latest research, oxyresveratrol expresses tyrosinase inhibitory activity, suppresses melanin production, and exhibits a whitening function. It also possesses antibacterial, anti-inflammatory, antioxidant, anti-apoptotic, neuroprotective, anti-hyperglycemic, and cancer prevention and treatment properties [6–9]. This review summarizes oxyresveratrol’s reported pharmacological activities and mechanisms of action and reveals its outstanding...
performance in protecting the nervous system, combating liver diseases, and reducing intestinal inflammation. By considering the integration of the pathways of oxyresveratrol’s targets, this review suggests that oxyresveratrol might potentially have effects on the gut–liver–brain axis. This study aimed to provide new ideas and insights for the overall in-depth study of oxyresveratrol’s pharmacological effects.

Figure 1. Chemical structures of oxyresveratrol (A), resveratrol (B), pinosylvin (C), and piceatannol (D).

2. Oxyresveratrol’s Pharmacological Effects and Mechanisms

2.1. Oxyresveratrol’s Anti-Cancer and Anti-Malignant Tumor Effects

Cancer occurrence is a highly complex process. The influences of proto-oncogene activation, cell proliferation regulation, and the disorder of normal apoptosis programs might cause carcinogenesis [10]. Evidence suggests that oxyresveratrol displays anti-cancer effects via multiple pathways. Firstly, oxyresveratrol has a direct toxic effect on ovarian cancer, lung cancer, and cervical cancer cell lines by binding to the DNA of cancer cells, altering the DNA structure, and causing cancer cell death [11–13]. Secondly, oxyresveratrol inhibits cancer cell growth and proliferation by affecting the replication and repair of DNA in the G0/G1 phase and S phase of the cell cycle, significantly downregulating the expression of the DNA repair protein RAD51 gene (Rad51), which is related to the DNA homologous recombination repair pathway [14,15]. Thirdly, oxyresveratrol induces apoptosis in a variety of cancer cells. Studies showed that oxyresveratrol application led to the apoptosis of neuroblastoma cells (SH-SY5Y) and breast cancer cells (MDA-MB-231) [12,16]. Additionally, research has indicated that oxyresveratrol inhibits cell viability and induces apoptosis in osteosarcoma (Saos-2) cells [17].

Culturing with oxyresveratrol significantly inhibited cancer cell migration in colorectal cancer cells (CRCs) [18,19] and also in the liver cancer cell lines QGY-7701 and SMMC-7721. Oxyresveratrol also inhibited the tumor growth of hepatocellular carcinoma induced by H22 cells in a dose-dependent manner [20].

Oxyresveratrol could achieve its effects by increasing the number of normal cells, reducing apoptosis, and scavenging free radicals, especially in mitochondrial protection [21–26]. Mitochondria are the primary targets of oxidative damage and the apoptotic pathways [27], and mitochondrial dysfunction is a pathological manifestation of various diseases [28–30]. Trans-crotonaldehyde (TCA) is the molecule responsible for mitochondrial lipid metabolism and is an essential toxic product of oxidation [31,32]. Toxic TCA is considered to attack mitochondrial DNA [33,34] and is closely related to the molecular mechanism of cancer formation [35]. Studies have found that oxyresveratrol scavenges the aldehyde group (—CH=O) of mitochondrial toxic TCA to protect mitochondria [36].

In summary, oxyresveratrol exerts anti-cancer effects by directly damaging the DNA of cancer cells, and by inhibiting cancer cell proliferation and metastasis [37]. In addition, oxyresveratrol could ameliorate immunity by enhancing the cellular vitality of normal cells.
2.2. Oxyresveratrol’s Inhibiting Effect on Melanin Formation

Excessive melanin deposition can lead to esthetic skin problems [38]. Elevated levels of reactive oxygen species (ROS) activate the α-melanocyte-stimulating hormone in the epidermis to activate tyrosinase (TYR). This is regulated by melanogenesis-associated transcription factor (MITF), which catalyzes the hydroxylation of tyrosine to 3,4-dihydroxyphenylalanine (DOPA) [4]. DOPA is then oxidized to dopaquinone, and its derivatives are oxidatively polymerized to produce melanin [39]. Recent studies have demonstrated that oxyresveratrol inhibits the gene transcription and protein expression of the TYR gene family by suppressing the expressions of MITF and TYR-related protein-2 (TRP-2), thereby reducing the additive effect of melanin [4]. Additionally, oxyresveratrol functions as a non-competitive inhibitor of TYR, leading to decreased TYR activity and melanin content by facilitating ROS removal in cells [40,41]. Oxyresveratrol has multi-target and multi-link inhibitory effects on the production process of melanin and age pigments [42–44].

