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## Review

# The role of 8-OxoG and its repair systems in liver diseases progression: responsible mechanisms and promising natural products



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## ABSTRACT

The accumulation of deoxyribonucleic acid (DNA) oxidative damage mediated by reactive oxygen species (ROS) is closely associated with liver diseases. 8-Oxoguanine (8-OxoG), a prevalent DNA oxidation product, plays a significant role in liver disease progression. The base excision repair (BER) pathway, comprising over 30 proteins including 8-OxoG DNA glycosylase1 (OGG1), MutY homolog (MUTYH), and MutT homolog protein 1 (MTH1), is responsible for the clearance and mismatch repair of 8-OxoG. Abnormally high levels of 8-OxoG and dysregulated expression and function of 8-OxoG repair enzymes contribute to the onset and development of liver diseases. Consequently, targeting the 8-OxoG production and repair system with agonists or inhibitors may offer a promising approach to liver disease treatment. This review summarizes the impact of 8-OxoG accumulation and dysregulated repair enzymes on various liver diseases, including viral liver disease, alcoholic liver disease (ALD), metabolic dysfunction-associated steatotic liver disease (MASLD), cholestatic liver disease (CLD), liver fibrosis, cirrhosis, and liver cancer. Additionally, we review natural constituents as potential therapeutic agents that regulate 8-OxoG production, repair enzymes, and repair system-related signal pathways in oxidative damage-induced liver diseases.

## 1. Introduction

Reactive oxygen species (ROS) are normal byproducts of various metabolic processes in organisms, including hydroxyl radicals ( $\cdot\text{OH}$ ) and superoxide anion radicals ( $\cdot\text{O}_2$ ). Typically, there exists a dynamic equilibrium between oxidative and antioxidant systems. However, this balance can be disrupted by endogenous factors, such as excessive oxidant generation, or exogenous factors like smoking and ultraviolet radiation. Excessive ROS production may attack biomolecules, resulting in oxidative damage. Deoxyribonucleic acid (DNA) oxidative damage, frequently observed, includes base oxidation, deoxyribose oxidation, single-strand breaks (SSBs), DNA double-strand breaks (DSBs), and apurine/aprimidine (AP) sites. The guanine base (G) is particularly susceptible to oxidation, readily forming 8-oxoguanine (8-OxoG) due to its low oxidation potential, making it a biomarker for DNA oxidative damage<sup>1</sup>. Following 8-OxoG formation, 8-OxoG DNA glycosylase1 (OGG1), MutY homolog (MUTYH), and MutT homolog protein 1 (MTH1) are responsible for clearing the erroneous 8-OxoG and its paired adenine base (A), activating the base excision repair (BER) pathway to prevent disease occurrence and progression. Although the 8-OxoG repair system can mitigate the impact of 8-OxoG on the organism to some extent, accumulated unrepaired damage may significantly compromise genomic stability, leading to gene mutations, cell death, and various diseases, including liver disorders.

Liver diseases exhibit a strong correlation with DNA oxidative damage, encompassing viral liver disease, alcoholic liver disease (ALD), metabolic dysfunction-associated steatotic liver disease (MASLD), cholestatic liver disease (CLD), liver fibrosis, cirrhosis, and liver cancer. The oxidative DNA lesion 8-OxoG potentially plays a pivotal role in the initiation and progression of liver diseases, and its repair represents a significant therapeutic strategy. Mitigating excessive ROS in hepatocytes can decrease 8-OxoG formation and impede the onset of oxidative stress-induced liver diseases. An increasing number of natural products have demonstrated efficacy in treating liver diseases by inhibiting ROS production, targeting 8-OxoG repair enzymes, or modulating 8-OxoG-related signaling pathways. Consequently, natural compounds show promise as potential therapeutic agents for liver disease treatment by targeting 8-OxoG and its repair mechanisms.

This review concisely summarizes the formation, repair, and biological functions of 8-OxoG in the pathogenesis and progression of liver diseases. It aims to thoroughly explore the relationship between 8-OxoG and hepatic disorders, as well as its potential for targeted therapy in the future. Furthermore, the paper systematically examines the role of natural constituents in liver disease treatment based on 8-OxoG-mediated mechanisms, potentially offering new directions for research and therapeutic interventions.

## 2. Formation, pathogenic mechanism, and repair of 8-OxoG

Under oxidative stress, the guanine base G on DNA/RNA

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strands or free dGTP in the nucleotide pool undergoes oxidation on the 8<sup>th</sup> carbon atom, forming 8-OxoG or 8-Oxo-dGTP. These oxidized forms can be incorporated into DNA during replication or RNA during transcription<sup>2</sup>. The formation of 8-OxoG is preferentially observed in purine-rich sequences, particularly in the 5'-end (promoter region) or within GG repeat sequences<sup>3</sup>. Additionally, the promoter region, which is a potential G-quadruplex (G4) formation site, contains G-quadruplex-forming sequences (PQS) and exhibits a higher concentration of 8-OxoG.

