

Role of Nrf2 in chronic liver disease

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Author contributions: Tang W, Diallo M and Ponnusamy M drafted the manuscript; Jiang YF designed and revised the article. Supported by The Scientific Research Projects from the Development and Reform Commission of Hunan Province, China, No. 2011 (1318), No. 2012 (1493) and No. 2013 (1132)

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Received: March 11, 2014 Revised: May 8, 2014

Accepted: May 25, 2014

Published online: September 28, 2014

Abstract

Nuclear erythroid 2-related factor 2 (Nrf2) is a central regulator of antioxidative response elements-mediated gene expression. It has a significant role in adaptive responses to oxidative stress by interacting with the antioxidant response element, which induces the expression of a variety of downstream targets aimed at cytoprotection. Previous studies suggested oxidative stress and associated damage could represent a common link between different forms of diseases. Oxidative stress has been implicated in various liver diseases, including viral hepatitis, nonalcoholic fatty liver disease/steatohepatitis, alcoholic liver disease and drug-induced liver injury. Nrf2 activation is initiated by oxidative or electrophilic stress, and aids in the detoxification and elimination of potentially harmful exogenous chemicals and their metabolites. The expression of Nrf2 has been observed throughout human tissue, with high expression in detoxification organs, especially the liver. Thus, Nrf2 may serve as a major regulator of several cellular

defense associated pathways by which hepatic cells combat oxidative stress. We review the relevant literature concerning the crucial role of Nrf2 and its signaling pathways against oxidative stress to protect hepatic cell from oxidative damage during development of common chronic liver diseases. We also review the use of Nrf2 as a therapeutic target to prevent and treat liver diseases.

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Key words: Nuclear erythroid 2-related factor 2; Chronic liver disease; Oxidative stress; Reactive oxygen species; Hepatic injury; Hepatic protection

Core tip: Chronic liver disease is associated with an imbalance, comprising increased reactive oxygen species and decreased net antioxidant activity. Oxidative stress plays an important role in the pathophysiological changes of liver diseases. Nuclear erythroid 2-related factor 2 (Nrf2) can activate cytoprotective genes and has a crucial role against oxidative stress to protect hepatic cells from oxidative damage. This article focuses on the activation the Nrf2-mediated antioxidant response, which prevents the progression of chronic liver disease and presents new treatment opportunities. Accordingly, integrative therapeutic strategies including Nrf2 activators have great potential as therapeutic agents against oxidative stress during chronic liver injuries.

Tang W, Jiang YF, Ponnusamy M, Diallo M. Role of Nrf2 in chronic liver disease. *World J Gastroenterol* 2014; 20(36): 13079-13087 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v20/i36/13079.htm> DOI: <http://dx.doi.org/10.3748/wjg.v20.i36.13079>

INTRODUCTION

Nuclear erythroid 2-related factor 2 (Nrf2) is a transcription factor, first identified in 1994, that belongs to the Cap-n-collar basic leucine zipper family^[1]. It has a sig-

nificant role in adaptive responses to oxidative stress by interacting with antioxidant response element (ARE) sequences of antioxidant and cytoprotective genes^[2]. Nrf2 is considered the main mediator of cellular adaptation to redox stress. In its inactive state, Nrf2 is located in the cytoplasm where it interacts with the actin binding protein, Kelch-like ECH associating protein 1, and is rapidly degraded by the ubiquitin-proteasome pathway. However, upon exposure to oxidative or electrophilic stress, phosphorylation of Nrf2 leads to their dissociation and subsequent translocation of Nrf2 to the nucleus^[3,4]. In the nucleus, Nrf2 binds to ARE sequences and functions in partnership with other nuclear proteins as a strong transcriptional activator of ARE-responsive genes. ARE-mediated antioxidant proteins and enzymes^[5], such as heme oxygenase-1 (HO-1), NAD(P)H: quinone oxidoreductase 1 (NQO1), glutathione-S-transferases (GST), group C streptococcus (GCS) are involved in the detoxification of increased electrophiles and radicals^[6,7]. Therefore, the roles of the Nrf2/ARE pathway in liver diseases have been extensively investigated.