2.3. Oxyresveratrol’s Protective Effect on the Nervous System

With the intensification of global aging, the treatment of neurodegenerative diseases, especially Parkinson’s disease (PD) and Alzheimer’s disease (AD), has attracted increasing attention [45,46]. Endoplasmic reticulum stress (ERS) is a critical mechanism of PD pathology and triggers the pathways, showing protective effects in the early stages [47,48]. However, when the damage expands, apoptosis is triggered [49]. Various PD models have shown that oxyresveratrol significantly reduces the release of lactate dehydrogenase and the activity of cysteine-containing aspartate-specific protease-3 (caspase-3) by reducing ERS and inhibiting the transcription of activated transcription factor-4 (ATF4) via other pathways to reduce nerve cell apoptosis [50,51]. The amyloid precursor protein (APP) is a hallmark of AD, as the precursor of β-amyloid. In mouse cortical astrocytes, oxyresveratrol reduced APP by regulating AMP-activated protein kinase (AMPK)/unc-51-like autophagy activating the kinase-1 (ULK1)/mammalian target of rapamycin (mTOR)-dependent induction of autophagy, and significantly decreased neuronal cell loss [52,53]. In addition, oxyresveratrol works to protect cortical and hippocampal neurons from damage by β-amyloid.

Neuroinflammation is closely related to the occurrence and development of PD and AD [54,55]. Oxyresveratrol has anti-neuroinflammation effects, and it significantly reduces the release of IL-6 and MCP-1 in HMC3 cells stimulated by IL-1β and inhibits the activation of the PI3K/AKT/p70S6K pathway induced by IL-1β [56]. Moreover, oxyresveratrol effectively suppresses the release of pro-inflammatory mediators from BV-2 cells stimulated by lipopolysaccharide (LPS) and then exerts anti-inflammatory effects via the MAPKs and NF-κB signaling pathways [57,58]. Furthermore, it has demonstrated protective effects on various neural cell injury models, including acute hippocampal neuron cell death induced by kainic acid (KA), ethanol-induced DNA damage in the mouse cerebellum and cerebral cortex, and H₂O₂-induced PC12 cell-death experiments [59,60].

2.4. Oxyresveratrol’s Anti-Obesity Effect

Obesity is a hidden trouble that can lead to various diseases [61]. Thermogenesis is a new method to fight obesity, wherein the energy is consumed as calories instead of being stored as lipids [62]. The acceleration of mitochondrial biogenesis and the expression of thermogenesis-related genes in subcutaneous white adipose tissue initiates a browning program, resulting in the formation of beige adipose tissue [63]. Subsequently, beige fat converts energy into heat dissipation, presenting a novel strategy for preventing and treating obesity by inducing the beige coloration of white adipose tissue and enhancing energy expenditure [64]. In experiments, oxyresveratrol sped up energy conversion by increasing the expression of the thermogenesis-related uncoupling protein (UCP1) in adipose tissue and significantly activated carnitine palmitoyl transferase-1 (CPT1) [65]. In addition, oxyresveratrol accelerated the beige coloration of white adipose tissue by decreasing lipid accumulation and the expression of adipocyte markers during the differentiation of 3T3-L1
and C3H10T1/2 adipocytes, inducing thermogenic genes and inhibiting white adipocyte selection genes [66,67]. Oxyresveratrol treatment in obese mice that were fed a high-fat diet significantly reduced adipose tissue weight, prevented weight gain, and alleviated obesity-related symptoms.