The pathological processes associated with various diseases can be attributed to the genotoxicity of 8-OxoG and the coordination of OGG1-initiated BER and transcriptional regulation. 8-OxoG exhibits strong mutagenicity, pairing not only with cytosine C through the Watson-Crick rule but also with adenine A through the Hoogsteen rule. After two consecutive replications, a G:C to T:A transversion mutation occurs, leading to genetic information alterations and genome instability, potentially causing malignant cell transformation<sup>4</sup>. Furthermore, 8-OxoG can promote transcriptional mutation (TM), resulting in C > A transversion in mRNA *via* 8-OxoG:A base pairing and the production of erroneous proteins, contributing to various diseases such as cancer and Parkinson's disease<sup>1</sup>.

Beyond altering genetic information, 8-OxoG functions as an epigenetic modification affecting the integrity of transcriptional regulatory elements in promoters, including transcription factor (TF) recruitment, CpG island methylation, and histone modification distribution. Primarily, 8-OxoG generation at TF binding sites in promoters compromises the integrity of transcriptional regulatory elements, resulting in reduced binding of transcription factors (TFs) such as nuclear factor- $\kappa$ B (NF- $\kappa$ B), SP1, and cAMP-response element-binding protein (CREB). Additionally, 8-OxoG and its repair intermediate, the AP site, recruit repair proteins [e.g., OGG1, apurinic/apyrimidinic endonuclease 1 (APE1)] to oxidized promoter regions, facilitating TF binding and transcriptional activation<sup>1</sup>. OGG1 regulates transcription through its pre-base-excision role and BER enzymatic activity. OGG1 cysteine residues (OGG1-SOH) are recruited to DNA promoter regions, inducing structural changes in DNA, occupancy of TFs (including NF- $\kappa$ B, SP1, Myb, Egr-1, AP-1, TP53, HIF-1 $\alpha$ , and CREB1), and assembly of the transcriptional initiation complex due to decreased energy barriers, thereby initiating gene expression. Genes transcriptionally regulated by 8-OxoG typically have high GC-content promoters, such as pro-inflammatory genes [TNF- $\alpha$ , CXCL chemokine ligand 1 (CXCL1), CXCL2, CCL20, and IL-1 $\beta$ ], proto-oncogenes, and growth factors, contributing to inflammation and tumor development. The GC content in gene regulatory regions positively correlates with gene transcriptional activity<sup>5</sup>. Furthermore, OGG1-BER drives spatial transformation of G4 structures in promoters [vascular endothelial growth factor (VEGF), Kirsten rat sarcoma viral oncogene homolog (KRAS), and NEIL3] enriched with PQS, activating transcription<sup>6,7</sup>. Genome-wide mapping revealed that oxidative base-derived AP site, OGG1, and APE1 binding predominantly occur at G4 sequences<sup>8</sup>. These findings suggest that 8-OxoG regulates gene expression by controlling G4 structural transformation. However, the regulatory role of G4 on gene expression varies depending on PQS location in the coding or template strand, and further experimental support is needed to elucidate G4 structure formation in promoter regions *in vivo* and its stability effects on different gene expression. OGG1 also recruits chromatin modifiers/remodelers to regulate gene expression. For instance, CHD4/NuRD complex recruitment to oxidative DNA damage sites by OGG1 leads to the recruitment of repressive chromatin proteins like DNA methyltransferases (DNMTs) and euchromatic histone lysine methyltransferase 2 (EHMT2) to binding sites, maintaining transcriptional silence of tumor suppressor genes and promoting tumorigenesis<sup>9</sup>. In summary, OGG1 plays a crucial role in regulating

gene transcription through diverse mechanisms and exerts its regulatory function across wide genomic regions, including introns, promoters, exons, intergenic sequences, and untranslated regions of genes<sup>10</sup>. However, the specific mechanisms by which OGG1 regulates different genes remain poorly understood and require further investigation.

The accumulation of 8-OxoG exacerbates oxidative DNA damage and may activate oncogenes, triggering various pathological processes that lead to tumor development and aging. Consequently, timely repair of 8-OxoG is crucial. The BER pathway, initiated by DNA glycosidases, is responsible for cleaving and clearing 8-OxoG. This process involves more than 30 proteins, including APE1, poly-ADP-ribose-polymerase 1 (PARP1), X-ray repair complementing defective repair in Chinese hamster cells 1 (XRCC1), POL $\beta$ , and DNA ligase III (LIG3). Among these, XRCC1 is a key enzyme that interacts with other repair proteins<sup>11</sup>. Three primary repair enzymes—OGG1, MUTYH, and MTH1—are involved in eliminating 8-OxoG or 8-OxoGTP. OGG1 recognizes and cleaves the 8-OxoG in C:8-OxoG pairs. MUTYH specifically recognizes 8-OxoG:A pairs and cleaves the A base, which is incorporated by DNA polymerase before DNA replication. MTH1, the main nucleotide pool cleaning enzyme, hydrolyzes 8-OxoGTP into 8-OxoGMP, reducing 8-OxoGTP accumulation<sup>12</sup>. The recently discovered NEIL1 enzyme functions similarly to OGG1, cleaving 8-OxoG mismatched with G or A bases on DNA<sup>13</sup>. Fig. 1 illustrates the formation, pathogenic mechanism, and repair of 8-OxoG.

