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Article

Therapeutic Potential of Quercetin: New Insights and Perspectives for Human Health

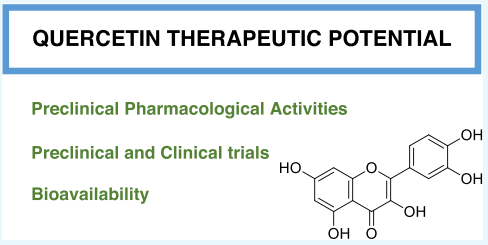
Bahare Salehi, Laura Machin, Lianet Monzote, Javad Sharifi-Rad,* Shahira M. Ezzat,* Mohamed A. Salem, Rana M. Merghany, Nihal M. El Mahdy, Ceyda Sibel Kılıç, Oksana Sytar, Mehdi Sharifi-Rad, Farukh Sharopov, Natália Martins,* Miquel Martorell,* and William C. Cho*

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ABSTRACT: Quercetin (Que) and its derivatives are naturally occurring phytochemicals with promising bioactive effects. The antidiabetic, anti-inflammatory, antioxidant, antimicrobial, anti-Alzheimer's, antiarthritic, cardiovascular, and wound-healing effects of Que have been extensively investigated, as well as its anticancer activity against different cancer cell lines has been recently reported. Que and its derivatives are found predominantly in the Western diet, and people might benefit from their protective effect just by taking them via diets or as a food supplement. Bioavailability-related drug-delivery systems of Que have also been markedly exploited, and Que nanoparticles appear as a promising platform to enhance their bioavailability. The present review aims to provide a brief overview of the therapeutic effects, new insights, and upcoming perspectives of Que.



1. INTRODUCTION

Quercetin (Que, Figure 1) is an antioxidant flavonol belonging to the flavonoid group and generally present as Que glycoside.[1−3] The Que aglycone is able to conjugate with glucose, xylose, or rutinose attaching to one of the Que's hydroxyl groups with the consequent creation of various Que glycoside forms.[4] Quercetin-3-*O*-glycoside mostly serves as a pigment in flowers, vegetables, and fruits.[5] Nutritional Que is present mainly as glycosides rather than as aglycones.[6] It shows a relatively higher bioavailability than other phytochemicals,[7] with its main sources being grapes, berries, cherries, apples, citrus fruits, onions, buckwheat, kale, tomatoes, red wine, and black tea.[3,8,9] However, the Que concentration can vary from one plant to another or even in different parts of the same plant.[10,11]

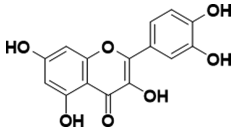


Figure 1. Chemical structure of Quercetin.

Nutritional flavonoids, as is the case of Que, are even more powerful antioxidants than vitamins C and E,[12] with those which contain in formula a 3-OH and 3′,4′-catechol revealing to be 10 times stronger toward peroxynitrite than ebselen.[13] In different food products, onion-derived Que (containing Que glucoside) revealed a higher bioavailability than apple-derived Que (containing Que rhamnoside and Que galactoside).[2]

Que and its derivatives exert key biological effects on cell cycle progression and cellular signal transduction pathway regulation.[14] Moreover, the metabolic plasticity of Que is a determinant in the plant adaptive reaction. This also has a great impact on the early-stage adaptation of plants to their local ecosystems.[15] At the same time, Que aglycones are effective regulators of auxin transport, related to plant growth and development.[16]

The anti-inflammatory and antioxidant effects of Que are essential for its activity as oxidative, kinase, and cell cycle inhibitors, as well as for neuronal survival. Que apoptosis-inducing effects are the key for its anticancer potential.[17] Que, like many other compounds with a flavone ring, also exerts a marked effect on the immunity and inflammation.[18] Thus this review aims to review the therapeutic effects of Que using modern research techniques.

2. RESULTS AND DISCUSSION

2.1. Preclinical Pharmacological Activities of Quercetin. *2.1.1. Effects on Diabetes Complications.* Many studies

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Table 1. Reported Pharmacological Activities for Quercetin

doses	*In vitro/in vivo/ex vivo*	route of administration	model	effect	refs
			Antidiabetic Effect		
20 mmol/L	*ex vivo*		INS-1 Pancreatic β-cells	potentiated insulin secretion, β-cells protected against oxidative damages	22
120 mg/kg/day for 8 weeks	*in vivo*	Oral	diabetic rats	decreased plasma triglycerides and weight of diabetic rats; decreased plasma cholesterol levels, fasting plasma insulin, and postprandial glucose and significantly increased insulin sensitivity index	22
30 mg/kg b.w. for 14 days	*in vivo*	Intraperitoneal	STZ-induced diabetic SD rats	decreased serum blood glucose levels, enhanced insulin levels, and improved dyslipidemia, decreased oxidative stress injury	23
10 and 15 mg/kg b.w. for 2 weeks	*in vivo*	Intraperitoneal	STZ-induced diabetic SD rats	regenerated pancreatic islets, increased insulin release, and reduced blood glucose and urine sugar levels.	24
10 and 15 mg/kg b.w. for 8 weeks	*in vivo*	Intraperitoneal	alloxan-induced diabetic mice	decreased serum glucose levels and oxidative stress and inhibited apoptosis	25
50 and 80 mg/kg b.w. for 45 days	*in vivo*	Oral	STZ-induced diabetic Wistar rats	regulated hyperglycemia, decreased the level of glycoprotein, scavenged ROS; modulated hepatic metabolism and antioxidant enzymes	26
100 mg/kg b.w. for 49 days	*in vivo*	Oral	STZ-induced diabetic SD rats	attenuated fasting and postprandial hyperglycemia, reduced blood glycated hemoglobin	20
25, 50 and 75 mg/kg for 28 days	*in vivo*	Oral	STZ-induced diabetic Wistar rats	decreased blood glucose and urine sugar. Enhanced plasma insulin and hemoglobin levels	27
100 and 200 mg/kg b.w. for 6 weeks	*in vivo*	Oral	STZ-induced diabetic Wistar rats	controlled the blood sugar, decreased insulin resistance, and protected pancreatic cells	28
50 mg/kg/day 4 weeks	*in vivo*	Intraperitoneal	after 2 weeks of HFD-fed, albino rats i.p. with a low dose of STZ 35 mg/kg	lowered blood glucose, increased serum insulin levels, preserved β-cell mass and function by increasing antioxidant activity	29
diet containing Que at 0.04% (wt/wt) and 0.08% for 6 weeks	*in vivo*	Oral	Type 2 diabetes C57BL/KsJ-db/db mice models	decreased plasma total cholesterol and increased HDL cholesterol, decreased lipid peroxides, attenuated mitochondrial dysfunction	30
50 and 100 μM	*ex vivo*		cultured C2C12 skeletal muscles	activated glucose uptake through an insulin-independent mechanism involving AMPK	31
	ex vivo		cytological experiments on skeletal muscles	decreased blood sugar level, increased GLUT4 expression, strengthened glucose uptake on skeletal muscle cells surface by stimulating AMPK	32
0.08% of diet combined with acarbose (0.03% of diet)	*in vivo*	Oral	db/db Mice	decreased plasma glucose level and improved insulin resistance, reduced cyclic adenosine phosphoric acid (cAMP) accumulation and the influx of free fatty acids, activated protein kinase A (PKA), preserving cyclic nucleotide-dependent phosphodiesterase 3B (PDE3B), and accumulating two acylglycerol (DAG)	33
			Effect on Diabetic Complications, (A) Effect on Diabetic Liver Disorders		
50 mg/kg b.w., per day for 30 days	*in vivo*	Oral	STZ-induced diabetic rats	increased CYP2E1 activity, reduced oxidative stress in liver, and decreased markers of liver damage	34
50 mg/kg daily for 7 days	*in vivo*	Oral	Alloxan-induced diabetes (75 mg/kg) in mice	decreased the number of vacuolated cells and the degree of vacuolization	35
15 mg/kg	*in vivo*	Intraperitoneal	STZ-induced diabetic rats	exerted significant preventive effect on liver cell damages	36
			(B) Effect on Diabetic Reproductive Disorder		
25 or 50 mg/kg for 5 weeks	*in vivo*	Oral	STZ-induced diabetic SD rats	enhanced sexual activity and mount frequency (MF) and intromission frequency (IF), also increased sperm count as well as motility	37
50 mg/kg for 5 weeks	*in vivo*	Oral	STZ-induced diabetic rats	reduced testicular damage	38
15 mg/kg for 8 weeks	*in vivo*	Oral	STZ-induced apoptosis of testicular cells in rats	attenuated diabetes-related testicular dysfunction and histopathologic changes	39
			(C) Effect on Diabetic Neurodegenerative Disorders		
5−20 mg/kg twice daily for 30 days	*in vivo*	Oral	STZ-induced diabetic rats	prevented changes in blood glucose, body weight, and performance in Morris water test and elevated the performance in plus-maze tasks	40
40 mg/kg, twice daily for 31−35 days	*in vivo*	Oral	STZ-induced diabetic mice in Morris water maze task	decreased escape latency and increased the time spent by mice in the target quadrant during the Morris water maze task	41
2.5, 5, and 10 mg/kg for 20 days		Intragastric	STZ-diabetic-induced brain injuries	decreased cerebral blood flow (CBF) and blood glucose level, prevented memory impairment, increased antioxidant enzymes activity, and attenuated brain energy metabolism and cholinergic dysfunction	42