REACTIVE OXYGEN SPECIES AND THE ROLE OF Nrf2 IN CHRONIC LIVER DISEASES

Previous studies suggested that oxidative stress and associated damage could represent a common link between different forms of chronic liver injury^[8-10]. The contribution of oxidative stress to lipid peroxidation is one of the critical factors involved in the genesis and the progression of nonalcoholic steatohepatitis (NASH)^[11]. Viral infection or alcohol abuse greatly increases the highly variable miscoding etheno-modified DNA like epsilon A levels by triggering lipid peroxidation^[12]. Oxidative stress plays an important role in the pathophysiological changes that progress to liver cirrhosis and finally to hepatocellular carcinoma. As a site of first-pass metabolism, the liver is highly susceptible to oxidative damage by reactive intermediates when it is exposed to high concentrations of xenobiotics and other chemicals. Therefore, there are several defense mechanisms to protect the liver against harmful chemicals and their potentially damaging metabolites. One of the most important protective mechanisms is the Nrf2/ARE pathway, which regulate phase II detoxifying enzyme genes and antioxidant-responsive genes, including HO-1, NQO1, GST, and GCS (Figure 1). The expression of phase II detoxifying enzyme genes in the wild-type and heterozygous Nrf2-knockout mice is clearly induced as compared to homozygous Nrf2-knockout mice in which the inducible expression of these genes is dramatically reduced^[13]. NQO1 is cytoprotective against oxidative stress by scavenging superoxides, preserving various endogenous antioxidants, and catalyzing reductive metabolism of chemicals^[7,14,15]. Therefore, NQO1 plays an essential role in protecting the cell against reactive oxygen species (ROS) and electrophiles. The role of

Nrf2 in transcriptional activation of NQO1 was further confirmed by results from studies on Nrf2^{-/-} mice. Mice lacking the Nrf2 gene exhibited a marked decrease in the expression and induction of NQO1^[16]. In addition, the Nrf2/ARE pathway induces the expression of antioxidant and cytoprotective genes, including antioxidant proteins and enzymes^[17,18]. The antioxidant proteins provide the necessary protection against oxidative and electrophilic stress^[19]. Several studies have shown that Nrf2 is also a prevailing factor in the regulation of ARE-mediated activation of other defensive genes, including GST, GCS, and HO-1^[20,21]. Therefore, activation of Nrf2 by glycyrrhetic acid^[22], sulforaphane^[23], or caffeine^[24] can induce the antioxidant enzymes system, protect the liver from oxidative stress, prevent inflammation and fibrosis, and attenuate liver injury. This indicates that Nrf2 has a crucial role against oxidative stress to protect hepatic cells from oxidative damage.

Nrf2 IN VIRAL HEPATITIS

Hepatitis B virus (HBV) and hepatitis C virus (HCV) infections are major risk factors in the pathogenesis of chronic liver diseases. Permanent overproduction of viral proteins can result in increased level of radicals and other ROS^[25,26]. Firstly, oxidative stress is common among HBV infected patients with chronic liver disease, and several studies have used HBV transgenic mice or HBV DNA transfection of cells *in vitro* to show that HBV can induce oxidative stress^[27-29]. A series of studies demonstrated that HBV, *via* its association with mitochondria, induces oxidative stress, which in turn leads to activation of a series of transcription factors, including nuclear factor-kappaB (NF-κB), signal transducer and activator of transcription-3 and rapidly accelerated fibrosarcoma-1 (Raf-1)^[30,31]. Recent research reported the capacity of HBV to stimulate the expression of a variety of cytoprotective genes that are regulated by Nrf2/ARE^[32-34]. The HBV-dependent induction of these genes is primarily initiated by HBV regulatory proteins, and is mediated by methyl ethyl ketone (MEK) and c-Raf^[35]. It was also demonstrated that increased augmentation of liver regeneration is regulated by Nrf2 during HBV infection, which acts as a liver regeneration and antioxidant protein and, therefore, links oxidative stress to hepatic regeneration to ensure survival of damaged cells^[36,37]. Secondly, oxidative stress has been recognized as a fundamental factor in the pathological changes observed during HCV infection. Oxidative injury occurs as a direct result of HCV core protein expression both *in vitro* and *in vivo*^[12]. One study demonstrated that HCV-mediated phosphorylation/activation of Nrf2 is mediated by the mitogen-activated protein (MAP) kinases (p38 MAPK) and janus kinase, and both ROS and Ca²⁺ signaling are necessary in the Nrf2-activation process^[38,39]. Another study investigated the molecular mechanisms underlying oxidative stress and stress response induced by the individual HCV proteins and indicated that all five proteins [core, E1, E2, non-

