

Review

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Review

Rodent Models of D-Galactose Induction of Accelerated Aging: A Platform for Exploring Kidney Aging Mechanisms and Anti-Kidney Aging Strategies

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Abstract

D-galactose (D-gal) induced accelerated aging is a popular and widely used experimental method in the field of aging and aging-related degenerative disorders. It has been shown that the major characteristics of D-gal induced aging process are increased oxidative stress, decreased antioxidant enzymes, elevated cell death, increased tissue fibrosis and accumulation of inflammatory mediators. This review focuses on D-gal induced kidney aging in mice and rats with discussions on both kidney aging mechanisms and anti-kidney aging regimens using this model. It is our belief that D-gal induction of accelerated kidney aging will continue to be used as a convenient platform for elucidating kidney aging mechanisms and exploring novel anti-kidney aging targets that may slow down kidney aging and retard the development of aging related renal disorders.

Keywords: D-galactose; apoptosis; kidney aging; oxidative stress; fibrosis; inflammation

1. Introduction

The kidney is a vital life-sustaining organ that is in charge of blood filtration and waste excretion. It is involved in numerous homeostatic processes such as blood pressure regulation, pH maintenance, hormone secretion, electrolyte and mineral retention as well as body's fluid volume regulation [1,2]. Under hypoglycemic conditions, the kidney can also make glucose via the gluconeogenic pathway [3]. Achieving all these functions requires strict maintenance of nephron's cellular membrane potential, tight regulation of membrane channels, transporters, and receptors [1]. All such highly regulated cellular pathways are supported and sustained by large amounts of ATP generated by mitochondrial electron transport chain and oxidative phosphorylation, which is oxygen dependent and is also the Achilles' heel of the kidney as generation of reactive oxygen species (ROS) and oxidative stress are inevitable and may worsen under a variety of pathological conditions [4].

The kidney also undergoes an inevitable aging process. Indeed, it exhibits structural changes and functional decline even during a healthy aging process [5,6]. This is mainly manifested by a gradual decline of glomerular filtration rate (GFR), which has been estimated to be 0.7-0.9 ml/min/1.3 m² on an annual basis [7]. While the mechanisms of this GFR decrease in healthy aging remain sketchy, it has been associated with a progressive loss of nephrons starting from 30 years of age [7]. Clinically, this age-related decline in renal function is reflected by glomerulosclerosis, tubular atrophy, hyalinosis, loss of renal mass, arteriosclerosis, and interstitial fibrosis [5]. Age-related chronic inflammation may also be involved in this renal functional decline [6]. Collectively, all these slow pathological or physiological changes can eventually result in nephron hyperfiltration and hemodynamic stress, leading to increased sensitization of the kidney to a variety of insults such as sepsis, ischemia, drug toxicity, metal toxicity, and obesity as well as diabetes [8–12]. Therefore,

normal kidney aging can contribute to acute kidney injury (AKI) and chronic kidney disease (CKD) [10,13–16].

Given that kidney aging, like all the other organs in the body, is a complex and irreversible physiological process, there has been increasing interest in studying the mechanisms by which the kidney ages. In this respect, animal models of kidney aging have played an invaluable role in our understanding of how the kidney ages. In this review, we focus on rodent models of aging induced and accelerated by D-galactose (D-gal) [17,18]. This aging model has been widely used for the studies of the biological aging process and the evaluation of anti-aging strategies involving caloric restriction mimetics and the testing of numerous natural products and drugs [17,19–22].

2. D-Gal Catabolism and Common Mechanisms of D-Gal Induced Aging

As opposed to natural aging that is time-consuming, D-gal-induced aging is an accelerated process, which is convenient to perform within a short period of time [18]. Animals involved usually exhibit least adverse effects and high survival rates [18]. D-gal is the third major monosaccharide of nutritional value next to glucose and fructose [23]. When combined with glucose, it forms a disaccharide known as lactose, which exists in milk and dairy products. When compared with the structure of glucose, D-gal shows almost an identical structure except for a slight different configuration at the C-4 position [23]. While being an energy supplier at normal concentrations in the body, high concentrations of D-gal is harmful to the body [24]. This is because at high levels, D-gal can form advanced end glycation products (AGEs) and can also be converted to hydroperoxide and aldose by galactose oxidase, leading to ROS generation [18,24]. Increased ROS production can cause oxidative stress, inflammation, fibrosis, mitochondrial abnormalities, and cell death [18,24]. It should be noted that high level of galactose can also activate aldose reductase leading to conversion of galactose to galactitol, the latter can cause osmotic stress and mitochondrial dysfunction [25,26]. Deficiencies in galactokinase and uridyltransferase can also divert galactose conversion to galactitol [27]. Figure 1 outlines the D-gal catabolic pathways.