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Table 1. continued

doses	*In vitro/in vivo/ex vivo*	route of administration	model	effect	refs
			(D) Effect on Diabetic Retinopathy		
150 mg/kg was administered per day for 20 weeks	*in vivo*	Gastric perfusion	diabetic retinopathy in adult male STZ-induced SD rats	alleviated retinopathy via downregulation of monocyte chemoattractant protein-1 (MCP-1), matrix metalloproteinase-9 (MMP-9), and vascular endothelial growth factor (VEGF) expression levels	43
			Cardiovascular Effect		
0.05 to 5 mg/kg	*in vivo*	Intravenous	conventional and spontaneously hypertensive rats	lowered blood pressure in both short- and long-term basis	44
88.7 μmol/kg p.o, 45 min; 14.7 μmol/kg i.v., 5 min	*in vivo*	Oral Intravenous	experimental anesthetized rats	potentiated the hypotensive impact of bradykinin (10 nmol/kg i.v.)	45, 46
1.5 g Que/kg for 7 days	*in vivo*	Oral	rat model	attenuated carotid hypertrophy and arterial blood pressure, reduced aorta medial wall thickening and normalized cardiac translocation	47, 48
5 mg/kg and 10 mg/kg for 5 several weeks	*in vivo*	Oral	nitro-L-arginine methyl ester hydrochloride (L-NAME)-induced high blood pressure in Wistar Kyoto mice	reduced mean arterial pressure (12%) and heart rate (in STR) after 13 weeks	49
10 mg/kg b.w., for 6 weeks	*in vivo*	Oral	STZ-induced suffering from diabetes male Wistar Kyoto mice	regenerated vascular function and reduced blood vessels sugar level and oxidative pressure	50
20 mg/kg/day for 4 weeks	*in vivo*	Oral	young male normotensive control (C) and automatically hypertensive rats (SHR) over the period of their 5−8th week of age	damaged Na, K-ATPase action when all ATP and Na levels examined	51
10 mg/kg/day for 7 days	*in vivo*	Oral	pretreatment to Wistar mice before induction of myocardial infarction by subcutaneous hypodermic injection of isoproterenol (100 mg/kg) at a period of 24 h for two times	reduced ST-segment level, decreased fat peroxidation in plasma and heart, and decreased free fatty acids levels in serum, serum phospholipids, total cholesterol, and triglycerides.	52
			Autophagy		
20 μM	*in vitro*		human umbilical vein endothelial cells (HUVECs)	promoted cell survival	53
100 mg/kg (in vivo) and 10−60 μmol (in vitro)	*in vitro* and *in vivo*	Intragastric	pulmonary arterial smooth muscle cells (PASMCs)	induced apoptotic and autophagic responses	54
100 mg/kg	*in vivo*	Gavage	C57BL/6J mice on ethanol-containing Lieber De Carli liquids diets	reduced ethanol-induced liver injury and suppressed autophagic flux	55
			Anti-Alzheimer's Effect		
50 mg/kg b.w., 2 times a week for 4 weeks	*in vivo*	Oral	homozygotic transgenic mouse line B6.129S7-Sod2tm1Leb/J Hydrogen peroxide- and Aβ-induced neurotoxicity	decreased ROS levels, improved the typical morphology of mitochondria, prevented mitochondrial dysfunction	56
50 mg/kg b.w., every day for 10 weeks	*in vivo*	Oral	male C57BL/6J mice AMP-activated protein kinase activity on tau hyperphosphorylation	enhanced AMP-activated protein kinase activity, reduced tau hyperphosphorylation, and improved cognitive deficit	57
25 mg/kg b.w., every 2 days for 2 months	*in vivo*	Oral	male SAMP8 mice model of AD	improved cognition deficit, enhanced memory impairments, reduced astrogliosis	58
30 mg/kg b.w. every day for 8 days	*in vivo*	Intraperitoneal	scopolamine-induced cognitive dysfunction and neurodegeneration in male albino Wistar rats	abridged transfer latency, reduced avoidance response, decreased in 3,4-methylene dioxy amphetamine, acetylcholinesterase levels, increased brain catalase and glutathione levels	59
10 mg/kg b.w. every day for 12 weeks	*in vivo*	Oral	aluminum-induced neurodegeneration in male albino Wistar rats	decreased ROS production, amplified mitochondrial superoxide dismutase activity	60
25 mg/kg b.w. every day for 3 months	*in vivo*	Intraperitoneal	triple transgenic mouse model of AD	reduced Alzheimer's pathology, protected cognitive deficit, improved emotional function	61
500 mg/kg b.w. every day for 10 days	*in vivo*	Oral	five familial transgenic mouse model of AD	increased brain apolipoprotein E, reduced insoluble Aβ levels	62
1% in mouse chow for from 3 to 13 months	*in vivo*	Oral	double transgenic female mice mouse model of AD	decreased neuroinflammation, reduced neurodegeneration	63
10 and 50 mg/kg b.w. at 30 min, 12 h, and 24 h after subarachnoid hemorrhage	*in vivo*	Intraperitoneal	adult male SD rats, rat model of subarachnoid hemorrhage	improved brain damage, provided neuroprotection	64