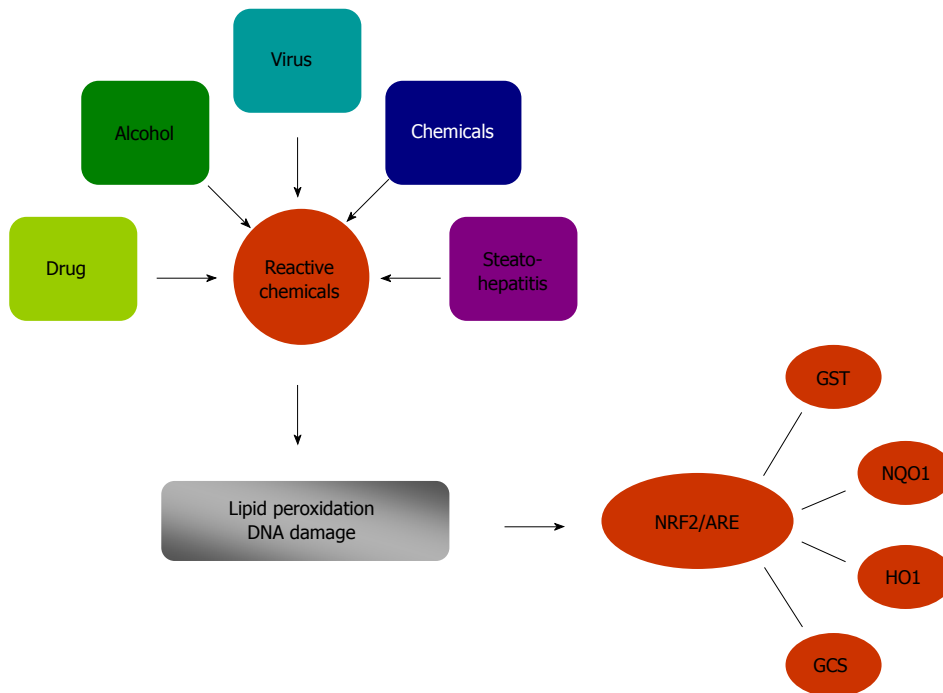


Figure 1 Nrf2 in chronic liver diseases. NRF2: Nuclear erythroid 2-related factor 2; ARE: Antioxidant response element; GST: Glutathione-S-transferases; NQO1: NAD(P)H: quinone oxidoreductase 1; HO1: Heme oxygenase-1; GCS: Group C streptococcus.

structural protein 4B (NS4B), and nonstructural protein 5A (NS5A)] of HCV stimulated generation of ROS and Nrf2 activation by protein kinase C in response to ROS. Especially in the early stage of expression, HCV proteins induced a strong upregulation of the antioxidant defense system *via* Nrf2 to protect HCV infected hepatic cells from oxidative damage⁴⁰. In addition, expression of core, E1, E2, NS4B, and NS5A proteins resulted in the activation of Nrf2 in a ROS-independent manner. The effect of core and NS5A was mediated through casein kinase 2 (CK2) and phosphoinositide-3 kinase (PI3K), whereas those of NS4B, E1, and E2, were not mediated by either protein kinase C, CK2, PI3K, p38 MAPK, or extracellular signal-regulated kinase^{41,42} (Figure 2). Increasing levels of HO-1, a key cytoprotective gene, help to protect liver cells from the damaging effects of the HCV. A mechanism for this action was to increase expression of the positive transcription factor Nrf2⁴³. Some studies have demonstrated that Nrf2 activation could also prevent and potentially alleviate liver diseases. These findings indicated that the anti-HCV action of drugs^{44,45} was reflected the stimulation of Nrf2-mediated HO-1 expression. These results suggested that targeting the Nrf2/HO-1 signaling pathway might be a promising strategy for drug development. In conclusion, Nrf2 activation appears to be a common mechanism for potential protective effects against oxidative stress due to viral hepatitis