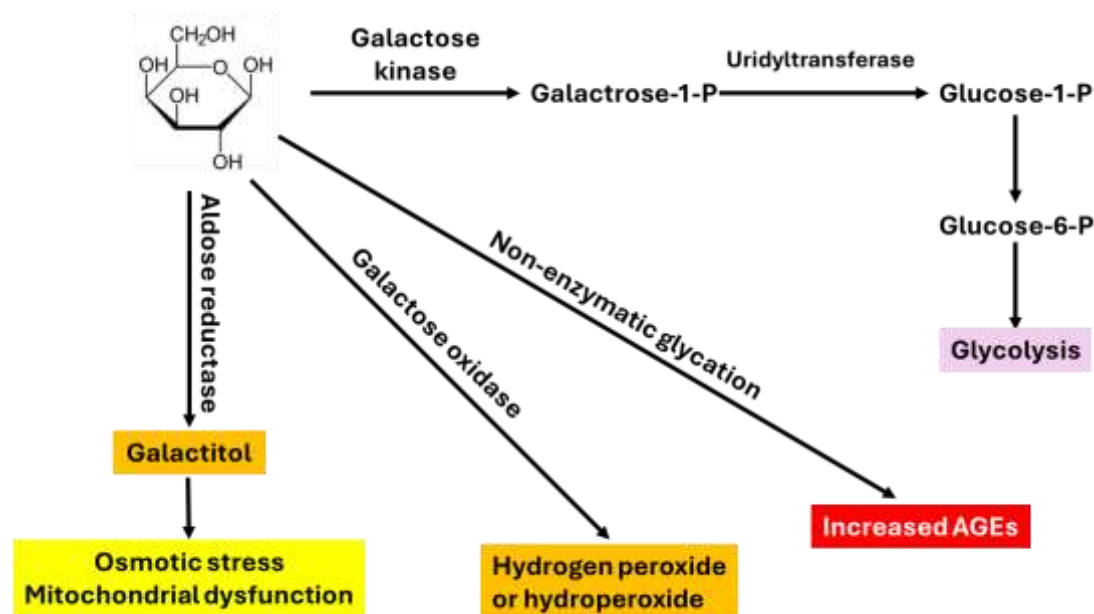


Figure 1. Catabolic pathways of D-galactose. Feeding into the glycolytic pathway is used to supply cellular energy by generating ATP. Metabolites such as galactitol, hydroperoxide, and advanced glycation end products (AGEs) resulting from the other three pathways all have detrimental effects on the kidney as well as other organs and tissues.

D-gal accelerated aging in rodents was first discovered by Xu et al in the 1980s [28]. Since then, D-gal has been extensively used for the studies of aging and age-related degenerative disorders in a variety of animal organs [18]. It has also been used for aging studies in lower organisms such as *Drosophila melanogaster* [29]. Animals treated with D-gal show a shortened lifespan, mitigated immune response, declined cognition with oxidative stress often being the common underlying mechanism of all the observed phenomenon [17]. Furthermore, numerous aging markers have been found in D-gal induced aging. These include increased AGEs and their corresponding receptors, telomere shortening, aldose reductase, sorbitol dehydrogenase, and senescence associated β -galactosidase (SA- β -gal) [18,30,31]. β -amyloid, β -amyloid protein cleaving enzyme-1 and enhanced expression of senescence-linked genes have also been the characteristics of D-gal induced aging in a variety of animal models [18,32,33].