2.5. Oxyresveratrol’s Protective Effect on the Liver

Liver damage can cause serious harm to the body, ranging from fatty liver to liver fibrosis and cirrhosis, which can eventually lead to liver failure or liver cancer [68,69]. Oxyresveratrol significantly reduces serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels in different liver injury models [70]. It also decreases the expression of inflammatory factors and inhibits the liver toll-like receptor 4 (TLR4)/NF-κB signaling pathway, helping to prevent liver cell degeneration and inflammatory cell infiltration [71]. It also inhibits the expression and activation of caspases, reduces the hepatocyte apoptosis stimulated by galactosamine (LPS/d-GalN), and blocks the generation of ROS and the cell death of hepatocytes induced by tert-butyl hydroperoxide (TBHP) [72].

Non-alcoholic fatty liver disease (NAFLD) is one of the world’s most prevalent liver diseases. Currently, few drugs can be used clinically to treat NAFLD [73]. In hepatocyte models, it was observed that oxyresveratrol could inhibit the induction of sterol regulatory element-binding proteins (SREBP-1C) by liver X receptor (LXR) agonists. This led to a downregulation of lipid genes, while the genes related to fatty acid oxidation were promoted in hepatocytes. Additionally, liver lipogenesis was reduced, and fatty liver disease formation was prevented [74].

Oxyresveratrol not only relieves the symptoms of liver damage and non-alcoholic fatty liver disease but also affects the process of hepatic fibrosis (HF). The activation of hepatic stellate cells (HSCs) is the most critical event in HF. Yes-associated protein 1 (YAP) and transforming growth factor β1 (TGF-β1) may be critical regulators of hepatic stellate cell (HSC) activation. Oxyresveratrol acts on the Hippo/YAP and TGF-β1/Smad signaling pathways to influence liver fibrosis [75].

2.6. Oxyresveratrol’s Protective Effect on the Intestines

The intestinal tight junction (TJ) ensures the integrity of the intestinal mucosa, provides an effective barrier for the normal absorption of nutrients, and protects against intestinal pathogens, allergens, and toxins [76,77]. It is also vital in the recovery from inflammatory bowel disease (IBD) [78]. Oxyresveratrol enhances the expression of intestinal tight junction proteins and the integrity of the intestinal TJ barrier [79,80]. Furthermore, oxyresveratrol stimulates the expression of mucoprotein 2 (MUC2) in human intestinal goblet cells, maintaining and renewing the intestinal mucus to ensure the stability of the intestinal mucus barrier [81–83].

2.7. Oxyresveratrol’s Antibacterial Effect

Oxyresveratrol has an inhibitory effect on bacteria and fungi. The minimum inhibitory concentration (MIC) of oxyresveratrol to Staphylococcus aureus is 128–256 µg/mL [84]. In addition, oxyresveratrol has a dose-dependent inhibitory effect on various oral bacteria, such as Streptococcus mutans and Streptococcus gordonii, and could exert antibacterial effects by significantly downregulating glucosyltransferase expression, inhibiting glucan synthesis, affecting biofilm formation, and eventually reducing the survival rate of Streptococcus mutans [85–87]. Methicillin-resistant Staphylococcus aureus (MRSA) treatment with oxyresveratrol was found to promote cell membrane permeability and inhibit growth and reproduction [88,89]. Oxyresveratrol can suppress the bacterial production, population movement, and agglutination ability of Gram-negative bacteria, the uropathogenic Escherichia coli (UPEC), by inhibiting UPEC biofilm formation [90]. In addition, oxyresveratrol initiates the mitochondria-related apoptotic pathway by activating the mitochondria-mediated apoptosis of Candida albicans, and it has an antifungal effect by inhibiting the activity of Trichophyton rubrum [91,92].
2.8. Oxyresveratrol’s Anti-Inflammatory Effect

Inflammation is a primary pathological reaction that can be related to many diseases [93,94]. The persistent presence and high expression of inflammatory mediators can trigger cascade reactions, such as inducing cell proliferation and increasing ROS production [95]. Oxyresveratrol effectively suppresses the inflammatory response triggered by LPS in an estrogen receptor (ER)-dependent manner by modulating the NF-κB signaling pathway [96–99]. This modulation leads to a decreased expression of inflammatory factors and a reduced production of matrix metalloproteinase 13 (MMP-13), thus attenuating the inflammatory response [100]. In an alcoholic ulcer mouse model, oxyresveratrol had a significant inhibitory effect on inflammatory infiltration and ulcers and exerted an anti-inflammatory effect by markedly reducing the transcription levels of various pro-inflammatory factors [101]. In a skin inflammation model, oxyresveratrol reduced the number of CD3, CD4, and CD8 T cells in the sensitized skin of mice [102]. Oxyresveratrol could improve the inflammatory status of dermatitis models, both in vitro and in vivo. It effectively inhibited excessive cell proliferation by downregulating TNF-α in a dose-dependent manner in the keratinocytes and also inhibited AKT phosphorylation [103].