### 3. Roles of 8-OxoG in liver diseases

Given the prominent characteristic of liver oxidative damage, 8-OxoG and its repair system may be crucial factors in the pathogenesis of liver diseases. For instance, the accumulation of 8-OxoG in the mitochondrial DNA (mtDNA) isolated from livers of OGG1<sup>-/-</sup> mice is 20-fold higher than that of wild-type mice<sup>14</sup>, which is associated with the occurrence of fatty liver and liver cancer. Consequently, investigating the role of 8-OxoG and its repair enzymes in the pathogenesis of liver diseases is essential for disease prediction and treatment. The development and treatment strategies of liver diseases related to 8-OxoG are illustrated in Fig. 2.

#### 3.1. Roles of 8-OxoG in viral liver disease

Viral hepatitis is an infectious liver disease caused by hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), and other viruses, potentially leading to hepatic failure, liver cirrhosis, and liver cancer. Studies have shown significantly elevated levels of 8-OxoG in HBV-infected cells, mice, and patients. Research indicates that HBx increases 8-OxoG levels *via* inhibition of MTH1 and MTH2 expression in liver cells<sup>15</sup>. The C-terminal domain of HBx has been identified as crucial for ROS production and 8-OxoG formation<sup>16</sup>. Furthermore, polymorphisms in DNA repair genes, including OGG1, have been associated with overall survival in chronic HBV-infected hepatocellular carcinoma (HCC) patients<sup>17</sup>. Elevated 8-OxoG levels have also been observed in the livers, peripheral blood mononuclear cells (PB-MCs), and circulating leukocytes of chronic HCV patients<sup>18-20</sup>. In HCV-infected cells, NEIL1 gene expression and glycosylase (NEIL1-specific) activity were found to be impaired, potentially contributing to the progression of liver diseases<sup>21</sup>. These findings suggest that 8-OxoG accumulation and associated repair enzymes play a significant role in the progression of viral liver diseases.

#### 3.2. Roles of 8-OxoG in fatty liver disease

Fatty liver, characterized by excessive fat accumulation with-

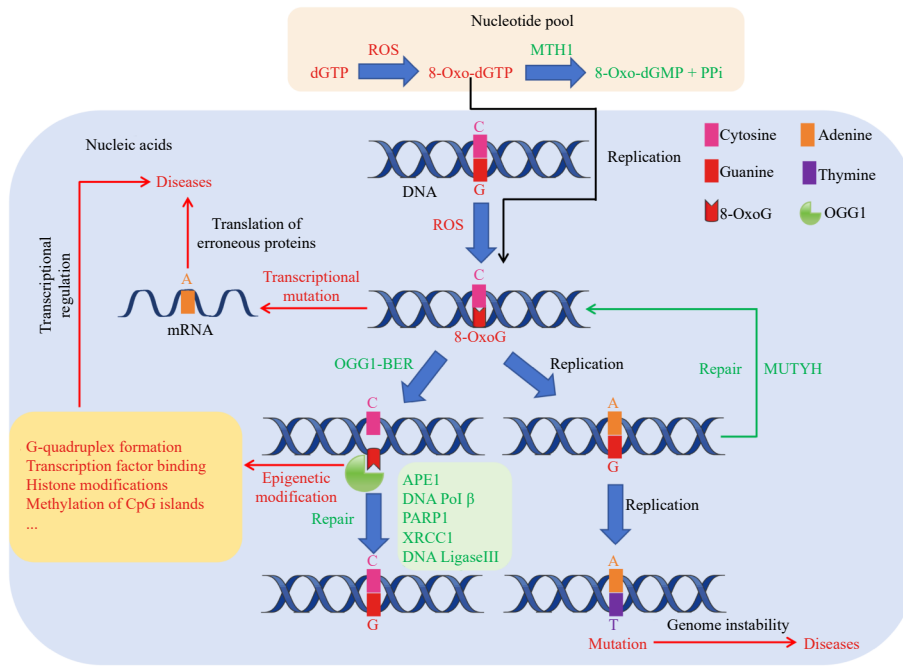


Fig. 1 Formation, pathogenic mechanism, and repair of 8-OxoG.

in hepatocytes, encompasses alcoholic and non-alcoholic fatty liver, as well as specific types induced by certain medications or other diseases. While 8-OxoG expression is absent in healthy livers, nuclear expression of 8-OxoG is observed in hepatocytes and sinusoidal cells of patients with metabolic dysfunction-associated steatohepatitis (MASH). The 8-OxoG index exhibits a significant correlation with the extent of necro-inflammation<sup>22</sup>. As the condition progresses from steatosis to MASH, the proportion of 8-OxoG<sup>+</sup> hepatocytes increases<sup>23</sup>. Impaired DNA repair mechanisms may contribute to the development of MASLD. High-fat diet (HFD) induces oxidative stress, resulting in DNA damage and compensatory upregulation of the BER pathway, which enhances OGG1 expression. This suggests that OGG1-mediated repair of oxidative damage, such as 8-OxoG, is part of the cellular response to oxidative stress, including that induced by HFD. OGG1 deficiency accelerates obesity development, hepatic lipid accumulation, and glucose tolerance impairment in HFD-fed mice. OGG1-mutant

mice demonstrate accumulated 8-OxoG, obesity, insulin resistance, and hyperglycemia. Conversely, OGG1-transgenic animals exhibit improved mitochondrial metabolism, reduced diet-induced obesity, and diminished inflammation<sup>24</sup>.