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Table 1. continued

doses	*In vitro*/*in vivo*/*ex vivo*	route of administration	model	effect	refs
			Anti-Alzheimer's Effect		
5 and 10 μM	*ex vivo*		cultured neurons Aβ42-induced oxidative cell toxicity	decreased oxidative stress, reduced neurotoxicity	65
	ex vivo		cell culture (PC12) H_2O_2-induced neurodegeneration	reduced oxidative stress, abated neurotoxicity	66
0.5% in AIN93G diet for 5 weeks	*in vivo*	Oral	Aβ precursor protein 23 mice murine model of AD	reduced memory dysfunction, decreased oxidative stress	67
			Wound Healing Effect		
0.1, 1.0, and 10.0% concentration (w/v)	*in vivo*	Topical	experimentally wounded male rats	reduced wound area and increased wound contraction	68
			Antiarthritic Effect		
10−100 mg/kg	*in vivo* mice	Intraperitoneal	TiO_2-induced arthritis model	inhibited knee joint mechanical hyperalgesia, edema and leukocyte recruitment	69
30 mg/kg	*in vivo* mice (C57BL/6 mice)	Oral	collagen-induced arthritis (CIA)	reduced arthritic inflammation and protected cartilage and bone from destruction.	70
			Antimicrobial Effect		
100 mg/kg	*in vivo* mice	Subcutaneous	*Streptococcus suis* (virulent SS2 ZY05719 strain)-infected mice	reduced *Streptococcus suis* virulence	71
5−30 mg/kg (in vivo) and 10−250 μM (in vitro)	*in vitro* and *in vivo*	Intraperitoneal	human mononuclear and polymorphonuclear leukocytes, and rat whole blood.	protected from gentamicin-induced oxidative stress	72
			Effect on Liver Diseases		
100 mg/kg	*in vivo* mice	Oral	chronic-plus-single-binge-ethanol feeding C57BL/6J mice	protected liver from ethanol-induced liver fat accumulation and liver damage	73
5−20 mg/kg	*in vivo* rats	Subcutaneous	rotenone-induced hepatocellular dysfunction	attenuated rotenone-induced liver-metabolic imbalances	74
			Antioxidant Effect		
30 mg/kg b.w.	*in vivo*	Orally	streptozotocin-induced diabetic rat	decreased lipid peroxidation in both serum and liver tissue and controlled oxidative stress	75
5.7 μM (for DPPH assay) and 0.78 μM (Fe^{3+}-EDTA/H_2O_2 system)	*in vitro*		erythrocytes	exerted free-radical scavenging and ROS scavenging activity	76
87.5, 90.4, and 78.6 μg/mL (for DPPH, FRAP, and OH radical scavenging assays, respectively)	*in vitro*			attenuated oxidative stress through decreasing DPPH and OH radicals and reduction of ferric iron.	77
10 mg/kg b.w.	*in vivo*	Intraperitoneal	LPS-mediated oxidative stress in spleen and bone marrow of *Funambulus pennanti*.	increased SOD, catalase, and GPx activities and decreased lipid peroxidation of bone marrow and spleen tissues	78
different serial concentrations from 3.33 mg/mL stock solution	*in vitro*			attenuated oxidative stress	79
25 and 50 mg/kg b.w. day for 6 days	*in vivo*	Orally	phenylhydrazine-mediated oxidative stress male SD rats	controlled oxidative injury through modulating gene expression, and suppressed ROS generation, improved arterial blood pressure as well as resistance of peripheral vascular; increased response to bradykinin, acetylcholine, as well as phenylephrine in a dose-dependent manner; controlled blood glutathione; decreased plasma MDA levels, nitric oxide and superoxide anions.	80

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had shown that Que is a promising drug target for treating diabetes (Table 1). A number of mechanisms have been proposed for the antihyperglycemic action of Que, among which insulin sensitivity enhancement, glycogen synthesis promotion, and insulin resistance improvement are common. Que promotes the insulin sensitization effect by stimulating pancreatic β-cell proliferation, improving glucose metabolism and insulin secretion.[19] Que has also been reported as an α-glucosidase and α-amylase inhibitor.[20] In addition, Que improved plasma insulin levels and decreased blood glucose in streptozotocin (STZ)-induced diabetes models through maintaining the mass and function of β-cells and thus increasing the serum insulin effect. On the other hand, in alloxan-diabetic animal models, Que reduced islet cell failure, enhanced the insulin secretion of β-cells, and further prevented diabetes through decreasing oxidative stress.[21]

Que stimulate glucose uptake on isolated cells through stimulating the GLUT4 expression and endogenous GLUT4 translocation by upregulating the estrogen receptor-α, subsequently enhancing phosphorylation of both phosphatidylinositol-3-kinase/Akt (PI3K/Akt) and AMP-activated protein kinase/Akt (AMPK/Akt) signal pathways, increasing the glucose uptake in skeletal muscle cells.[31,32] Que enhances the glucose utilization by acting on glucose transport and insulin-receptor signaling, which plays a similar role to rosiglitazone such as glycogen phosphorylase (GP) and peroxisome proliferator-activated receptor γ (PPARγ) agonist.[81,82] The molecular interactions of the ligands, Que, gallic acid, and metformin were compared on various diabetes mellitus-related protein targets, such as GP and PPARγ. Que possesses good binding affinity to both targets.[27]

Que could restore the interference caused by hyperglycemia by modulating endothelial nitric oxide synthase (eNOS) and inducible nitric oxide synthase (iNOS).[83,84] In addition, Que may activate silencing factor 1 (silent information regulator 1, SIRTl) to increase insulin sensitivity.

2.1.1.1. Effect on Diabetic Liver Disorders. The increase of CYP2E1 in liver in the case of diabetes has been reported[85] thus and the enzyme inhibition mainly prevents the liver oxidative damage. In an in vivo study on rats, it was found that STZ-induced diabetes caused hyperglycemia, body weight loss, damaged hepatocyte ultrastructure, together with increased protein levels and CYP2E1 activity in liver. Thus, Que administration (50 mg/kg b.w., per day, during 30 days) led to a marked decrease in CYP2E1 activity, together with pro-oxidant−antioxidant balance promotion.[86] Other studies are shown in Table 1.

2.1.1.2. Effect on Diabetic Nephropathy. Que may improve the kidney shape altered by hyperglycemia through protein kinase C (PKC) activity inhibition, transforming growth factor β 1 (TGF-β1) expression downregulation, extracellular matrix formation reduction, and renal hypertrophy delay.[87] Que can also prevent renal pathological changes, delay diabetic nephropathy progression, and improve the glycolipid metabolism in type 2 diabetic rats. Moreover, Que could prevent diabetes-induced oxidative stress in renal tissues.[88] Que attenuated the tissue dyslipidemic due to lipid deposits in diabetic rats with kidney disease via activating AMPK phosphorylation and suppressing sterol regulatory element binding protein (SREBP)-1c in kidney, thereby preventing renal progression.[89]

2.1.1.3. Effect on Diabetic Reproductive and Neurodegenerative Disorders. Many animal studies proved the improving effect of Que on diabetes-induced reproductive dysfunction processes, such as sexual dysfunction, testicular dysfunction, or infertility (Table 1). Moreover, studies that proved the Que protective effect on diabetes-induced neurodegenerative diseases are shown in Table 1.

2.1.1.4. Effect on Diabetic Retinopathy. The involved mechanisms in diabetes-induced diabetic retinopathy mainly include oxidative stress, inflammation, neurodegeneration, and damaged retinal vasculature.[90] An *in vitro* experiment on human retinal endothelial cells proved that Que inhibited high-glucose-induced cell proliferation by reducing the vascular endothelial growth factor (VEGF) expression.[91] Furthermore, Que exerted protection against STZ diabetes-induced retinal neurodegeneration by reducing oxidative damage and NF-κB-mediated inflammation,[92] ameliorating neurotrophic factors levels and inhibiting the neurons apoptosis.[93]

2.1.2. Effect on Cardiovascular Diseases. Many studies were traced on the effects of Que on cardiovascular diseases (Table 1). The inhibitory effect of Que on the angiotensin-converting enzyme activity by converting bradykinin and angiotensin I was studied by Häckl et al.[45] Bradykinin has a more significant effect on the blood pressure in rats on pretreatment with captopril or Que. Que also reduced the hypertensive response to angiotensin I.[94] Moreover, the long-term use of Que diminished the risk of elevation of systolic blood pressure (SBP) levels in spontaneously hypertensive rats with a limited or full protection of most of the consequences caused by N^{ω}-Nitro-L-arginine methyl ester hydrochloride (L-NAME).[49]