2.9. Oxyresveratrol’s Effect on Blood Sugar Regulation

Blood sugar is an essential indicator of physical health as related to insulin and glucagon secretion [104–106]. Oxyresveratrol enhances insulin secretion in INS-1 cells and has shown an anti-glycosylation effect by capturing methylglyoxal and inhibiting the production of advanced glycation end products (AGEs) [107–109]. It might also regulate blood sugar by improving β-cell dysfunction and insulin resistance and stabilizing or enhancing the activity and expression of glucokinase (GK) [66,110]. Blood sugar levels were significantly reduced in diabetic ICR mice treated with oxyresveratrol because it inhibited maltose hydrolysis and reduced intestinal cell glucose transport [111–113].

2.10. Oxyresveratrol’s Other Pharmacological Effects

Oxyresveratrol’s pharmacological effects indicate its ability to regulate and improve various bodily functions. In addition, oxyresveratrol undergoes metabolic transformations via double-bond reduction, dihydroxylation, and demethylation under the mediation of colonic microbiota, affecting the species and quantity of intestinal endophytic bacteria [114,115]. The oxidative stress induced by hydrogen peroxide (H₂O₂) causes apoptosis in human lens epithelial cells (HLECs) and triggers cataract formation. Oxyresveratrol has a specific protective effect on cataracts by reversing the oxidative stress and apoptosis of HLECs induced by H₂O₂ [116].

3. Oxyresveratrol and the Gut–Liver–Brain Axis

3.1. Gut–Liver–Brain Axis

Based on the summary of oxyresveratrol’s pharmacological effects and mechanisms, oxyresveratrol shows outstanding performance in protecting the nervous system, treating liver injury and intestinal inflammation, and affecting the activity of intestinal microorganisms. According to this evidence, oxyresveratrol may potentially act on the gut–liver–brain axis.

The gut–liver–brain axis is a complex network within the body, involving dialog between various systems such as the gastrointestinal tract, liver, and central nervous system [117,118]. It is implicated in multiple diseases and significantly affects human health. Experimental findings have shown intestinal material leakage occurring in various liver diseases, with significantly elevated levels of endotoxins and lysophosphatidic acid in the patients’ circulatory systems [119–126]. This might activate the neuroinflammatory processes, leading to neurological complications [127–129]. Additionally, the interaction between the gut and brain via the nervous and circulatory systems has been observed in various disorders related to the gut–brain axis, indicating that the dysbiosis of the gut microbiota and accumulation of toxic substances from the intestines are closely associated with disease progression [130–134]. Meanwhile, the neurons and the brain provide feedback information to the liver via the vagus nerve’s parasympathetic branch, which also
innervates the intestines. Thus, intestinal tract–liver–central nervous system interactions influence various diseases. The inherent beneficial interactions within the gut–liver–brain axis contribute to the nervous system’s development and maintenance [135].

The main drug treatments for diseases related to the gut–liver–brain axis, such as antibiotics, probiotics, targeted drugs, and so on, only focus on specific areas at once [136–138]. Based on oxyresveratrol’s pharmacological effects, it has been found that oxyresveratrol exhibits significant efficacy in simultaneously treating intestinal dysbiosis, intestinal inflammation, and liver diseases and in providing neuroprotection. This offers hope for a holistic approach to treating diseases associated with the gut–liver–brain axis. Network pharmacology and molecular docking studies have been conducted to determine the relationship between oxyresveratrol and the gut–liver–brain axis regarding the related targets and pathways.

