Table 1. Effect of melatonin on animal models of MS. The human equivalent dose (HED) of melatonin for a 75 kg adult is calculated by normalization of body surface area (43).

Findings	Melatonin Dose	Daily HED for a 75 kg adult	Ref
In rats fed from weaning with a high-fat diet melatonin decreased body weight gain, feed efficiency and plasma glucose, leptin and triglyceride levels	30 mg/kg/day p.o.	365 mg	(44)
In high-fat diet-fed mice, melatonin improved insulin sensitivity and glucose tolerance	100 mg/kg/day p.o.	610 mg	(45)
In ovariectomized rats, melatonin was effective to reduce obesity	2 - 3 mg/kg p.o.	25-36 mg	(46-48)
In olanzapine-treated rats, melatonin was effective to reduce obesity	0.05 mg/kg p.o.	0.6 mg	(49)
Melatonin and its analog piromelatonin inhibited weight gain and improve insulin sensitivity in high-fat fed rats	5 mg/kg p.o.	60 mg	(50)
In high-fat fed rats, melatonin attenuated body weight increase, the increase in plasma glucose, insulin, adiponectin, leptin, triglycerides and cholesterol levels, and counteracted disrupted 24 h patterns	2.3 mg/kg p.o.	25 mg	(51)
Melatonin improves inflammation processes in liver and pancreas of senescence-accelerated prone male mice (SAMP8)	1 mg/kg p.o.	6 mg	(52, 53)
Melatonin improved mitochondrial function and increased life span in SAMP8 mice	10 mg/kg p.o.	60 mg	(54)
Melatonin reduced body weight gain, visceral adiposity, blood triglyceride and insulin levels and TBARS under a high calorie diet in rats.	4 mg/kg p.o.	48 mg	(55)

In young male Zucker diabetic fatty rats melatonin treatment reduced mean weight gain without affecting food intake, decreased in a non-significant way blood pressure, and improved dyslipidemia	10 mg/kg p.o.	120 mg	(56)
Melatonin improves MS induced by high fructose intake in rats without affecting food intake	2.3 to 20 mg/kg p.o.	25-120 mg	(57-61)
Melatonin and its analog piromelatonin reduced blood pressure in spontaneously hypertensive rats	5 mg/kg p.o.	60 mg	(62)
Melatonin prevents the development of the MS in male rats exposed to different light/dark regimens	120 mg/kg p.o.	1.45 g	(63)
Melatonin attenuates high fat diet-induced fatty liver disease in rats	5 - 10 mg/kg p.o.	60-120 mg	(64)
Melatonin ameliorates low-grade inflammation and oxidative stress in young Zucker diabetic fatty rats	10 mg/kg p.o.	120 mg	(65)
Melatonin improves hyperglycemia, hypertriglyceridemia, polyphagia, and polydipsia in streptozotocin diabetic rats	2.5 to 20 mg/kg p.o.	25-240 mg	(66, 67)
Protective effects of melatonin against metabolic and reproductive disturbances in polycystic ovary syndrome in rats	1-2 mg/kg i.p.	12-24 mg	(68)
Melatonin normalizes clinical and biochemical parameters of mild inflammation in diet-induced MS syndrome in rats	2.3 mg/kg p.o.	25 mg	(69)
Melatonin counteracts changes in hypothalamic gene expression of signals regulating feeding behavior in high-fat fed rats	2.3 mg/kg p.o.	25 mg	(70)
Melatonin reduces obesity and restores adipokine patterns and metabolism in obese (ob/ob) mice	100 mg/kg p.o.	610 mg	(71)
Melatonin nephroprotective action in Zucker diabetic fatty rats involves an inhibitory effect on NADPH oxidase	2.5 mg/kg p.o.	25 mg	(72)

Melatonin prevents type 2 diabetes in high carbohydrate diet-fed male Wistar rats	0.8 mg/kg p.o.	10 mg	(73)
Melatonin decreases fasting blood glucose, total cholesterol, LDL levels and MDA levels, and restores the vascular responses and endothelial dysfunction in diabetic, high-fat diet fed rats	10 mg/kg p.o.	120 mg	(74)
Maternal melatonin supplementation during murine diabetic pregnancy improves the tolerance to myocardial ischemia/reperfusion injury in the offspring, via restoring cardiac IRS-1/Akt signaling	10 mg/kg p.o.	60 mg	(75)
In rats with diet-induced obesity exposed to circadian disruption, treatment with melatonin alone or in combination with metformin modifies progression of metabolic dysfunction through improved adiposity, circadian activity, insulin sensitivity, and islet cell failure	20 mg/kg p.o.	240 mg	(76)
Melatonin prevents non-alcoholic fatty liver disease in high-fat diet induced obese mice by decreasing body weight and reducing inflammation via modulation of the MAPK-JNK/P38 signaling pathway	10 mg/kg p.o.	60 mg	(77)
Melatonin reverses liver apoptosis, mainly through intrinsic pathway and reversed endoplasmic reticulum stress and mitochondrial function in rats subjected to bile duct ligation	400 mg/kg i.p.	4.85 g	(78)
Melatonin reduces body weight, liver steatosis, and low-grade inflammation, and improves insulin resistance and gut microbiota in high-fat diet fed mice	50 mg/kg p.o.	300 mg	(79)
The increased food intake, water consumption, hyperglycemia, glucose intolerance, and insulin resistance in T2DM rats were improved by melatonin or Neu-P11 treatment. Treatment increased glucocorticoid receptor expression and suppressed 11β-hydroxysteroid dehydrogenase 1 activity in the hippocampus by enhancing glucocorticoid sensitivity and HPA feedback	20 mg/kg p.o.	240 mg	(80)
Using mice fed a high-fat diet (HFD) as an obesity model, spindle disorganization, chromosome misalignment, and elevated reactive oxygen species (ROS) levels were documented in oocytes from obese animals. Melatonin administration not only reduces ROS generation, but prevents spindle/chromosome anomalies in oocytes, through the SIRT3-SOD2-dependent mechanism consequently promoting the developmental potential of early embryos.	30 mg/kg p.o.	180 mg	(81)

Oral supplementation with melatonin reduces oxidative damage and concentrations of inducible nitric oxide synthase, VEGF and matrix metalloproteinase 9 in the retina of rats with streptozotocin/nicotinamide induced pre-diabetes	0,32 mg/kg p.o.	4 mg	(82)
Melatonin counteracted oxidative damage, inflammation and apoptotic cell death in lung tissue of diabetic rats.	20 mg/kg p.o.	240 mg	(83)
Melatonin improves the therapeutic role of mesenchymal stem cells on glucose, insulin, total antioxidant, and malondialdehyde level in diabetic rats	10 mg/kg p.o.	120 mg	(84)
Melatonin improves insulin resistance and hepatic steatosis through attenuation of alpha-2-HS-glycoprotein in high-fat diet mice. It reduced body weight gain and improved insulin sensitivity and glucose intolerance by the upregulation of muscle p-AKT protein expression. ER stress in the liver and serum of HFD mice was decreased by melatonin treatment.	100 mg/kg p.o.	1.2 g	(85)
In diabetic rats melatonin prevented fluorescein leakage and oxidative damage seen in the retina	20 mg/kg p.o.	240 mg	(86)