Moreover, the effects Que on vasoconstrictor and vasodilator reactions in the porcine-separated heart were studied by Suri et al.[95] who reported that Que enhances both the cyclic guanosine monophosphate (cGMP) content of the artery and cGMP-dependent relaxations to glyceryl trinitrate (GTN) and sodium nitroprusside (SNP) as well as restricted receptor-mediated contractions of the porcine. In addition, Que at nutritionally essential levels reduced the responsiveness of typical L type Ca^{2+} channels to the pharmacological stimulation managed by (*S*)-(−)-methyl-1,4-dihydro-2,6-dimethyl-3-nitro-4-(2-trifluoromethylphenyl) pyridine-5-carboxylate (Bay K 8644), leading to cardioprotection. Dietary Que and its derivative epicatechin can improve the endothelial function through modulation of the blood nitric oxide concentration; they can also inhibit nicotinamide adenine dinucleotide phosphate oxidase (NADPH oxidase) that activates eNOS and hence enhance vascular activity.[96]

Another research has confirmed Que safety effect against myocardial ischemia-reperfusion injury (MIRI) in rabbits.[97] Que restricted MIRI-induced NADPH oxidase 2 (NOX2), eNOS, and iNOS mRNA and protein expression. The actions of extracellular signal-regulated kinase (ERK1/2), p38 MAP kinase (mitogen-activated protein kinase), Akt, and glycogen synthase kinase-3 β (GSK3β) were considerably enhanced with pressure overload and attenuated by Que therapy. Moreover, Que may also improve the cardioprotective impact of amlodipine against damage activated in the heart by ischemia/reperfusion.[98]

Que also reduced the transcriptional action of NF-κB in human hepatocytes.[99] In human C-reactive protein (CRP) transgenic mice, Que quenched interleukin-1β (IL-1β)-induced CRP appearance, as effected by sodium salicylate. In mice, Que significantly attenuated coronary artery illness by 40% (sodium salicylate by 86%).[99] Yan et al.[100] hypothesized

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that the Que heart hypertrophy prevention may be modulated by preventing activator protein 1 (c-fos, c-jun proteins) and initiating PPAR-γ signaling pathways.

Furthermore, in rat aorta, Que (0.1−100 μM) relaxed the contraction induced by pretreatment with 5 mM norepinephrine in a concentration-dependent manner. Finally, it was concluded that Que induces Ca^{2+} elevation, leading to NO production and Ca^{2+}-activated K^+ (KCa) channel activation in endothelium cell.[101] Wang et al.[102] reported that Que may act as a cardioprotector by initiating the PI3K/Akt signaling process and modulating the expression of Bcl-2 and Bax proteins through a study on male Sprague−Dawley rats.

In a placebo-controlled double-blind study, administration of 730 mg of Que per day for 28 days caused significant reductions in systolic (−7 ± 2 mm Hg), diastolic (−5 ± 2 mm Hg), and mean arterial pressures (−5 ± 2 mm Hg) in level 1 hypertensive patients.[103] Overweight or obese subjects ranged between 25 and 65 years were exposed to a double-blind study of 6 weeks to examine the effects of Que (150 mg Que daily).[104] Que plasma concentrations in fasting conditions increased from 71 to 269 nmol/L during Que treatment. Moreover, Que reduced SBP and HDL cholesterol levels, while total cholesterol levels, triacylglycerol (TAG), and the LDL:HDL cholesterol and TAG:HDL cholesterol rates were unaltered.

Que showed anti-inflammatory properties in patients with coronary artery disease (CAD), through a decrease in the transcriptional activity of the NF-κB. To prove this effect, Chekalina et al.[105] designed a study to determine the effect of Que on the indicators of chronic systemic inflammation in CAD patients. The study involved 85 CAD patients, stable angina pectoris, functional class II, and heart failure.[105] Thirty patients received Que at a daily dose of 120 mg for 2 months, while the remaining 55 patients considered as the control group received β-blockers, statins, and aspirin. An increase in the levels of IL-1β and tumor necrosis factor-α (TNF-α) and a moderate increase in IL-10 levels were detected in the serum of patients with CAD. Under the influence of Que, levels of IL-1β and TNF-α were reduced and IL-10 levels tended to decrease. Also, Que decreased the expression of the inhibitor of kappa $\beta\alpha$ (Ik$\beta\alpha$) gene relative to the control group.

In a 10-week double-blind randomized clinical test on 72 females having type 2 diabetes, the subjects were assigned to Que (500 mg capsule daily) and placebo groups. The biochemical parameters were compared between the baseline and the end of the study. Consequently, Que consumption reduced systolic hypertension considerably relative to the placebo group, and the HDL levels were significantly reduced in both categories along with changes in total cholesterol levels, LDL, and triglycerides. Moreover, Que decreased the serum concentration of TNF-α and IL-6.[106]

In another clinical study, 23 healthy men were fed 4.3 g of onion extract (containing 51 mg of Que) once a day for 30 days.[107] The onion extract consumption did not considerably affect fasting flow-mediated vasodilation (FMD) but enhanced the postprandial FMD considerably.

2.1.3. Autophagy. Autophagy is a degradation process through which macromolecules, misfolded proteins, and organelles are degraded by lysosomes and recycled,[108] which constitutes an indispensable process for cellular homeostasis.[109] In this context, targeting autophagy by natural products is considered a potential therapeutic strategy for the prevention and treatment of several disorders.

Que has been reported to promote autophagic responses and thus protects human umbilical vein endothelial cells (HUVECs) against high-glucose-induced damage.[53] This study showed that Que can significantly promote cell survival via the induction of glutathione (GSH) and Beclin-1 and microtubule-associated protein light chain-3- II (LC3-II)/LC3-I ratio as well as reduction of oxidative stress marker levels. This promising activity can be beneficial in ECs insufficiency, and this will provide a high therapeutic potential for diabetic angiopathy.[53]

Similarly, Que has significant capacity to induce apoptotic and autophagic responses in pulmonary arterial smooth muscle cells (PASMCs).[54] This activity was connected to the ability of Que to induce the expression and transcriptional activity of the autophagy regulator, forkhead box protein O1 (FOXO1). This indicates that Que is a promising candidate for treating hypoxia-associated pulmonary arterial hypertension via promoting hypoxia-induced autophagy. This is specifically applied in combination with autophagy inhibitors.[54]

Intriguingly, Que has significant abilities to ameliorate lysosome damage-mediated autophagy dysfunction in alcohol liver disease (ALD).[55] mTOR-TFEB-mediated activity was associated with the induction of lysosomal-associated membrane protein 1 (LAMP-1), LAMP2, and Ras-related protein (Rab7) expression as well as reduction of LC3-II and p62 levels.[55]

2.1.4. Effect on Alzheimer's Disease. Que is used for the development of anti-Alzheimer's disease (AD) formulations due to its neuroprotective effect against oxidative stress and excitotoxicity via regulating apoptosis mechanisms.[65] Diverse mechanisms have been suggested for the Que neuroprotective actions including amyloid-β (Aβ) aggregation inhibition, intracellular neurofibrillary tangles (NFTs) formation inhibition, amyloid precursor protein (APP) inhibition, cleaving enzyme (BACE1) inhibition, acetylcholinesterase (AChE) inhibition, and others attenuating the oxidative stress in AD (Table 1).