3.2. Network Pharmacological Research

Eighty-seven targets of oxyresveratrol were found after screening and deduplication via the Traditional Chinese Medicine Systems Pharmacology Database Analysis Platform (TCMSP) and the SwissTargetPrediction website. In total, 4566 targets relating to the gut–liver–brain axis were obtained after screening and deduplication via the GeneCard Database and DisGeNET website.

Fifty-six target genes were obtained when oxyresveratrol’s targets and the gut–liver–brain axis-related targets intersected on the jvenn platform (https://jvenn.toulouse.inrae.fr/app/example.html, accessed on 13 January 2024), as shown in Figure 2A. The overlapping target library was imported into the String website, then Cytoscape 3.9.1 software was used to visually analyze the protein–protein interaction (PPI) network to obtain Figure 2B (the circle’s size in the figure represents the betweenness centrality from large to small).

![Figure 2](image_url)

**Figure 2.** Screening of the common targets of oxyresveratrol (drug) and the gut–liver–brain axis (disease) (A) and PPI network construction for the screened targets (B).

After calculation using the CytoNCA plug-in of the Cytoscape 3.9.1 software, the node scores from the PPI network were screened by the higher-than-median value of betweenness centrality, closeness centrality, degree centrality, eigenvector centrality, local average connectivity-based method centrality, and network centrality to obtain the network core targets ESR1, BCL2, EGFR, PTGS2, GSK3B, AR, and SRC, as shown in Table 1.
Table 1. Screening of core genes.

<table>
<thead>
<tr>
<th>Rank</th>
<th>Target Name</th>
<th>Betweenness Centrality</th>
<th>Closeness Centrality</th>
<th>Degree Centrality</th>
<th>Eigenvector Centrality</th>
<th>Local Average Connectivity-Based Method Centrality</th>
<th>Network Centrality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>ESR1</td>
<td>26.02</td>
<td>1</td>
<td>19</td>
<td>0.31</td>
<td>10.74</td>
<td>19</td>
</tr>
<tr>
<td>2</td>
<td>BCL2</td>
<td>21.10</td>
<td>0.95</td>
<td>18</td>
<td>0.30</td>
<td>10.56</td>
<td>17.21</td>
</tr>
<tr>
<td>3</td>
<td>PTGS2</td>
<td>17.39</td>
<td>0.90</td>
<td>17</td>
<td>0.28</td>
<td>10.35</td>
<td>15.97</td>
</tr>
<tr>
<td>4</td>
<td>EGFR</td>
<td>17.83</td>
<td>0.90</td>
<td>17</td>
<td>0.28</td>
<td>10.12</td>
<td>15.64</td>
</tr>
<tr>
<td>5</td>
<td>GSK3B</td>
<td>12.34</td>
<td>0.86</td>
<td>16</td>
<td>0.27</td>
<td>10.38</td>
<td>14.94</td>
</tr>
<tr>
<td>6</td>
<td>AR</td>
<td>8.32</td>
<td>0.83</td>
<td>15</td>
<td>0.27</td>
<td>10.40</td>
<td>13.73</td>
</tr>
<tr>
<td>7</td>
<td>SRC</td>
<td>5.04</td>
<td>0.76</td>
<td>13</td>
<td>0.24</td>
<td>9.23</td>
<td>11.06</td>
</tr>
</tbody>
</table>

The top 10 terms in the Biological Process (BC), Cellular Component (CC), and Molecular Function (MF) categories in the Gene Ontology (GO) enrichment analysis of the target genes (Figure 3A) and the top 30 pathways in the Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis (Figure 3B) were obtained using the Rstudio 4.2.3 software. According to the GO enrichment results, oxyresveratrol might affect the gut–liver–brain axis by regulating processes such as peptidyl-serine phosphorylation and modification, the oxidative stress response, and arachidonic acid metabolism in the Biological Process category. In the Cellular Component category, it could influence the cellular membranes and nuclear membrane structures. In the Molecular Function category, oxyresveratrol’s mechanism of action includes protein tyrosine kinase activity; oxidoreductase activity, involving the incorporation or reduction of molecular oxygen; and oxygen binding. These results indicate that oxyresveratrol mainly affects the gut–liver–brain axis by modulating kinase activity and redox reactions.