3. Kidney Aging Induced by D-Gal

D-gal treatment of animals capitulates many aspects of the aging process. These include increased oxidative damage to proteins, lipids, and DNA as reflected by increased protein carbonyl formation, lipid peroxidation products malondialdehyde, and DNA damage adducts 8-oxo-deoxy guanine (8-oxo-dG) [34–37]. Additionally, NADPH oxidases such as NADPH oxidase 4 (NOX4) [34], AGEs, nitric oxide are all increased in conjunction with decreased antioxidant enzymes such as superoxide dismutase (SOD), catalase, glutathione peroxidase and glutathione reductase. Glutathione and total antioxidant capacities also decreased [38–41]. Moreover, kidney inflammation was enhanced, following D-gal administration, which was reflected by upregulation of signaling pathways including NF- κ B, iNOS, COX2, TNF- α , and IL-6 [41–44].

Decline in renal function after D-gal treatment was also obvious as both blood urea nitrogen and creatinine increased while kidney index decreased [34]. Additionally, kidney injury markers such as cystatin C and uric acid contents also increased [34]. Structurally, histological analysis revealed lesions within the nephrons including both glomerular damage and tubular damage. Glomerular structure analyzed by transmission electron microscopy indicated a thicker and uneven basement membrane induced by D-gal, demonstrating podocyte cell damage [40,44]. Figure 2 depicts the common mechanisms by which D-gal accelerates kidney aging. At this point, however, we would also like to briefly overview methods used to determine oxidative stress, inflammation, and fibrosis.

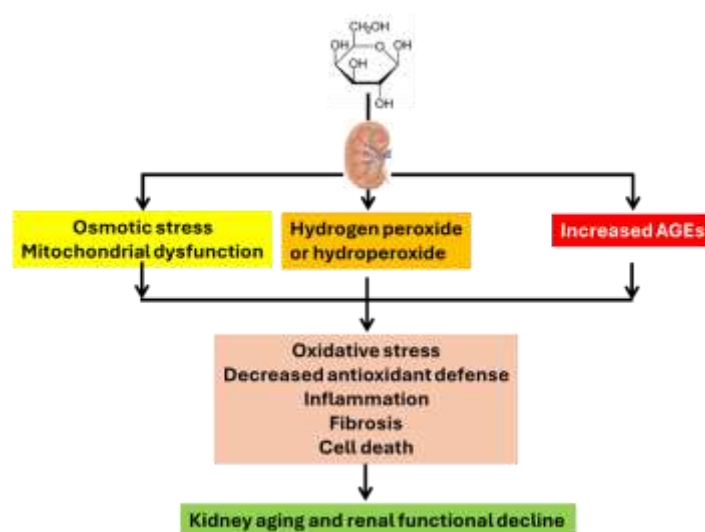


Figure 2. Common mechanisms by which D-gal induces kidney aging. These include oxidative stress, decreased antioxidant defense, inflammation, fibrosis, and cell death.

3.1. Analysis of Oxidative Stress

Determination of oxidative stress usually consists of three aspects: 1) measurement of ROS production such as superoxide anion and H₂O₂; 2) measurement of oxidative damage to macromolecules such as proteins, DNA, and lipids; 3) measurement of antioxidant capacities such as SOD, catalase, and glutathione.

3.1.1. Measurement of ROS

ROS can be measured as content of H₂O₂ [45] or by reduction of acetylated cytochrome c in an SOD-inhibitable manner [46]. ROS can also be measured by chemical probes such as 2, 7-dichlorofluorescein [47]. Additionally, total oxidant status can also be measured by a ferrous oxidation-xylenol orange assay [48–50].

3.1.2. Measurement of Oxidative Damage to Macromolecules

This assessment includes protein oxidation, DNA oxidative damage, and lipid peroxidation. Protein oxidation can be measured as protein carbonyls derivatized by a probe called 2,4-dinitrophenylhydrazine (DNPH) [51]. DNP-derivatized proteins can be measured spectrophotometrically [52,53] or by Western blot assay using anti-DNP antibodies [54]. The advantage of the Western blot assay is that carbonylation of individual proteins in a given sample can be visualized. This contrasts with the spectrophotometric assay that measures total protein carbonyls in a given sample.