Que and its bioactive molecules are helpful to ameliorate neurogenesis and neuron longevity modulating signaling pathway such as P13 kinase, AKT/PKB tyrosine kinase, and protein kinase C in AD.[61,110]

Many *in vitro* studies demonstrated that the hydroxylfunctional groups of the B-ring of Que play an important role in Aβ aggregation inhibition and disrupt the mature fibrils by forming hydrogen bonds with the β-sheet structure of Aβ.[110] Moreover, other studies have shown that Que increased *in vitro* neuronal culture survival.[17] Additionally, Que at 100 μM displayed a considerable inhibition of β-site APP cleaving enzyme 1 (BACE1) *in vitro* in a cell-free system by 11.85%.[111]

The other characteristic pathological implication of AD is the appearance of NFTs, with the core protein being tau, and its accumulation into tangles involves phosphorylation.[112] Que efficiently inhibited tau pathology via different mechanisms such as reducing hyperphosphorylation of tau protein with retrogressive action on the hyperphosphorylation process,[111] inhibiting GSK3β activity and consequently inhibiting hyperphosphorylation of tau protein or possessing anti-HSP70 activity, and thus reducing tau pathology via attenuating the hyperphosphorylated tau level.[110]

The decline in cholinergic neurotransmission is a reliable and early symptom of AD, and AChE is a noteworthy therapeutic target for symptomatic improvement in AD.[113] Que *in vitro* competitively inhibits AChE and diminished

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AChE activity in the hippocampal region.[110] In one study, Que (50 mg/kg b.w.) stopped the increase of AChE activity due to diabetes in the cerebral cortex and hippocampus. In relation to this, through restoring the function of acetylcholine (ACh), Que mitigated the cholinergic signaling and facilitated regaining lost memory in diabetic rats.[114] In another study, a single dose of Que avoided the memory impairment caused by scopolamine.[115] Moreover, a molecular docking study predicted that Que is superior to conventional AchE inhibitor drugs.[116]

2.1.5. Effect on Tyrosinase Activity. Tyrosinase is the key enzyme in the pathway of melanogenesis, which involves three pigmentary specific enzymes in melanosomes[117] and is widely present in mammalians, plants, bacteria, and fungi.[118,119] Tyrosinase catalyzes the hydroxylation of monophenols to *O*-diphenols (monophenolase activity), then to *O*-quinone (diphenolase activity), and finally to melanin. Excessive melanin accumulation leads to several pigmentation disorders, such as melasma age spots, freckles, and melanoma.[120] Inhibiting tyrosinase overexpression may decrease the generation of melanin. Que could inhibit both monophenolase and diphenolase activities of tyrosinase, and it inhibits diphenolase reversibly and competitively (IC_{50} of $3.08 \pm 0.74 \times 10^{-5}$ mol/L).[121]

2.1.6. Effect on Arthritis. Arthritis is associated with decreased motion anility, and its symptoms generally include swelling, pain, stiffness, and redness.[122] There are over 100 types of arthritis, and the most common are osteo, gout, and rheumatoid arthritis. Genetic, hormonal, and environmental factors have been related to arthritis. Treatment of arthritis includes drug steroids, nonsteroidal anti-inflammatory drugs (NSAIDs), and/or surgery.[123,124] A prolonged use of steroids may lead to osteoporosis and fractures, while a prolonged use of NSAIDs can lead to gastric ulcers and renal damage. Chronic joint inflammation can lead to destruction of joints, thus requiring partial or total replacement of the destroyed tissues surfaces via arthroplasty.[124]

Que was reported to reduce pain and inflammation associated with arthritis.[69] This dietary flavonoid inhibited, in mice, knee joint mechanical hyperalgesia, edema, and leukocyte recruitment in a dose-dependent manner without adverse effects on other organs such as liver, kidney, or stomach.[69] Que mechanisms included inhibition of oxidative stress, cytokines and COX-2 production, and proteoglycan degradation as well as activation of nuclear factor-erythroid 2-related factor 2/heme oxygenase-1 (Nrf2/HO-1) signaling pathway.[69]

Additionally, Que has been reported as a potential drug for the treatment of rheumatoid arthritis.[70] The administration of Que was effective alone than methotrexate or in combination with methotrexate to reduce joint inflammation, in mice, and to provide the highest protection.[70] The mechanisms included reduction of TNF-α, IL-1β, IL-17, and monocyte chemoattractant protein-1 (MCP-1) levels.

Therefore, Que represents a promising natural compound to treat pain and inflammation associated with arthritis.

2.1.7. Effect on Microbial Infections. *Streptococcus suis* is a globally distributed zoonotic Gram-positive bacterial pathogen.[125,126] *S. suis*-associated human infection, mostly from the pig industry, may lead to meningitis, septicemia, endocarditis, and deafness.[127] Suilysin, a cytotoxic toxin secreted by *S. suis*, plays a potential role in infection. Thus, the effective interference of suilysin is a line of defense in the treatment of *S. suis* infection.

Que has been shown, in mice, to inhibit suilysin activity as well as decreasing *S. suis*-induced cytotoxicity. Its mechanism included the effective reduction IL-1β, IL-6, and TNF-α levels.[55] Additionally, Que was effective to inhibit reactive oxygen species (ROS) production and lipid peroxidation in gentamicin-induced oxidative stress.[72] Intriguingly, this study, which was performed *in vitro* on human leukocytes and *in vivo* on whole rat blood, showed that Que has more inhibitory capacity than ascorbic acid, the reference inhibitor.[72] Thus, Que may be considered as a potential candidate for the treatment of *S. suis* infection by targeting suilysin and its associated inflammation.

2.1.8. Effect on Liver Diseases. Liver plays an indispensable role in energy metabolism, protein synthesis, production of biochemicals necessary for digestion, and detoxification of various metabolites and drugs.[128] According to recent statistics, liver diseases cause approximately 2 million deaths/year worldwide, accounting for approximately 3.5% of worldwide deaths.[129] Additionally, alcohol consumption was reported, according to the global burden of disease (2018), to account for approximately 10% of global deaths among populations aged 15−49 years in 2016.[73] Que was shown to ameliorate ethanol-induced liver steatosis in chronic-plus-binge-ethanol feeding mice.[73] This therapeutic potential was associated with the improvement of lipophagy. Additionally, Que attenuates liver damage, increased serum triglyceride, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) levels.[73] Moreover, some xenobiotics can have severe adverse effects leading to liver toxicity. Among xenobiotics, rotenone, a natural pesticide, has been reported to cause liver toxicity.[130] Que displayed significant ameliorative activity in rotenone-induced hepatocellular dysfunction.[74]

2.1.9. Anticancer Effects. Many reports were detected on the anticancer activity of Que, and they are summarized in Table 2.

2.1.10. Antiparasitic Activity of Quercetin. Despite the pharmacological properties of Que, interest has been focused on its antiparasitic potential. In this sense, the capacity of this flavonol to affect the parasite growth and disease progression has been demonstrated in different preclinical models, as well the potential of Que-related compounds (Table 3). In this sense, the main reports have been dedicated to evaluate the *in vitro* potentialities on the main protozoa parasites that cause the major mortality and morbidity, including *Leishmania*, *Trypanosoma*, and *Plasmodium*. Nevertheless, other reports related to activity against *Toxoplasma gondii*, *Giardia lamblia*, and *Entamoeba histolytica* have also been evidenced (Table 3).