MUTYH activity functions as a genetic and environmental regulatory factor influencing the progression of fatty liver disease. In fatty livers, decreased MUTYH expression inhibits mtDNA repair, resulting in the accumulation of oxidative DNA damage in the liver<sup>24</sup>. MUTYH<sup>-/-</sup> mice fed a high-fat and high-cholesterol (HFHC) diet supplemented with high iron exhibited the highest incidence of liver tumors<sup>25</sup>. Overexpression of MTH1 demonstrated improved liver metabolism in mice fed an HFD<sup>26</sup>. The knockout of NEIL1 induced MASLD, further indicating that oxidative DNA damage may play an early role in MASLD development<sup>27</sup>.

In conclusion, a correlation exists between 8-OxoG with its repair system and fatty liver disease. Consequently, reducing ROS

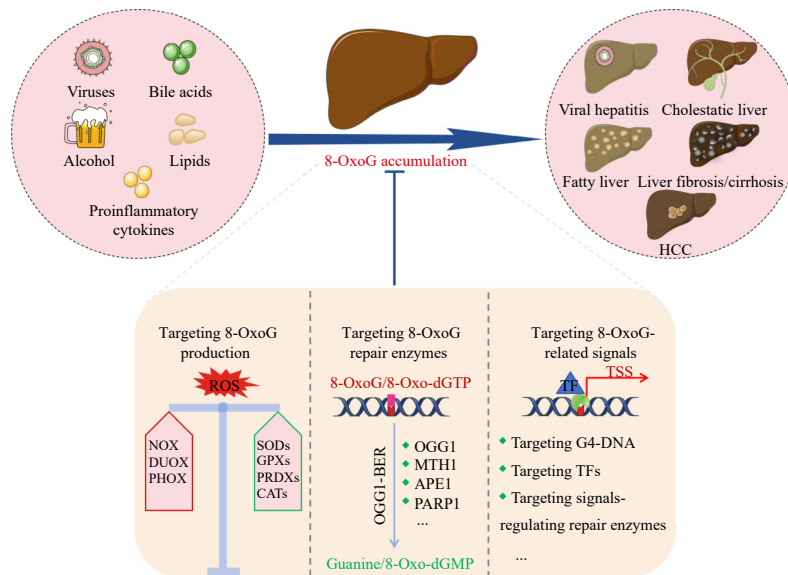


Fig. 2 Development and treatment strategies of liver diseases related to 8-OxoG.

production or activating the repair system of liver cells may offer potential therapeutic approaches for fatty liver diseases.

### 3.3. Roles of 8-OxoG in cholestatic liver disease

Cholestasis is a pathological and physiological process that impairs bile secretion and excretion, leading to liver injury, fibrosis, cirrhosis, and liver cancer. It can be caused by viruses, alcohol, drugs, or immune-related factors. The primary clinical manifestations include primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC). Various bile acids (BAs) can induce oxidative stress in liver cells and bile duct cells. Glycine goose deoxycholic acid (GCDC) stimulates ROS production and GSH depletion in bile duct cells, resulting in oxidative DNA damage and an increased proportion of 8-OxoG<sup>+</sup> cells<sup>28</sup>. In lithocholic acid (LCA) and bile duct ligation (BDL)-induced mouse cholestatic livers, OGG1 expression was upregulated, indicating an enhanced oxidative stress response<sup>29,30</sup>. Targeting cluster of differentiation (CD)103<sup>+</sup>T<sub>RM</sub> cells represents a promising strategy for PBC treatment, while MTH1 gene deletion reduced the accumulation and lifespan of CD103<sup>+</sup>T<sub>RM</sub> cells in the liver through the PARP1-TGFβ-Smad signaling pathway<sup>31</sup>. In patients with PSC and CCA, MUTYH and NEIL1-mutant proteins with impaired catalytic function were identified<sup>32</sup>.

The aforementioned results indicate the potential role of 8-OxoG and its repair system as novel regulators in CLD. Further investigation into the relationship between 8-OxoG and CLD may elucidate the therapeutic potential of targeting 8-OxoG to mitigate oxidative damage in hepatocytes and cholangiocytes.

### 3.4. Roles of 8-OxoG in liver fibrosis and cirrhosis

Liver fibrosis represents a wound healing response to chronic liver injury, characterized by the activation of hepatic stellate cells (HSCs), which play a critical role in its development. Studies have shown that 8-OxoG accumulates in α-SMA-positive stromal cells in patients with advanced liver fibrosis. Specifically, the downregulation of cytoglobin (CYGB), an antioxidant enzyme, in pSMAD2<sup>+</sup>8-OHdG<sup>+</sup> HSCs leads to increased oxidative DNA damage and elevated levels of ROS in activated HSCs<sup>33</sup>. Research has demonstrated that OGG1 expression is downregulated while the percentage of 8-OHdG<sup>+</sup> cells is upregulated in carbon tetrachloride (CCl<sub>4</sub>)-induced rat livers<sup>34</sup>. Additionally, MTH1 expression is downregulated in the fibrotic liver of mice induced by concanavalin A<sup>35</sup>. Notably, 8-OxoG also accumulates in the livers of patients with liver cirrhosis<sup>36</sup>.