DNA oxidative damage can be measured by quantitation of 8-oxo-dG, a DNA adduct resulting from DNA oxidation [55]. 8-oxo-dG can be determined in many specimens such as blood, urine, and tissue homogenates [56]. DNA fragmentation caused by oxidation can also be measured by a TUNEL assay, which is also used to measure the magnitude of apoptosis [57].

Lipid peroxidation can be measured by quantitation of either malondialdehyde (MDA) or 4-hydroxynonenal (HNE) [53,58]. The latter can also be analyzed as a protein conjugate by Western blot assay using anti-HNE antibodies [58].

3.1.3. Measurement of Antioxidant Defense System

Cellular antioxidant capacities can be measured by a variety of parameters. These include activities of antioxidant enzymes such as superoxide dismutase, catalase, glutathione peroxidase, peroxiredoxins and thioredoxins [59–61]. Glutathione, the major cellular antioxidant [62,63], is often measured in conjunction with the determination of antioxidant enzymes. Additionally, total antioxidant capacity can also be quantitated to reflect overall cellular antioxidant status [64–66].

3.1.4. Measurement of Inflammation and Fibrosis

Determination of inflammation can be conducted by measuring pro-inflammatory cytokines such as IL-6 and IL-1 β [67,68]. Level of TNF- α and activation of the NF- κ B signaling pathway can also be measured to indicate the magnitude of inflammation [68–70]. For analysis of tissue fibrosis, accumulation of collagen and extracellular matrix proteins can often be measured to indicate the magnitude of fibrosis [71–73].

In addition to the common mechanisms such as oxidative stress, inflammation, and fibrosis discussed above, certain specific mechanisms have also been found to contribute to D-gal induced kidney aging. For example, ferroptosis, iron-mediated cell death, has been reported to be linked to D-gal-induced kidney aging via promotion of tubular senescence [74]. Table 1 summarizes some uncommon but outstanding mechanisms by which D-gal accelerates kidney aging.

Table 1. Uncommon and specific mechanisms involved in D-gal-induced kidney aging.

mechanisms	Animal models Reference	D-Gal dosage (mg/kg/day)/ route/duration		Specific
[74]	Mouse	300, S.C.	8 weeks,	Ferroptosis
upregulation	Mouse [75]	500, S.C.,	12 weeks	Caveolin-1
polarization	Mouse [76]	500, S.C.,	8 weeks	M1 macrophage
	Mouse [77]	150, I.P.,	8 weeks	BRD4 upregulation
transcription	Mouse [78]	150, S.C.,	8 weeks	Enhanced TRPC3
upregulation	Mouse [79]	150, S.C.,	6 weeks	Cannabinoid receptor 2

3.2. General Experimental Approaches of D-Gal Induced Aging in Rodents

In the literature, experimental protocols reported, but not limited to kidney aging studies, for D-gal accelerated aging in mice or rats vary widely in terms of dosage, route of administration, and duration of induction. Different laboratories usually have different protocols. The dosage of D-gal can range from 100 mg/kg/day to 1000 mg/kg/day. However, most investigators use a dosage between 120 mg/kg/day to 800 mg/kg/day (See Tables 1 and 2). With respect to D-gal administration, the most used route of ingestion is via subcutaneous injection. Intraperitoneal injections have also been conducted by some investigators. Moreover, D-gal in drinking water ranging from 5% to 40% (w/v) [80,81] and in solid diet ranging from 30%-50% (w/w) [82,83] have also been used. For duration of D-gal induction, 4 weeks to 13 weeks have been reported. When anti-aging compounds were tested, a compound could be given concurrently or a few weeks after D-gal ingestion was started. Nonetheless, for a given individual laboratory, the protocol usually remained the same so that results from studies to studies could be compared. Figure 3 shows the general protocols.