In another context, the antiparasitic activity of several natural-derived products has been attributed to the presence of Que or derived compounds (Table 4), which constitutes one of the most common metabolites in plants. Currently, an attractive alternative to synthetic drugs is the search for active molecules from natural sources, such as the medicinal plants that have been used in the treatment of parasites since ancient times. As could be observed, several plant-derived products with antiparasitic activity have been correlated with the presence of Que or some of the related compounds. In general, different families and plant species have been studied on parasites of medical relevance, including protozoa and helminths. Also, in this case, we note that some studies have

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Table 2. Reported Anticancer Activity of Quercetin

extract/compound	doses	*In vitro*/*in vivo*	route of administration	model	effect	refs
Que	5 μM	*in vitro*		H1975 and A549 human lung cancer cell lines	Que significantly inhibited nickel-mediated invasion in H1975 and A549 human lung cancer cell lines; inhibited inflammatory mediators secretion; inhibited mRNA as well as protein expression of TLR4 and Myd88; reduced IKKβ as well as IκB phosphorylation; reduced NF-κB nuclear level; reduced MMP-9 expression; TLR4/NF-κB signaling pathway deactivation.	131
Que	50 and 75 μM	*in vitro*		PA-1 human ovarian cancer cell line	Que significantly reduced cell viability through a dose-dependent manner; enhanced apoptosis in invasive ovarian cancer cell lines (further assured by AO/EtBr dual stain, DAPI stain as well as DNA fragments); reduced Bcl-2 and Bcl-xL; increased Bad, Bid, Bax, caspase 3, caspase 9, as well as cytochrome c; enhanced mitochondrial-induced apoptotic pathways, so suppresses the invasive ovarian cancer cell growth.	132
Que	50 μM	*in vitro*		HSC-6 and SCC-9 human oral cancer cells	Que inhibited viability of cells, their migration and invasion (using MTT assay and western blot assay); decreased MMP-9 and MMP-2 abundance; downregulated miR-16 and upregulated HOXA10 (using qRT-PCR), where the relation linking miR-16 and HOXA10 has been tested using luciferase activity assay, RNA immunoprecipitation (RIP) as well as western blot analysis.	133
Que	10 mg/mL	*in vitro*		NPC039 nasopharyngeal cancer cell line.	Que decreased cell viability up to 36% compared to control after only 24 h (using MTT assay); suppressed VEGF expression and NF-κB activity (using RT-PCR and ELISA).	134
Que	40 μM	*in vitro*		LPS-mediated inflamed WI-38 lung fibroblast cells	Que may control LPS-mediated inflammation in lung fibroblasts through increasing cell viability and decreasing its apoptosis (using CCK-8 assay and Annexin V-FITC/PI Stain, respectively); reduced miR-221 expression level (using qRT-PCR), IL-6 as well as TNF-α (using ELISA) in the cells; suppressed NF-κB as well as JNK signaling pathways (using western blot).	135
Que	50 μM	*in vitro*		D44+/CD24− cancer stem cells and MCF-7 breast cancerous cell line.	Que may have a potential role in treating breast cancer through suppressing breast cancerous stem cells (CD44+/CD24−) via suppressing PI3K/Akt/mTOR- pathway; suppression of cell viability, formation of clones, and generation of mammospheres; arrest of G1 phase; suppression of Cyclin D1 as well as Bcell lymphoma2 overexpression; enhancement of Bcl-2-like protein4 expression; downregulation of α estrogen receptor.	136
Que	30 μM	*in vitro*		MCF-7 and MDA-MB-231 human breast cancer cell lines	Que may have a notable effect in controlling breast cancer through suppressing cancer cells mobility (trans-well invasion as well as wound healing assays) by suppressing glucose uptake as well as lactic acid production and reducing PKM2, GLUT1, and LDHA levels, so limiting the tumor cell migration; downregulation of MMP-2, MMP-9, and VEGF expression (western blot); induction of autophagy through deactivating Akt-mTOR pathway.	137
Que and its metabolites	IC_{50} value: Que 14.0 mg/mL and its metabolites, methyl-Que 11.0 mg/mL and Que glucuronide 4.0 mg/mL.	*in vitro*		HL-60 Leukemic cells	Que and its metabolites (after microbial transformation), methylQue and Que glucuronide, proved their efficacy as cytotoxic agents (using MTT as well as TB assays).	138
Que	50 mg/kg b.w./day, for 9 days.	*in vivo*	Intraperitoneal	cisplatin-induced toxicity in kidney and tumor tissues Male Fischer F344 rats	Que succeeded in controlling the nephrotoxicity caused by cisplatin without affecting its antitumor action through decreasing the oxidative stress, inflammation and apoptotic effects.	139
Que	40 μM	*in vitro*		CD44+/CD133+ and CD44+ prostate cancerous stem cells	Que may control prostate cancer in stem cells through inhibiting their proliferation through downregulation of MK expression, which led to reduction in cell migration and formation of spheroids; co-treatment of MK siRNA with Que decreased cell survival, increased apoptosis, and arrested G1 phase more efficiently than the single therapy; the co-therapy deactivated PI3K, AKT, and ERK1/2 pathways and decreased p38, ABCG2, and NF-κB expression.	140
Que	20, 40, 60, 80, or 100 μM	*in vitro*		U2OS and Saos-2 bone cancer cell lines	Que can inhibit cancerous cell proliferation and invasion through suppression of PTHR1 by reducing its expression; decreased cell viability and its adhesion and migration; attenuated MMP-2 and MMP-9.	141
Que	20 and 40 μM	*in vitro*		A431-III cell lines.	Que may have a potential effect in inhibiting metastasis of cancerous cells. Que decreased protein level as well as RPS19 activity through blockade of Akt/mTOR/c-Myc pathway.	142
Que	2, 4, and 8 μM	*in vitro*		Human A375 melanoma cells	Que combined with curcumin suppressed the cancerous cell proliferation through decreasing cell viability (MTT assay), decreasing the number of colonies (using colony assay), and altering Wnt/β-catenin signaling pathway (using western blot)	143
Que	20 μM	*in vitro*		Human MCF-7 breast cancer cell line	Que, combined with doxorubicin, enhanced the antiproliferative effect of breast cancerous cells through decreasing the cell viability (using SRB assay)	144
Que	20, 40, 60, and 80 μM	*in vitro*		Human SW480 cells and clone 26 colon cancer cell lines	Que decreased the cell viability of the cancerous cells (using MTT assay); decreased cyclin D1 expression (using RT-PCR and western blot); downregulation of Wnt/β-catenin pathway.	145
Que	20 μM	*in vitro*		4T1 murine mammary cancer cells	Que presented a dose-dependent suppression of cell progression and prompted apoptosis in cancerous cell; inhibited luciferase activity; inhibited Wnt/β-catenin pathway through decreasing β-catenin protein stabilization.	146

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Table 2. continued

extract/compound	doses	*In vitro*/*in vivo*	route of administration	model	effect	refs
Que	10 μM	*in vitro*		Human SK-Br3, MDA-MB-453, and MDA-MB-231 breast cancer cell lines	using a lower dose of Que also succeeded in arresting G1 phase of cancerous cell cycle through trapping E2F1; inhibited pRb phosphorylation of pRb; DNA damage; Chk2 activation; downregulated cyclin B1 as well as CDK1; inhibited the employment of NF-Y to cyclin B.	147
Que	25, 50, and 75 mg/kg b.w.	*in vivo*	Intraperitoneal	Murine Dalton's lymphoma cells transplanted- AKR strain mice	Que had a potential role in the downregulation of PKC activity due to their antioxidant activity; improved apoptotic potential, as detected by measures of caspase 3, caspase 9, PARP, PKCa, as well as nuclear condensation; decreased cell survival; stimulated death receptor-induced apoptosis through TNFR1 in the cancerous cells.	148

been conducted on animal models, which provide interesting and more comprehensive information.

As could be appreciated in previous overview (Tables 3 and 4), remarkable efforts have contributed to elucidate the Que mechanism of action. In this sense, the antiparasite effect has been correlated with the disruption of mitochondrial function and the inhibition of different important enzymes and molecules including heat shock proteins (HSP), acetylcholinesterase enzyme, DNA topoisomerases, and kinases. Probably, the different targeted molecules promote the death in parasite by apoptosis, which has been evidenced in particular with the increase of ROS and DNA degradation. In addition, indirect biological effects of Que could have positive antiparasite effects, due to the induction of microbicidal response such as the production of nitric oxide and some cytokines.