These investigations indicate a strong correlation between 8-OxoG, its repair mechanism, and the activation of HSCs in liver fibrosis progression. Examining the function of 8-OxoG and its associated repair enzymes in liver fibrosis and cirrhosis may reveal novel therapeutic targets from an oxidative stress perspective.

### 3.5. Roles of 8-OxoG in liver cancer

A common characteristic of risk factors for liver cancer development is inflammation, which leads to oxidative DNA damage and 8-OxoG accumulation. The expression of 8-OxoG in HCC tissues is significantly elevated compared to normal liver tissues and is associated with poor survival rates in HCC patients<sup>37</sup>. 8-OxoG is also considered a risk factor for HCC in patients with chronic HCV infection<sup>38</sup>. Increased levels of 8-OxoG have been observed in DNA extracted from liver tissues (including liver cells, Kupffer cells, and infiltrating lymphocytes) and white blood cells of patients with chronic HCV-related liver disease<sup>39</sup>.

OGG1<sup>-/-</sup> mice demonstrate elevated 8-OxoG accumulation and liver tumor incidence<sup>40</sup>. OGG1 expression correlates positively with liver cancer occurrence and progression, potentially

serving as a novel target for HCC treatment<sup>41</sup>. MTH1-deficient mice exhibit a higher liver tumor incidence rate 18 months post-birth<sup>42</sup>. Suppressing MTH1 and MTH2 expression may enhance 8-OxoG-mediated liver cancer incidence and progression in HBV infections<sup>38</sup>. HCV-infected liver cancer cells display increased 8-OxoG levels and decreased NEIL1 activity<sup>21</sup>. MTH1 downregulation inhibits HepG2 cell growth and proliferation, as well as HepG2-derived xenografts in nude mice<sup>43</sup>. MUTYH expression is also elevated in HCC patient tumor tissues and positively correlates with poor outcomes<sup>44</sup>.

This evidence suggests that mutations or deficiencies in 8-OxoG repair enzymes contribute to tumorigenesis, including liver cancer. Following tumor initiation, 8-OxoG repair enzymes sustain cancer cell proliferation, metastasis, and other activities, thereby promoting liver cancer progression. Targeting this enzyme system or increasing ROS production in liver cancer cells may offer potential strategies for tumor prevention.

### 3.6. Evidence and perspectives of 8-OxoG-BER agonists or inhibitors in liver diseases

Given the significant role of BER enzymes in liver disease progression, this section summarizes the reported 8-OxoG-BER agonists and inhibitors, as well as their potential therapeutic applications in liver diseases.

OGG1 inhibitors, including O8, SU0268, and TH5487 (also known as OXC-201), have been extensively investigated. While the efficacy of OGG1 inhibitors in liver disease treatment remains unclear, their potential as anti-cancer or anti-inflammatory agents has been documented. OGG1 agonists, such as TH12117, TH1078, and TH12161, have also demonstrated therapeutic potential in human diseases like Alzheimer's disease and obesity *via* enhancing catalytic efficiency<sup>45</sup>. Given OGG1's role in regulating inflammation and metabolic function, we hypothesized that targeting OGG1 could be a promising approach for treating liver diseases.

Several MTH1 inhibitors have been developed that specifically target the active site, including TH1579 (known as Karonudib in clinical form), TH588, TH287, (S)-crizotinib, IACS-4619, and IACS-4759. Research has demonstrated the anti-tumor effects of these MTH1 inhibitors in various cancers, including B-cell lymphoma, gastric cancer, osteosarcoma, and HCC<sup>12</sup>. While these findings suggest the potential efficacy of MTH1 inhibitors in treating liver cancer, further preclinical studies and clinical trials are necessary to substantiate this hypothesis.

APE1, a crucial BER enzyme, is responsible for cleaving AP sites. Several APE1 inhibitors, including methoxyamine (MX, clinically known as TRC102), CRT0044876, AR03, and gossypol, have been developed for cancer therapy<sup>46</sup>. AR03 has been shown to inhibit oxidative phosphorylation and induce mitochondrial dysfunction in HepG2 cells<sup>47</sup>, suggesting the potential of APE1 inhibitors in treating HCC. Additionally, the natural product gossypol demonstrates anti-HCC activity *via* apoptosis activation<sup>48,49</sup>. Furthermore, gossypol has been found to ameliorate liver fibrosis in diabetic rats induced by HFD and streptozocin<sup>50</sup>. These findings indicate that APE1/AP site inhibitors may represent a promising new approach for improving therapeutic outcomes in liver diseases.