In the top-30 KEGG pathway analysis shown in Figure 3B, the first enrichment pathway is the PI3K-Akt signaling pathway including 14 out of 54 genes. This pathway and the subsequent P53 pathway are closely related to cell proliferation and cancer development [139,140]. The NF-κB signaling pathway and arachidonic acid metabolism are related to inflammation [141,142]. The serotonergic synapse pathways are related to the nervous system. Additionally, oxyresveratrol’s target genes were also enriched in other pathways.
related to the gut–liver–brain axis, such as various liver disease pathways, the neurotrophin signaling pathway, the Parkinson’s disease pathway, and cellular adhesion signaling pathways. These enrichment results closely align with oxyresveratrol’s pharmacological effects, as outlined in the preceding section.

3.3. Molecular Docking of Oxyresveratrol and Core Targets

Based on the findings presented in Table 1, oxyresveratrol and its core targets were subjected to docking analysis using the LeDock V1.0 software. The binding energy values indicate a strong affinity between oxyresveratrol and most of the core targets, with binding energies below $-5.0$ kcal/mol [143], except the target BCL2, with the binding energy between BCL2 and oxyresveratrol above $-5.0$ kcal/mol. The results of the docking process were visualized using the PyMOL 2.5.4 software and the Ligplot+ v.2.2 software, as depicted in Figures 4 and 5.

![Figure 4. Three-dimensional representations of oxyresveratrol in complex with (A) ESR1; (B) PTGS2, and (C) EGFR. The proteins are shown as colored cartoons, while the oxyresveratrol is represented as cyan sticks. Hydrogen bonds are represented as yellow dashed lines. Two-dimensional representations of oxyresveratrol in complex with (D) ESR1; (E) PTGS2; and (F) EGFR. Hydrogen bonds and hydrophobic contacts are shown as green and red dashed lines, respectively. The ligands are represented as violet lines.]
Figure 5. Three-dimensional representations of oxyresveratrol in complex with (A) GSK3B; (B) AR and (C) SRC. The proteins are shown as colored cartoons, while the oxyresveratrol is shown as cyan sticks. Hydrogen bonds are represented as yellow dashed lines. Two-dimensional representations of oxyresveratrol in complex with (D) GSK3B; (E) AR; and (F) SRC. Hydrogen bonds and hydrophobic contacts are shown as green and red dashed lines, respectively. The ligands are represented as violet lines.

Oxyresveratrol was able to establish hydrogen bonds and hydrophobic interactions with amino acid residues in ESR1, EGFR, PTGS2, GSK3B, AR, and SRC proteins during the docking process, as evidenced by the data in Figures 4 and 5, and Table 2. Core targets in the KEGG analysis, such as EGFR and GSK3B, were implicated in the PI3K-Akt signaling pathway, hepatocellular carcinoma pathway, and hepatitis C pathway. Meanwhile, SRC was associated with the Gap junction pathway, and PTGS2, EGFR, and GSK3B were identified as key targets in the NF-κB signaling pathway. Additionally, PTGS2 and GSK3B were linked to pathways related to neurodegeneration. There were lower binding energies ($<-5.0$ kcal/mol) when these targets were docking with oxyresveratrol, indicating a fa-
favorable binding affinity between oxyresveratrol and these core targets. The visual representations suggest hydrogen bonds and hydrophobic interactions between oxyresveratrol and amino acid residues of the target proteins during binding, potentially leading to alterations in the proteins’ spatial structures and functional domains, consequently affecting their activity.

Table 2. Molecular docking results of oxyresveratrol and the core targets.