In general, the development of drugs to treat parasitic diseases has been scarce, due to the fact that these diseases are more often presented in developing countries. However, as can be appreciated, Que and derivatives could constitute a source to explore new drugs with a wide antiparasitic spectrum. Several studies have been reported to prove the *in vitro* activity; although few reports described potentialities of this flavonol in animal models. However, some formulation has been designed and evaluated on experimental *in vivo* model, which is described in next work.

2.2. Quercetin in Preclinical and Clinical Trials. *2.2.1. Preclinical Anticancer Effects.* Cancer is an important problem in both developed and developing countries. Plants are important and promising sources for the treatment of cancers as well as many other diseases due to the secondary metabolites that they contain. Therefore, scientists are trying to discover new plant species and new active substances against different types of cancers, as well.[181]

Polyphenols, flavones, and flavonoids have great anticancer potential in different types of cancers.[182] Que is an important flavonoid that might be considered as an important agent in various cancer cells, and since it is predominantly found in Western diet, we might benefit from its protective effect just by taking it via our diets of as a food supplement. Moreover, Que is considered to be a chemopreventive that acts on signal transduction pathways as modulators to prevent, inhibit, or reverse carcinogenesis. By this activity, it shows many activities such as apoptosis, cell migration, differentiation and proliferation, oxidative balance, and inflammation.[183] It also shows antioxidative activity and inhibits enzymes that activate carcinogens.[184]

2.2.1.1. Pancreatic Cancer Preclinical Effects. Zhou et al.[185] studied the efficacy of Que against pancreatic cancer, and it was observed that apoptosis resistance was reverted and proliferation, angiogenesis, cancer stem-cell marker expression were reduced with Que treatment, which is a dietary polyphenol. In another study by Serri et al.,[186] the combination of gemcitabine with Que exerted a synergistic effect especially in the migration of pancreatic cancer cells. Though this is an *in vitro* study, it is worth mentioning that since pancreatic adenocarcinoma is one of the most fatal types of cancer, it is resistant to drugs, demonstrates aggressive behavior, leads to unpredictable genetic mutations, and is usually diagnosed at a late stage and usually after metastasis.

2.2.1.2. Osteosarcoma Preclinical Effects. Osteosarcoma is a bone disease; it is known to be a malignant neoplasm mostly in teenagers and also in adults, and it is a worldwide health

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Table 3. Quercetin and Related Compounds with Reported Effects on Parasites of Medical Importance Using Different *In Vitro* or *In Vivo* Models

parasite target	experimental models/mechanism of action	refs
	Quercetin	
Encephalitozoon intestinalis	*in vitro*/antiparasitic activity	149
Giardia lamblia and *Entamoeba histolytica*	*in vitro*/high antigiardia activity and slight antiamebic activity	150
Leishmania amazonensis	*in vivo*/antileishmanial effect on due to the ROS generation and disrupted parasite mitochondrial function.	151
Leishmania braziliensis	*in vitro*/inhibition of promastigote forms due to the increase of the reactive oxygen species production, phosphatidylserine exposure, and loss of plasma membrane integrity. Reduction of parasites number in infected macrophages associated with the reduction of TNF-α and increase of IL-10 synthesis.	152
Leishmania donovani	*in vitro*/high activity but slight selectivity for parasite DNA topoisomerase I	153
Leishmania mexicana	*in vitro*/inhibition of parasite cathepsin L	154
Leishmania panamensis	*in vitro*/selective inhibition of nuclear DNA topoisomerase II enzymes from promastigotes	155
Plasmodium falciparum	*in vitro*/antiplasmodial potential	156
Plasmodium falciparum and *Plasmodium berghei*	*in vivo*/high reduction of parasitaemia in animal model	157
Toxoplasma gondii	*in vitro*/inhibits the synthesis of heat shock proteins (HSP90, HSP70, and HSP27).	158
Trypanosoma brucei	*in vitro*/inhibition of RNA triphosphatase Cet1	159
Trypanosoma brucei	inhibition of hexokinases 1	160
Trypanosoma brucei	*in vitro*/caused a loss of mitochondrial membrane potential and marked DNA degradation.	161
Trypanosoma brucei gambiense	*in vitro*/induced the death of parasite by apoptosis	162
	4-Hydroxycoumarin Derivatives (Isosters of Quercetin)	
Trypanosoma cruzi	*in vitro*/moderate trypanocidal activity	163
	Isoquercitin	
Entamoeba histolytica	*in vitro*/inhibition of parasite viability and growth	164
	Quercetin Analogues	
Plasmodium falciparum	*in vitro*/antiplasmodial potential	156

problem. Que is reported to be beneficial against this disease by inhibiting the proliferation and apoptosis of human osteosarcoma cells U2OS/MTX300. It also reduces the invasion, adhesion, proliferation, and migration of osteosarcoma cells with the inhibition of parathyroid hormone receptor 1.[141]

2.2.1.3. Ovarian Cancer Preclinical Effects. Ovarian cancer is a fatal form of reproductive cancers due to its late diagnosis and silent and obscure symptoms,[182] and it is the most leading cause of mortality among other gynecological cancer types.[187] Common cancer therapies also tend to encounter resistance by these cells. On the other hand, Que was shown to be cytotoxic to cancer cells but does not exert harmful effect on health ones. It is considered to show effect due to its anti-inflammatory, pro-oxidative, apoptotic, cell cycle arrest induction, and antiproliferation effects and is known to be an ideal agent especially in combination with other anticancer drugs.[188]

In the treatment of ovarian cancer, usually platinum drugs (i.e., cisplatin, oxaliplatin) are used. However, these drugs have side effects and lead to drug resistance; therefore, other solutions were sought. In a study in which two human epithelial ovarian cancer cell lines (A2780 and its cisplatin resistant form A2780^{cisR}) were used, it was concluded that the administration of Que 2 h before the usage of platinum drugs might sensitize cancer cells to the action of platinum drugs, and this would be beneficial in dealing with the development of drug resistance.

2.2.1.4. Breast Cancer Preclinical Effects. The beneficial property of Que was established in 1995 in a study by Singhal et al.,[189] in which it was recommended in the treatment of relapsed breast carcinoma cases that cannot be operated. In highly invasive breast cancer cells, Que was administered along with doxorubicin and it was found to potentiate the antitumor effects of the synthetic drug. By combining these two substances together, Que was also shown to reduce the side effects of the synthetic drug in nontumoral cells; therefore, it is considered to be a promising agent in the development of chemotherapeutic combinations in the treatment of breast cancer.[190]

2.2.1.5. Cervical Cancer Preclinical Effects. Que was found to be beneficial against cervical cancer in addition to ovarian cancer and breast cancer. It exerts this effect via p63 induction and NF-κB inhibition and thus inhibits cancer progression. Due to these properties, it can be concluded that the compound might be a candidate for anticancer drug design.[191]

2.2.1.6. Leukemia Preclinical Effects. Acute myeloid leukemia (AML) is an important type of hemolytic malignancy that arises from the disorder of hematopoietic stem cells,[192] and it is the most common acute type of leukemia in adults.[193] In this disease, leukemia cells undergo mutations,[193] and since conventional treatments also have cytotoxicity and side effects, many plant-derived agents are being used in the treatment of this disease and Que was also tested against this type of malignancy and shown to possess antileukemia ability since it contributes as an apoptosis inductor[194] and also it can sensitize