PARP1 plays a crucial role in the BER pathway, and various PARP inhibitors, including niraparib, olaparib, talazoparib, rucaparib, and veliparib, have demonstrated significant anti-tumor therapeutic effects in clinical trials, including those for HCC<sup>12</sup>. Furthermore, PARP1 inhibitors (olaparib, AIQ, and PJ34) have shown promise in mitigating high-fat or alcohol-induced liver injury, suggesting potential applications in treating ALD and MASLD<sup>51</sup>. Consequently, PARP1 inhibitors may offer therapeutic benefits for liver diseases.

While current 8-OxoG-BER agonists or inhibitors are not extensively utilized in liver disease treatment, they have established a proof-of-principle for clinical value and provided guidance for further research.

#### 4. Potential natural constituents for liver disease therapy targeting 8-OxoG

Natural products play crucial roles in treating various human diseases and serve as a rich source of novel chemical scaffolds for drug design, contributing to the discovery of effective and safe new medications<sup>52</sup>. Drawing from the pathological mechanism of 8-OxoG in liver diseases, we have summarized the natural constituents that exhibit anti-liver disease activities by targeting 8-OxoG. Further exploration of natural compounds directly targeting 8-OxoG and its repair system may represent a promising direction for developing liver disease treatments. In this review, we have categorized these compounds into three subsets based on their potential for drug development from the perspective of 8-OxoG.

##### 4.1. Targeting 8-OxoG production

ROS are a significant source of 8-OxoG, and regulating ROS production could be a potential avenue for treating liver diseases. Numerous natural products have been reported to control ROS production in liver diseases *via* modulation of antioxidant systems, including superoxide dismutases (SODs), glutathione peroxidases (GPXs), peroxiredoxins (PRDXs), and catalase (CAT). Curcumin (**1**) attenuated liver injury induced by aflatoxin B1 *via* increasing the levels of SOD, CAT, and GPX<sup>53</sup>. Phyllanthin (**2**) enhanced SOD activities to exert hepatoprotective effects against DEN-induced injury<sup>54</sup>. Geniposide (**3**) demonstrated protection against CCl<sub>4</sub>-induced liver fibrosis *via* upregulation of hepatic GPX and SOD levels<sup>55</sup>. Gastrodin (**4**) increased hepatic SOD, GPX, and CAT levels in alcohol-induced mice<sup>56</sup>. Juglone (**5**) inhibited dimethylnitrosamine (DMN)-induced liver fibrosis in rats *via* elevation of SOD activity<sup>57</sup>. Additionally, carnosol (**6**) exhibited hepatoprotective effects against MASLD through upregulation of PRDX3<sup>58</sup>. 18β-Glycyrrhetic acid (18β-GA) (**7**) and celastrol (**8**) ameliorated hepatic fibrosis *via* targeting PRDXs in activated HSCs<sup>59,60</sup>. The potential natural compounds against liver diseases through targeting 8-OxoG production are presented in Table S1.

##### 4.2. Targeting 8-OxoG repair enzymes

The repair of 8-OxoG plays a critical role in preventing liver diseases, suggesting that targeting 8-OxoG repair enzymes may offer potential therapeutic strategies. Research has demonstrated that OGG1 is essential for fibrogenic gene activation in lung fibrosis, and inhibiting OGG1 *via* small-molecule inhibitors could mitigate pulmonary inflammation and lung fibrosis<sup>61,62</sup>. Qiu et al. identified 6 natural compounds from *Panax japonicus* as 8-OxoG DNA glycosylase (Fpg) inhibitors<sup>63</sup>, among which chikusetsusaponin V (**9**) induced apoptosis in HepG2 cells<sup>64</sup>. Furthermore, ginsenoside Re (**10**) has shown promise in ameliorating HFD-induced insulin resistance, inhibiting lipid accumulation<sup>65</sup>, and improving hepatic inflammation and fibrosis in *db/db* mice<sup>66</sup>.

Targeting APE1 presents a promising therapeutic approach for HCC treatment *via* promoting lipid peroxidation accumulation and ferroptosis<sup>67</sup>. APE1 inhibitors derived from *Panax japonicus* have demonstrated efficacy in killing tumor cells by inhibiting APE1's enzymatic activity without altering its protein expression<sup>68</sup>. For instance, β-sitosterol (**11**) has shown protective effects against liver injury induced by alcohol<sup>69</sup>, CCl<sub>4</sub><sup>70</sup>, and HFD<sup>71</sup>. Oleanolic acid (**12**) has exhibited multiple beneficial ef-

fects, including inhibition of ethanol-induced liver injury, prevention of MASLD progression, alleviation of liver fibrosis, and mitigation of LCA or ANIT-induced cholestatic liver injury<sup>72</sup>. Ginsenoside Rg1 (**13**) has demonstrated the ability to ameliorate alcoholic liver injury<sup>73</sup>, regulate liver lipid metabolism in MASLD rats<sup>74</sup>, and inhibit liver fibrosis<sup>75</sup>. Chikusetsusaponin IV (**14**) has shown anti-HCC activity<sup>64</sup>. Ginsenoside Rg3 (**15**) has been found to inhibit thioacetamide (TAA)-induced liver fibrosis<sup>76</sup>, liver cancer<sup>77</sup>, and HFD-induced hepatic steatosis<sup>78</sup>.