Nrf2 IN NAFLD/NASH

Nonalcoholic fatty liver disease (NAFLD) is a common cause of chronic liver disease worldwide, especially in developed countries⁴⁶. The progression of NAFLD de-

pends on multiple mechanisms operating simultaneously to produce cell injury, apoptosis, inflammation, fibrosis, and, ultimately, NASH^{47,48}. Following the accumulation of triglycerides in the liver, impairment of mitochondrial respiratory chain activity results in the overproduction of ROS and the depletion of mitochondrial glutathione⁴⁹⁻⁵¹. Other characteristics of NASH include reduced superoxide dismutase⁵², catalase activity⁵³ and upregulated cytochrome P450 2A5 (CYP2A5), which is modulated through Nrf2⁵⁴ and increased lipid peroxidation within hepatocytes^{55,56}. Nrf2 also modulates genes involved in metabolic homeostasis⁵⁷. Nrf2 activation with 1-[2-cyano-3,12-dioxooleana-1,9(11)-dien-28-oyl] imidazole (CD-DO-Im) has been shown to effectively prevent hepatic lipid accumulation in wild-type mice, but not in Nrf2-disrupted mice⁵⁸⁻⁶⁰. When feeding the high-fat diet to the wild-type and the Nrf2-null mice, the wild-type mice increased hepatic fat deposition without inflammation or fibrosis (*i.e.*, simple steatosis), while the Nrf2-null mice had significantly more hepatic steatosis and substantial inflammation^{61,62}. Nrf2 expression and activation is reduced in the liver, with histological criteria of NASH⁶³. Another way in which Nrf2 activation might be protective against NAFLD and NASH is through several preventive effects on inflammation⁶⁴. Several chemotherapeutic agents have been shown in a variety of cell culture and rodent systems to induce Nrf2 and cause simultaneous repression of NF- κ B⁶⁵. Evidence shows that Punicalagin may be a useful nutrient for the treatment of NAFLD by activating Nrf2, resulting in improved mitochondrial function, elimination of oxidative stress and inflammation. Probiotics also showed remarkable induction of Nrf2

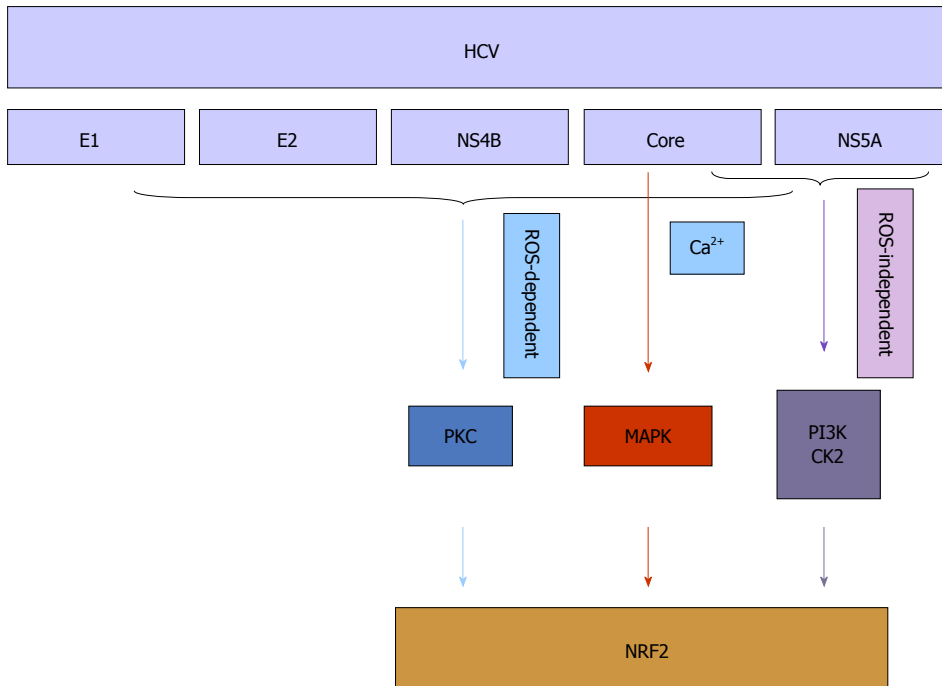


Figure 2 Nrf2 in chronic hepatitis C virus infection. HCV: Hepatitis C virus; NS4B: Nonstructural protein 4B; NS5A: Nonstructural protein 5A; ROS: Reactive oxygen species; PKC: Protein kinase C; MAPK: Mitogen activated protein kinase; PI3K: Phosphoinositide 3-kinase; CK2: Casein kinase 2; NRF2: Nuclear erythroid 2-related factor 2.