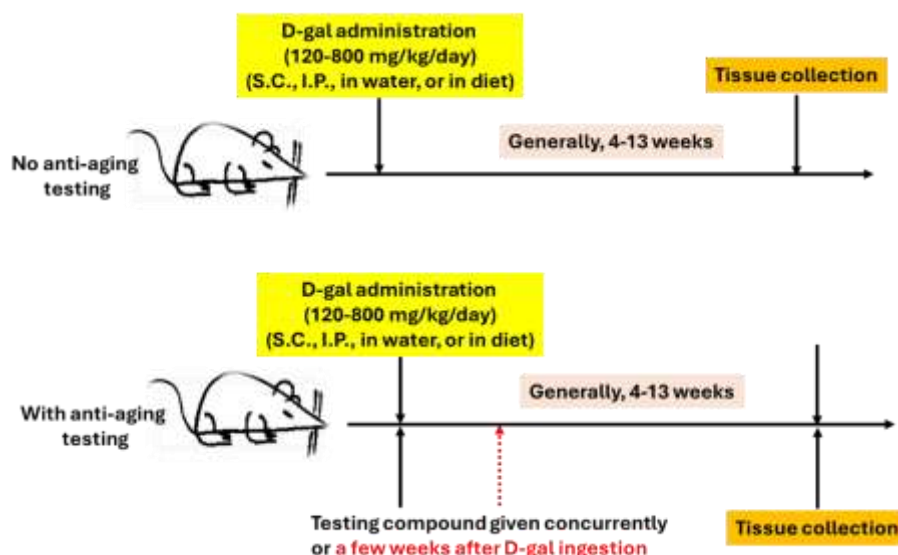


Figure 3. General protocols used for D-gal induced overall aging or kidney aging as well as the testing of anti-aging treatments.

4. D-Gal-Induced Aging Model as a Platform for Evaluating Anti-Kidney Aging Strategies

As similar to any other animal models, D-gal induced aging in rodents has also been widely used for testing strategies designed for anti-kidney aging purposes. Among these strategies, many are natural products such as polyphenols, plant extracts, chemical, and pharmacological drugs. Table 2 lists various agents that have been evaluated. D-gal dosage, route of administration, and duration of the experiments are also given. Numerous agents show common anti-kidney aging mechanisms including counteracting oxidative stress, mitigating inflammation, and attenuating renal fibrosis as well as increasing autophagy or mitophagy [75,84–86].

Table 2. Beneficial effects of various agents such as plant natural products, pharmacological drugs, and chemicals on kidney aging induced by D-galactose.

Chemical/compound/ Reference	D-gal-mg/kg/day duration/route	Mechanisms
Serum free, adipose conditioned medium/Mouse [87]	100, S.C., 8 weeks	Suppressing IL-6/STAT3
Mild moxibustion/Rat [88]	300, I.P., 4 weeks	Sirt1/p53 signaling
Vitamin B12/Rat [31]	300, I.P., 120 days	Decreasing AGEs accumulation
Exercise/Rat [89]	150, S.C., 8 weeks	Decreased SGLT2 expression

Moderate beer consumption/Mouse [90]	25, S.C., 8 weeks	Modulating gut dysbiosis
Dendrobium officinale extract/Mouse [91]	120, S.C., 8 weeks	Inhibiting oxidative stress
Ginsenoside Rg1/Mouse [92]	120, I.P., 7 weeks	Suppressing oxidative stress/inflammation
Adropin/vitamin D/Rat [93]	120, I.P., 8 weeks	MAPK/HIF α /VEGF/eNOS
Polygonatum sibiricum polysaccharides/Mouse [94]	150, I.P., 8 weeks	Modulating gut microbiota
Zuoguiyin (traditional Chinese medicine)/Rat [95]	125, S.C., 8 weeks	Sirt1/PPAR γ signaling
Ganoderma lucidum/Mouse [96]	600, S.C., 8 weeks	Increasing α -klotho expression
Black rice anthocyanins [97]	500, S.C., 13 weeks	Nrf2/NF- κ B signaling
Fucoidan oligosaccharide/Rat [86]	150, S.C., 8 weeks	Inhibiting oxidative stress
Arctium lappaL. Polysaccharides/Mouse [98]	150, I.P., 8 weeks	Inhibiting oxidative stress
Alpinate oxyphyllae fructus/Rat [99]	150, N/A, 6 weeks	Inhibiting oxidative stress/inflammation
Box A of HMGB1/Rat [100]	150, S.C., 8 weeks	Inhibiting DNA damage
Tropisetron/Mouse [35]	200, S.C., 8 weeks	Sirt1 upregulation
Piperlongumine 1-3/Mouse [101]	500, I.P. 10 weeks	Sirt1 upregulation
Silk sericin/Mouse [102]	250, I.P., 60 days	Diminishing oxidative stress
Sulforaphene/Mouse [103]	300-800, S.C. varying	Inhibiting oxidative stress
Exogenous hydrogen sulfide/Mouse [85]	150, S.C., 10 weeks	Mitophagy activation
Lactobacillus brevis/Mouse [104]	300, S.C., 5 weeks	Increased antioxidant enzymes
Resveratrol/Mouse [105]	1000, S.C., 8 weeks	Decreasing AGEs
Resveratrol/Mouse [106]	1 mg/kg, I.P., 4 weeks	Increasing klotho expression
Methyltransferase-like protein 3/Mouse [107]	500, S.C., 8 weeks	Promoting miR-181a maturation
Gemfibrozil/Mouse [108]	150, I.P., 6 weeks	Inhibiting oxidative stress