Several MTH1 inhibitors derived from natural compounds have been developed using high-throughput *in vitro* assays based on MTH1-catalyzed enzymatic reactions, including echinacoside, α-mangostin, thymoquinone (TQ), and baicalin. Echinacoside (**16**), isolated from *Cistanche salsa*, demonstrates anti-HCC effects<sup>79</sup>. Research indicates that echinacoside (**16**) also prevents liver injury induced by alcohol<sup>80</sup>, CCl<sub>4</sub><sup>81</sup>, acetaminophen<sup>82</sup>. α-Mangostin (**17**), a natural xanthone from *Mangosteen pericarp*, is another potential MTH1 inhibitor that binds to the active site of MTH1<sup>83</sup>. It exhibits hepatoprotective effects in various liver conditions, including acetaminophen or LPS/D-galactosamine-induced acute liver injury<sup>84,85</sup>, HFD-induced fatty liver<sup>86</sup>, TAA-induced liver cirrhosis<sup>87</sup>, and HCC<sup>88</sup>. TQ (**18**) and baicalin (**19**) are potential MTH1 inhibitors showing anti-tumor activity against breast cancer cells<sup>89</sup>. TQ (**18**) also alleviates MASLD in mice<sup>90</sup>, lipopolysaccharide-induced liver fibrosis in rats<sup>91</sup>, and BDL-induced cholestatic liver injury<sup>92</sup> while exhibiting anti-HCC effects<sup>93</sup>. Similarly, baicalin (**19**) ameliorates BDL-induced cholestasis, improves HFD-induced obesity, inhibits CCl<sub>4</sub>-induced liver fibrosis, and attenuates alcohol-induced liver injury<sup>94</sup>.

PARP1 plays a crucial role in BER by recruiting repair factors including XRCC1 and Pol β<sup>95</sup>. Natural compounds also serve as significant sources of PARP1 inhibitors. Song et al. identified 8 potent PARP1 inhibitors from natural products *via* virtual computer screening combined with an experimental enzyme assay<sup>96</sup>. Phloretin (**20**) has been shown to ameliorate hepatic steatosis in HFD-induced obese mice<sup>97</sup>, attenuate succinate-induced liver fibrosis<sup>98</sup>, and inhibit HCC<sup>99</sup>. Indirubin (**21**), a bis-indole alkaloid derived from *Muricidae*, demonstrated the ability to alleviate CCl<sub>4</sub>-induced liver fibrosis<sup>100</sup>. Previous research has established the protective effects of chlorogenic acid (**22**) against CCl<sub>4</sub>-induced liver inflammation and fibrosis, HFD-induced liver fat deposition, BDL-induced cholestatic liver injury, and alcohol-induced liver injuries<sup>101</sup>. Puerarin (**23**) has been found to ameliorate liver lipid accumulation in MASLD rats<sup>102</sup>, alleviate TAA or CCl<sub>4</sub>-induced hepatic fibrosis<sup>103,104</sup>, and inhibit alcoholic liver injury<sup>105</sup>. Biochanin A (**24**) has been shown to delay the progression of MASLD<sup>106</sup> and exert hepatoprotective effects on TAA-induced liver cirrhosis rats<sup>107</sup>.

The pharmacological activity and mechanisms of these natural compounds in liver diseases require further investigation both *in vitro* and *in vivo*. A deeper understanding of repair enzyme inhibitors' response is crucial for the translational and clinical development of these agents, as well as for identifying patients who would derive the most therapeutic benefit from these inhibitors. Table S2 presents potential natural compounds that target 8-OxoG repair enzymes in the treatment of liver diseases.

##### 4.3. Targeting 8-OxoG-related signals

Beyond targeting 8-OxoG or its repair system, regulating 8-OxoG-mediated signals remains a promising approach. The presence of 8-OxoG in promoter G4 sequences may influence the formation and structural transformation of G4, functioning as a transcriptional switch to regulate gene expression and control disease progression. Thus, exploring novel G4-targeting compounds may present an attractive strategy for disease treatment based on 8-OxoG-mediated mechanisms. Research has demon-

strated that 8-OxoG modulates the binding of TFs to the regulatory G4 motif of KRAS, enhancing the transcription of oncogenic KRAS<sup>108</sup>. Several natural products have been identified as KRAS promoter G4 binders, including berberine (25), coptisine (26), and sanguinarine (27)<sup>109</sup>, exerting significant anti-HCC effects<sup>110-112</sup>. The generation of 8-OxoG within a G4 structure in the VEGF gene promoter region induces G4 formation with the fifth guanine tract, increasing VEGF transcription<sup>113</sup>. Chelerythrine (28)<sup>114</sup>, quercetin (29)<sup>115</sup>, kaempferol (30)<sup>116</sup>, and gallic acid (31)<sup>117</sup> have been shown to interact with the G4 structure in the VEGF promoter region. These natural products also demonstrate inhibitory effects on HCC<sup>118-121</sup>. Additionally, 8-OxoG functions as an epigenetic regulator in the transcription of oncogenic MYC *via* promoting G4 structure formation and facilitating TF binding<sup>8</sup>. Berberine (25) and coptisine (26) have also been identified as stabilizers of the MYC-G4<sup>109</sup>.