and its targeted antioxidative enzymes; they enhanced Nrf2 expression by precluding ubiquitination, which suppressed hepatic oxidative stress and prevented the progression of NAFLD^[66]. Another mechanism for potential treatment of NAFLD and NASH is through activation of superoxide dismutase and catalase, which are antioxidant enzymes with decreased activity in this disease state. Finally, it is possible that activation of Nrf2 could play a role in regulating transforming growth factor- β (TGF- β). A recent study demonstrated that sulforaphane attenuates hepatic fibrosis through Nrf2-mediated inhibition of TGF- β signaling in a human hepatic stellate cell line^[67]. In addition, activators of Nrf2 could abolish fibrosis in a rat model of NASH^[68]. Altogether, activation of the Nrf2-mediated antioxidant response, which protects hepatic cells from oxidative damage, prevents the progression of NAFLD and presents new opportunities for treatment of NASH patients^[69].

Nrf2 IN ALCOHOLIC LIVER DISEASE

Chronic alcohol consumption has long been associated with progressive liver disease^[70,71]. The liver is the major site of ethanol metabolism and thus sustains the most injury from chronic alcohol consumption^[72,73]. The metabolism of alcohol takes place *via* three main enzymatic pathways: oxidation of ethanol by alcohol dehydrogenase in hepatocytes, microsomal oxidation catalyzed by cytochrome P450 2E1 (CYP2E1), and nonoxidative metabolism catalyzed by fatty acid ethylester synthase^[74-77]. First, ethanol metabolism by alcohol dehydrogenase results in acetaldehyde, which is a weak profibrogenic factor. Some

important downstream effects of increased acetaldehyde production include GSH depletion, lipid peroxidation, and the generation of ROS and acetaldehyde adducts^[78]. There is increasing evidence that homocysteine activates the Nrf2-mediated antioxidant response, which protects cells from oxidative damage^[79], whereas Nrf2 dysregulation of GSH synthesis contributes to the pathogenesis of alcoholic liver disease (ALD)'s pathological conditions^[80,81]. In alcohol-related liver disease, free radicals play a part in the pathogenesis of liver damage. Chronic ethanol treatment increases the production of ROS, lowers cellular antioxidant levels, and enhances oxidative stress in many tissues, especially the liver^[82]. Second, ethanol metabolism by CYP2E1 occurs during chronic alcohol consumption, when alcohol dehydrogenase reaches saturation, and results in the generation of additional acetaldehydes, ROS, and free radicals. Activation of Nrf2 is critical in combating the oxidative stress caused by ROS generated during the normal catalytic cycle of CYP2E1. This is supported by preclinical studies showing that ethanol-induced CYP2E1 expression also results in upregulation of Nrf2 and its targets, namely HO-1^[83]. It has been reported that Nrf2-null mice have increased liver-associated mortality when fed high doses of ethanol compared with wild-type mice. This detrimental effect of alcohol on Nrf2-null mice was shown to be the result of increased lipogenesis, depletion of total and mitochondrial glutathione, and a Kupffer cell-mediated aggravation of the inflammatory response. This suggested that Nrf2 plays a role in protecting against ethanol-induced damage^[84]. Ethanol induced oxidative stress *via* induction of CYP2E1 upregulates Nrf2 activity, which in turn regu-

lates ethanol induction of CYP2A5 and protects against ethanol-induced steatosis^[85]. The prominent microvesicular steatosis and mild necrosis in hepatic histopathology were notably attenuated in accordance with the modulation of Nrf2 in clinical administration of artemisia capillaris for alcoholic-associated liver injury^[86]. It remains unclear whether Nrf2 plays a major role in the pathogenesis of this disease state. Bardag-Gorce *et al.*^[87] found that the Nrf2 level was significantly decreased in the liver of a rat model of alcoholic liver disease. However, Wang *et al.*^[88] came to the opposite conclusion, that hepatic very low-density lipoprotein receptor (VLDLR) overexpression plays an important role in the pathogenesis of ALD. Oxidative stress-induced Nrf2 activation plays a critical role in alcohol-induced VLDLR upregulation in hepatocytes, and enhances VLDLR expression in primary hepatocytes^[89,90]. Hence, further research is required to determine the role that Nrf2 activation might play in alleviating alcoholic liver disease.