Dendrobium nobile alcohol extract/Mouse [109]	125, S.C., 8 weeks	Anti-oxidative stress
β -catenin inhibitors, KYA1797K/Mouse [110]	150, S.C., 6 weeks	Suppressing mitochondrial dysfunction
Rosa roxburghii tratt glycosides-quercetin/Mouse [111]	100, S.C, 6 weeks	Anti-oxidative stress
Calcium dobesilate/Mouse [112]	500, P.O., 6 weeks	Inhibiting oxidative stress
Klotho/Mouse [113]	500, S.C., 6 weeks	Inhibiting DNA methyltransferase
Astaxanthin/exercise/Rat [114]	100, I.P., 6 weeks	Nrf2 activation
Maltol/Mouse [115]	800, I.P., 7 weeks	p53/p21/p16, PI3K/Akt pathways
Lithium chloride/Rat [116]	300, I.P., 6 weeks	Increasing enzymatic antioxidants
Alginate oligosaccharide/Mouse [36]	200, S.C., 8 weeks	Nrf2/NQO1/HO-1 activation
20(R)-ginsenoside Rg3/Mouse [117]	800, S.C., 8 weeks	Anti-oxidative stress
Quercetin/Rat [118]	120, S.C., 6 weeks	Anti-oxidative stress
Urolithin A/Mouse [119]	150, S.C., 8 weeks	Anti-oxidative stress/inflammation
Collagen polypeptide [120]	300, S.C., 8 weeks	Attenuating oxidative stress
Small-leaved Kuding tea polyphenols/Mouse [121]	120, I.P., 6 weeks	Anti-oxidative stress
Chitosan oligosaccharide/Mouse [122]	250, S.C., 8 weeks	Anti-oxidative stress
Rhein lysinate/Mouse [123]	100, S.C., 8 weeks	Enhancing antioxidant activity
Chlorogenic acid/Mouse [40]	100, S.C., 8 weeks	Antioxidation, anti-inflammation
Korea red ginseng/Rat [8]	100, I.P. 8 weeks	Suppressing oxidative injury
Ethyl acetate extraction from <i>Idesia polycarpa</i> [124]	100, S.C., 6 weeks	Anti-oxidation
Exercise/Rat [125]	100, I.P., 9 weeks	Inhibiting oxidative stress
Selenoarginine/Mouse [126]	150, S.C., 6 weeks	Enhanced antioxidant defense
Que Zui tea/Mouse [127]	300, S.C., 10 weeks	Inhibiting oxidative stress