<table>
<thead>
<tr>
<th>Target</th>
<th>RSCB-PDB Code</th>
<th>Resolution (Å)</th>
<th>Binding Energy (kcal·mol(^{-1}))</th>
<th>Hydrogen Bond Residues</th>
<th>Hydrophobic Residues</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESR1</td>
<td>8DU8</td>
<td>1.47</td>
<td>-5.88</td>
<td>Glu353, Leu387, Arg394, and Gly521</td>
<td>Leu349, Leu384, Met388, Leu391, Phe404, Ile424, Hsd524 and Leu525</td>
</tr>
<tr>
<td>PTGS2</td>
<td>5IKR</td>
<td>2.34</td>
<td>-6.42</td>
<td>Ala199, Asn382 and Hsd386</td>
<td>Ala202, Glu203, Hsd207, Phe210, Tyr385, Trp387, Hsd388, Leu390, and Leu391</td>
</tr>
<tr>
<td>EGFR</td>
<td>5HG8</td>
<td>1.42</td>
<td>-5.83</td>
<td>Gln791, Met793, and Thr854</td>
<td>Leu718, Val726, Ala743, Cys775, Met790, Pro794, Gly796, Leu844, and Phe856</td>
</tr>
<tr>
<td>GSK3B</td>
<td>7SXJ</td>
<td>1.85</td>
<td>-5.14</td>
<td>Asp133, val135, Pro136, Glu137, and Asp200</td>
<td>Ala83, Val110, Leu118, Leu132, Tyr134, Thr138 Arg141, and Cys199</td>
</tr>
<tr>
<td>AR</td>
<td>8E1A</td>
<td>1.20</td>
<td>-6.46</td>
<td>Leu704, Asn705, Met745, Arg752, and Phe764</td>
<td>Leu707, Gly708, Glu711, Met742, Val746, Met749, Ala577, Phe891, and Met895</td>
</tr>
<tr>
<td>SRC</td>
<td>8JN8</td>
<td>1.90</td>
<td>-5.92</td>
<td>Phe281, Gly282, Thr299, Asp389, and Lys426</td>
<td>Gly279, Cys280, Glu283, Lys289, Leu300, Arg391, Ala411, and Ile414</td>
</tr>
</tbody>
</table>

4. Discussion

Oxyresveratrol achieves a variety of pharmacological activities by acting mainly on inflammation, tight junctions, and cancer pathways [144], the PI3K/AKT signaling pathway [145], insulin regulatory pathways, AD and other neurodegenerative disease pathways, lifespan regulatory pathways, etc. Oxyresveratrol’s effects on anti-intestinal inflammation, liver-injury treatment, and nervous system protection are closely related to the gut–liver–brain axis [146–150].

The study of the gut microbiome–liver–brain axis system model has become the focus of nervous system research [151–153], and increasing evidence shows a connection between inflammatory bowel disease, neurodegenerative diseases, and neuroinflammatory diseases [154]. Epidemiological, clinical pharmacological, and nutritional studies have confirmed that oxyresveratrol has various pharmacological effects, such as anti-cancer effects [144,155], protection against oxidative stress and neurodegenerative diseases [156,157], and the treatment of liver, intestinal tract, and nervous system diseases. Dysbiosis of the intestinal microbiota activates the intestinal immune system, thereby enhancing intestinal permeability and bacterial translocation, leading to neuroinflammation, cerebrovascular changes, and the formation of AD-related β-amyloid and PD-related α-synuclein aggregation. In turn, the nervous system can regulate the function of the gastrointestinal tract via the parasympathetic nerves. Oxyresveratrol’s pharmacological effects, which were observed in the experimental studies, along with the network pharmacological research and molecular docking results above, highlight the specific targets and pathways associated with oxyresveratrol. These findings suggest that oxyresveratrol may regulate the pathways related to the gut–liver–brain axis through action-related targets. Although oxyresveratrol has low solubility in water and low stability, it is relatively safe when taken orally [158]. Fortunately, significant progress has been made in the research and improvement of oxyresveratrol pharmacokinetics [159–163]. Therefore, oxyresveratrol has excellent research value and development potential in treating intestinal axis pattern-related diseases.
5. Conclusions

From the above summary of the various pharmacological effects of oxyresveratrol, it can be inferred that oxyresveratrol exhibits therapeutic effects for diseases associated with the gut–liver–brain axis. Representations of oxyresveratrol’s pharmacological effects, network pharmacology analysis, and an examination of the molecular docking results of oxyresveratrol and the core targets in the pathways connecting to gut–liver–brain axis-related diseases reveal the multi-directional and multi-target treatment potential of oxyresveratrol for such diseases. However, further comprehensive and in-depth research is required to fully develop oxyresveratrol into a clinically effective drug in the long term.

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Pharmaceuticals 2024, 17, 1063


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