8-OxoG also facilitated the binding of TFs such as NF- $\kappa$ B, AP-1, and CREB1 to their DNA sequences, thereby promoting downstream gene expression. Consequently, targeting these recruited TFs could prove beneficial for liver disease treatment. Studies have demonstrated that asiatic acid (32)<sup>122</sup>, nobiletin (33)<sup>123</sup>, rutin (34)<sup>124</sup> and isobavachalcone (35)<sup>125</sup> could ameliorate liver injury *via* inhibition of NF- $\kappa$ B. Ovatiolide (36) inhibited HCC by reducing the expression of SP1<sup>126</sup>. Kolaviron (37) was found to inhibit *N*-dimethylnitrosamine (NDMA)-induced liver injury through downregulation of AP-1 DNA binding activity<sup>127</sup>. Berbamine (38) sensitized HCC to aspirin *via* blockade of CREB/ATF1 signaling<sup>128</sup>.

The efficiency of 8-OxoG repair is influenced by various signals. Notably, the peroxisome proliferator-activated receptor (PPAR) signal is involved in DNA damage repair associated with the BER pathway<sup>129, 130</sup>. While PPAR $\alpha$  activation promotes fatty acid oxidation in MASLD, potentially causing some oxidative stress, it also enhances antioxidant enzyme levels and inhibits the NF- $\kappa$ B signaling pathway and inflammatory response, ultimately reducing oxidative stress<sup>131</sup>. Consequently, PPAR $\alpha$ , acting as a redox signal regulator, can exert an anti-oxidative stress effect by suppressing inflammatory responses and enhancing the body's antioxidant defense system. Activating PPAR signaling may thus represent a promising treatment strategy for fatty livers with elevated 8-OxoG levels. Studies have shown that emodin (39) and umbelliferone (40) reduced hepatic lipid content by upregulating PPAR signaling in alcohol-induced mouse livers<sup>132, 133</sup>. Similarly, myricetin (41) and plumbagin (42) inhibited HFD-induced steatosis through PPAR signal activation<sup>134, 135</sup>.

## 5. Discussion

The disruption of redox homeostasis leads to various organ diseases, with liver diseases being closely associated with DNA oxidative damage. 8-OxoG represents the most prevalent product of oxidative attack, and the BER pathway, mediated by OGG1, MUTYH, MTH1, and other proteins, plays a crucial role in the clearance and mismatch repair of 8-OxoG. These have emerged as significant targets for numerous diseases, including inflammation and cancer<sup>19</sup>. The coordinated changes between initiated repair and transcription elucidate the etiological association between 8-OxoG and pathological processes. Investigating the role of 8-OxoG and its repair enzyme system in liver diseases is of considerable importance for understanding the pathogenesis of liver diseases from an oxidative stress perspective and developing novel therapeutic targets for hepatic disorders.

Extensive research has provided substantial evidence that 8-OxoG and its associated repair enzymes play crucial roles in the etiology and progression of various liver diseases, including viral hepatitis, steatosis, cholestatic injury, fibrosis, cirrhosis, and hepatocellular carcinoma. These findings underscore the necessity

for further investigation into the underlying mechanisms. Therapeutic approaches targeting any stage of 8-OxoG formation or repair processes may hold potential for treating liver diseases. A novel strategy combining 8-OxoG repair enzyme inhibitors with ROS-inducing therapies, such as chemotherapy, radiotherapy, and immunotherapy, could potentially enhance cell death signaling and improve treatment outcomes for hepatocellular carcinoma. However, it is important to note that BER systems are essential for healthy tissues as well. Consequently, treatment plans must be carefully designed to mitigate the potential toxic side effects associated with BER inhibitors.

A growing body of research indicates that numerous natural products demonstrate potential as repair enzyme inhibitors and hepatoprotective agents<sup>63</sup>. Given the significant role of 8-OxoG in liver disease progression and the abundance of natural products, the utilization of natural compounds presents a promising therapeutic approach for liver diseases targeting 8-OxoG. Future development of anti-liver disease drugs may focus on several aspects: targeting 8-OxoG production, modulating activities of 8-OxoG repair enzymes, and regulating 8-OxoG-related signaling pathways. These pathways include targeting G4-DNA, TFs recruited by 8-OxoG, and signals regulating 8-OxoG repair, such as PPAR. Additionally, binding with DNA, particularly promoters and GG-repeats, offers another avenue for intervention. Furthermore, rational structural modification of these natural products may guide the design of specific 8-OxoG agonists or inhibitors, potentially opening new avenues for the development of novel liver disease therapeutics.

In conclusion, this review elucidates the formation and pathogenic mechanisms of 8-OxoG, as well as its repair system in liver diseases. The paper also provides an overview of natural constituents that exhibit both anti-liver disease effects and 8-OxoG regulation activities. These findings suggest the significant potential of natural products in the treatment of liver diseases. However, their suitability for clinical application necessitates further rigorous investigation.

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## Supporting information

Supporting information for this work can be obtained by contacting the corresponding authors *via* E-mail.

## Declaration of competing interest

These authors have no conflict of interest to declare.

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