Lycopene/Mouse [128]	150, I.P., 8 weeks	Improving insulin signaling
L-theanine/Rat [30]	200, S.C., 8 weeks	Decreasing AGEs' toxicity
<i>Vitex agnus-castus</i> extracts [129]	500, S.C., 45 days	Suppressing apoptosis
Vitamin E/selenium/carrot anthocyanins [43]	400, I.P., 6 weeks	Inhibiting oxidative stress
<i>Artemisia annua</i> L extract [130]	100, S.C., 6 weeks	Enhancing antioxidants
Troloxerutin/Mouse [34]	500, S.C., 8 weeks	Inhibiting DNA damage
<i>Angelica sinensis</i> extract [42]	200, S.C., 8 weeks	Attenuating oxidative stress
<i>Centella asiatica</i> /Rat [131]	60, I.P., 70 days	Inhibiting oxidative stress
Antarctic ice microalgae polysaccharides/Mouse [132]	120, I.P., 6 weeks	Inhibiting oxidative stress
<i>Apocynum venetum</i> polyphenols/Mouse [133]	120, I.P., 6 weeks	Inhibiting oxidative stress
<i>Radix isatidis</i> protein/Mouse [134]	800, S.C., 7 weeks	Anti-oxidation
Ginsenoside Rg1/Mouse [41]	120, S.C., 6 weeks	Alleviating oxidative stress
Empagliflozin/Mouse [135]	800, S.C., 8 weeks	Inhibiting sirt1/oxidative stress
<i>Ulva Lactuca</i> polysaccharide/Mouse [136]	400, S.C., 10 weeks	Inhibiting oxidative stress
<i>Moringa Oleifera</i> see aqueous extract/Rat [81]	30% in water, 4 weeks	Increasing SOD expression
Hyperoside/Rat [84]	300, S.C., 4- and 8-weeks	Inhibiting autophagy
<i>Kaempferia parviflora</i> extract [137]	50, I.P., 60 days	Decreasing lipid peroxidation
Day-time restricted feeding/Mouse [138]	100, I.P., 16 weeks	Attenuating renal damage

5. Miscellaneous

5.1. Synergistic Detrimental Effects with Risk Factors

D-gal-induced acceleration of aging can be accentuated by other disease-causing risk factors such as high fat diet induced obesity and arsenite toxicity. For example, Park et al [8] reported that when D-gal induced aging rat was fed with a high fat diet, both oxidative stress and non-enzymatic protein glycation were further increased when compared with that of only D-gal induction.

Moreover, DNA damage, nephron apoptosis, and extracellular high mobility group box 1 were also additionally elevated, demonstrating aggravation of D-gal induced kidney aging by high fat diet. Similarly, Akbari et al [139] reported that when D-gal induced aging rat was treated with sodium arsenite, oxidative damage, downregulation of antioxidant defense, and cell death were all accentuated by arsenite on top of D-gal induced aging. It should be noted that this study was focused on the testis instead of the kidney. Nonetheless, it is conceivable that the kidney would exhibit a similar observation to that of the testis. Taken together, these studies demonstrate that D-gal induced aging could be worsened by other disease-causing risk factors.

5.2. D-Gal-Induced Aging as a Platform to Test the Anti-Aging Effects of Caloric Restriction Mimetics

Caloric restriction (CR) is a proven approach that can delay aging and age-related onset of diseases [140]. The underlying mechanisms of CR have been thought to involve modulation of mTOR and AMPK signaling pathways, oxidative stress, inflammation, mitochondrial abnormalities, and NAD⁺-dependent signaling pathway [141–146]. Given that CR has an incompliance issue in human, numerous researchers have focused on CR mimetics, in hopes that such mimetics can produce the same beneficial effects as that of CR. While no studies have been conducted exclusively on the kidney in terms of CR mimetics and D-gal-induced kidney aging, many studies have been performed on overall aging or on other organs using the D-gal aging platform. For example, chrysin, a glycolytic pathway inhibitor, has been shown to mimic CR in a rat model of D-gal aging [147]. It was found that chrysin inhibited all the D-gal induced aging biomarkers such as protein oxidation, lipid peroxidation, and protein glycation. Moreover, chrysin also significantly up-regulated the antioxidant defense system and downregulated the inflammatory response. Similarly, chitosan, a polysaccharide, has also been shown to exhibit CR effects in D-gal induced rat aging [21]. Table 3 lists CR mimetics that have been tested on the D-gal aging platform.

Table 3. Caloric restriction mimetics that have been tested using the D-gal aging induction animal model.

Reference	CR mimetics
[149]	Chrysin [147] Fisetin [20] Spermidine [148] Curcumin
[152]	Chitosan [21] Glucosamine [150] 2-Deoxy-d-glucose [151] Metformin
[153]	Goat milk
[154]	Caloric restriction per se

Day time restricted feeding

[138]

Note: these studies were not specifically on the kidneys.