Nrf2 IN DRUG-INDUCED LIVER INJURY (DILI)

Xenobiotic agents can initiate liver injury through reactive-intermediate formation, protein adduct accumulation, and alterations in drug-metabolizing enzymes. Acute hepatic failure secondary to acetaminophen (APAP) poisoning is associated with high mortality^[91]. APAP overdose is the most frequent cause of drug-induced liver failure in the United States and most of Europe^[92,93]. Therefore, APAP-induced toxicity has become an essential model for studying drug-induced liver disease^[94,95]. Electrophiles, radicals, and ROS are often generated as intermediates or by-products of APAP metabolism. These reactive intermediate toxicities provoke covalent bonding with biomolecules and leads to lipid peroxidation, and ultimately oxidative stress^[96-98]. Recently, studies showed that nimesulide-induced electrophile stress activates Nrf2 in human hepatocytes and mice^[99]. The oxidative stress that occurs with APAP toxicity suggests a role for Nrf2 in the toxicological events of APAP. This view is supported by several studies showing that Nrf2 plays a critical role in protecting the liver against DILI. Nrf2-deficient mice are highly susceptible to APAP-induced liver injury^[100]. In Nrf2-null mice, APAP exposure enhanced liver injury and mortality compared with wild-type mice^[101]. In addition, the Nrf2 activator CDDO-Im is protective against APAP hepatotoxicity by inducing HO-1, NQO1, and glutamate-cysteine ligase catalytic subunit in the wild-type, but not the Nrf2-null mice^[102]. However, some evidence indicates that autoprotection against APAP could contribute to this development of resistance to hepatotoxicity, and Nrf2 activation is expected to play a role in the protective adaptation. APAP treated hepatocytes showed enhanced antioxidant defense *via* delaying tyrosine phosphorylation of Nrf2 and its nuclear exclusion, ubiquitination and degradation^[103]. Pretreatment of mice with a low hepatotoxic dose of APAP resulted in resistance to the toxicity

of a subsequent higher dose of APAP. Upregulation of Lgals3, one of the genes supporting the Nrf2 hypothesis led to suppression of apoptosis and reduced mitochondrial dysfunction^[104]. The mechanisms underlying the protective effects of Chinese traditional medicines against *N*-nitrosodimethylamine, or CCl₄, or APAP-induced liver injury have been investigated. Treatment with rutin^[105], safflower^[106], betanin^[107], or Piper puberulum^[23] significantly increased Nrf2 and HO-1 expression in injured livers. These results indicated that the hepatoprotective effect of Nrf2 against DILI functions *via* the activation of Nrf2 and subsequent induction of the expression of genes controlled by Nrf2. Furthermore, oleanolic acid is a triterpenoid with many beneficial effects and has been demonstrated to protect against varieties of hepatotoxicants *via* activation of Nrf2^[108]. However recently, high-doses and long-term use was reported to produce hepatotoxicity^[109]. Apart from DILI, endotoxemia correlates with the degree of liver failure and may contribute to worsening of liver diseases. In most cases, lipopolysaccharide (synonymous with endotoxin) is a liver failure causing endotoxin, which lowers the hepatic GSH levels by inhibiting sumoylation of Nrf2^[110]. Thus, Nrf2 may serve as a major regulator of several cellular defense associated pathways by which hepatic cells combat oxidative stress by xenobiotics.

CONCLUSION

Oxidative stress is implicated in the pathogenesis of liver disease. During oxidative stress, Nrf2 is activated to protect the liver *via* target gene expression. Therefore, Nrf2 activators have great potential as therapeutic agents against oxidative stress during chronic liver injury.

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P- Reviewer: Jie H, Pal A, Penkova-Radicheva M, Wateshi K
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