5.3. Potential Difference Between D-Gal Oral Intake vs. D-Gal Injection

Martinovic et al [155] recently reported a potential difference between chronic oral intake of D-gal and I.P. or S.C. D-gal injections. The authors used male Wistar rats and addressed a systematic oxidative stress issue upon chronic oral intake of D-gal that was administered at 200 mg/kg and 500 mg/kg, respectively. The effects of oral intake were also compared with that of natural aging in rats. It was found that oxidative stress elevated in the heart, liver, and kidney; and this elevation is similar to that observed in 30 months old rats. In contrast to pronounced oxidative stress, only minor histopathological lesions were detected with nearly normal organ function. Taken together, the authors suggest that chronic oral intake of D-gal only imposes milder effects on organs and may induce only certain features of natural aging. Therefore, to mimic a significant aging process, D-gal administration via S.C. or I.P. injections should be performed.

5.4. Effects of Ketone Bodies and Ketogenic Diet

Ketone bodies can provide an alternative source of energy to the brain and other peripheral organs under prolonged fasting or starved conditions [156,157]. They refer to three metabolic products, namely β -hydroxybutyrate, acetoacetate, and acetone [4]. Acetone is usually exhaled from the lungs and thus cannot be used as an energy source [3]. Ketone bodies are produced in the liver due to low carbohydrate in the body, which is usually triggered by a high glucagon to insulin ratio [4]. Under this condition, fatty acids are over burned, leading to excessive acetyl-CoA production that overwhelms the TCA cycle. Surplus acetyl-CoA is thus diverted for ketone body production [4]. Endogenous ketone bodies, particularly β -hydroxybutyrate, can also be highly enriched by ingestion of ketogenic diet or just β -hydroxybutyrate and its derivatives [158,159]. Ketone bodies have been shown to have renoprotective properties under a variety of renal pathological conditions including AKI, CKD, and DKD [160–163]. However, potential effects of ketone bodies on D-gal-induced kidney aging are yet to be comprehensively evaluated. Nonetheless, given that ketone bodies can protect the kidneys against numerous insults, it is conceivable that ketone bodies may show anti-aging effects in D-gal-induced kidney aging model.

5.5. Identification of Common Targets for Both Kidney Aging and CKD

Kidney aging increases the occurrence of CKD [6,7,16]. Therefore, the two processes may have common targets that can be explored for slowing down both kidney aging and development of age-related CKD such as DKD [164]. Guo et al recently reported such a potential target [11]. The authors found that AMP-activated protein kinase-related kinase-1 (NUAK1) was upregulated in both D-gal induced kidney aging and HFD/streptozotocin-induced DKD. Down-regulation of NUAK1 via gene expression manipulation ameliorated nephron senescence and DKD; and the underlying mechanism by which NUAK1 contributed to kidney aging and DKD involved ROS/p53 axis. The authors also discovered that asiatic acid [165,166], a traditional herbal element, could physically bind NUAK1 and inhibit its activities, thereby achieving a therapeutic purpose. This study also provides a novel strategy that can be adapted to further identification of more common targets that may be used to combat both kidney aging and CKD including DKD.

6. Conclusion and Future Perspectives

The natural aging process in rodents can be accelerated by D-gal administration. Here in this review article, we discussed this animal model of aging with a focus on kidney aging. Common mechanisms of D-gal-induced kidney aging include oxidative stress, inflammation, fibrosis, and cell death. In many studies, downregulation of the antioxidant defense system has also been demonstrated. Collectively, these pathological mechanisms can cause functional decline in the kidney, which can also be augmented by other disease-causing risk factors such as obesity and environmental metal toxicity. This animal model of kidney aging has also been widely used as a platform to test the anti-aging properties of numerous natural products, chemicals, and drugs. It has also been used to evaluate the anti-aging properties of many caloric restriction mimetics. It should be noted that different researchers often differ on D-gal dosages, route of administration, and duration of aging induction. This may create issues when comparing results from different laboratories is attempted. Nonetheless, this model will continue to lend its convenience and usefulness to the study of kidney aging mechanisms and to the evaluation of potential anti-kidney aging strategies.

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