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Table 4. Quercetin and Related Compounds from Plant-Derived Products with Reported Effects on Parasites of Medical Importance

family	natural source	isolated compound	parasite target	comments	refs
Amaranthaceae	*Atriplex lindleyi* Moq.	Que	*Plasmodium falciparum*	*in vitro* antimalarial activity.	165
Asteraceae	*Bidens pilosa* L.	Que-related glucopyranoside	Plasmodium spp.	reduction of parasitaemia in animal model.	166
	Pluchea carolinensis (Jacq.) G. Don	Que	*Leishmania amazonensis*	activity against promastigotes and amastigotes. No effect on animal model of leishmaniasis.	167
Crassulaceae	*Kalanchoe pinnata* (Lam) Pers.	Que aglycone-type structure	*Leishmania amazonensis*	activity against amastigotes and potent oral efficacy on cutaneous leishmaniasis.	168
Cucurbitaceae	*Momordica charantia* L.	Que-enriched subfraction	*Fasciola hepatica*	affect the embryonic development of eggs and strongly inhibited the miracidium hatching.	169
Fabaceae	*Dimorphandra gardneriana* Tul.	Que	*Leishmania infantum*	active on promastigotes and amastigotes.	170
	Quercus infectoria Olivier	Que	*Leishmania major*	extract showed *in vitro* and *in vivo* antileishmanial activity, which was correlated with Que amount.	171
Leguminosae	*Mezoneuron benthamianum* Baill.	Que	*Plasmodium falciparum*	*in vitro* antimalarial activity.	172
Malvaceae	*Guazuma ulmifolia* Lam.	ethanol extract	*Leishmania braziliensis*, *Leishmania infantum* and *Trypanosoma cruzi*.	significant antikinetoplastid *in vitro* inhibition.	173
Melastomataceae	*Miconia langsdorffii* Cogn.	Que derivatives	*Schistosoma mansoni*	cause a significantly reduction in motor activity of adult worms.	174
Meliaceae	*Azadirachta indica* A. Juss.	Que -3-rhamnoside, Que-3-rutinoside	*Plasmodium falciparum*	inhibition of substantial oxidant stress during malarial infection.	175
Myrtaceae	*Psidium acutangulum* Mart. ex DC	glycosylated Que derivatives	*Plasmodium falciparum*	*in vitro* antimalarial activity.	176
	Psidium brownianum Mart. ex DC. and *Psidium guajava* L.	Que and derivatives	*Trypanosoma cruzi*, *Leishmania brasiliensis* and *L. infantum*	potent *in vitro* antikinetoplastidae activity.	177
Poaceae	*Cymbopogon citratus* (DC.) Stapf	Que and derivatives	*Giardia lamblia*	*in vitro* and *in vivo* effect, correlated with phenolic compounds abundance.	178
Polygonaceae	*Fagopyrum esculentum* Moench	Que	*Leishmania donovani*	*in vitro* antileishmanial activity.	179
Rutaceae	*Diosma pilosa* I.J Williams	Que	*Plasmodium falciparum*	*in vitro* antimalarial activity.	180

acute myeloid KG-1 cells against a TNF-related apoptosis-inducing ligand, which is a biological cytokine.[193]

In chronic lymphocytic leukemia, Que was found to inhibit kinases such as PIM1, which is expressed in the lymphocytes of patients having chronic lymphocytic leukemia. It is recommended to be evaluated further in the stabilization of increasing lymphocyte counts.[195]

2.2.1.7. Colon Cancer Preclinical Effects. Colorectal cancer is an important health issue in developed countries. ErbB2 and ErbB3 are receptor tyrosine kinases associated with the growth of human colon cancer, and it was found that their expressions are high in HT-29 cells. In a study by Kim et al.,[194] Que decreased the levels of these two enzymes in a dose-dependent manner and thus inhibits cell growth of colon cancer cells and induces apoptosis in these cells.

In another study by Ranelletti et al.,[196] Que showed blocking action in the G0/G1 phase in HT-29 cancer cell lines, along with WiDr, COLO21, and LS-174T human colon cancer cell lines. This cell proliferation inhibition was dose-dependent and reversible. The growth of primary colorectal tumors was also demonstrated to be inhibited with Que according to another study by Ranelletti et al.[197] again.

2.2.1.8. Gastrointestinal Cancer Preclinical Effects. Que, which is found in foods in its free form in addition to the β-glycoside form like rutin and quercitrin, was reported to induce G1 arrest in human gastric cancer cells in a study conducted in 1990.[198] In AGS human gastric cancer cells, Que induced morphological changes and reduced total viability via apoptotic cell death; decreased antiapoptotic proteins of Mcl-1, Bcl-2, and Bcl-*x*; and increased the proapoptotic protein of Bad, Bax, and Bid.[199] Que protected intestinal porcine enterocyte cells against H_2O_2-induced apoptosis via the inhibition of the mitochondrial apoptosis pathway.[200]

2.2.1.9. Oral Cancer Preclinical Effects. Oral cancer has a high mortality rate throughout the world. It is among the most widespread tumors in the world with poor prognosis. Que has a beneficial effect via the regulation of miR-16 and HOXA10 in oral cancer cells, and with this regulation, it inhibits cell viability, migration, and invasion. These properties make it a promising agent in oncotherapy.[133]

2.2.1.10. Other Cancer-Related Preclinical Effects. In addition to possessing anticancer effect in various cancer types alone, Que exerts anticancer effect with other substances as combined. For example, it is reported to increase apoptosis in human lung cancer H1299 cells exposed to trichostatin A, i.e., it increases the antitumor activity of trichostatin A, which is a histone deacetylase inhibitor.[201] When combined with kaempferol, they show synergism and lead to a decrease in cell proliferation in human gut cell lines HuTu-80 and Caco-2 and also in PMC42 human breast cell line.[202]

It was also reported to activate apoptosis and different types of cancers, for example, it was found to inhibit cell proliferation in the nonsmall cell lung cancer strongly and also increased apoptotic cell population in cervical cancer by decreasing NF-κB expression.[203] Some researchers suggested that Que has a hormetic nature, that is, it has a biphasic dose−response relationship (for example, in low doses, it shows antioxidant effect; however, in high doses, it has pro-oxidant property).

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This hormetic feature of the compound makes it an excellent candidate in cancer prevention studies.[204] As a result, it has been concluded that Que is an important and efficient antioxidant and can be considered as a potent anticancer agent.[205]

2.2.2. Antiobesity and Antidiabetes Preclinical Effects. Obesity and diabetes are major health problems in developing and developed countries. These are multifactorial, complex, and chronic diseases and risk factors in the establishment of various ailments like hypertension, coronary heart disease, cancer, osteoarthritis, respiratory problems, etc.[206] They can also lead to metabolic syndrome that includes insulin resistance, hyperglycemia, dyslipidemia, and hypertension. Since chronic inflammation was considered as one of the factors contributing to obesity-related metabolic diseases, Que's anti-inflammatory effect might be beneficial against the development of these two important health problems.[207]

It is also beneficial in the development of diabetic nonalcoholic fatty liver disease (NAFLD) via the regulation of genes related to lipid metabolism and secretion of inflammatory mediators. Que was shown to contribute to the prevention of hepatic lipid accumulation and liver injury due to chronic-plus-binge-ethanol feeding.[73] As a conclusion, Que is demonstrated to have antidiabetic effects due to various positive activities, for example, it downregulates gluconeogenesis enzymes and reduces the making of glucose in hepatocytes.[208]

2.2.3. Antiaging Preclinical and Clinical Effects. Antioxidants influence the process of aging. Que alleviates human mesenchymal stem-cell senescence due to its property to promote self-renewal and differentiation; it also restores the heterochromatin architecture of human mesenchymal stem cells. Due to these beneficial properties, Que is considered as a geroprotective agent against premature aging.[210]

In a study performed on human volunteers, topical application of Que and its derivative Que-caprylate has positive effects in regard to elasticity, moisturization, and depth of wrinkles.[209] This study was performed for cosmetic purposes; however, there are other aspects of aging in relation to Que, or polyphenols in general. For example, progeroid syndromes are rare genetic disorders characterized with clinical properties of premature aging (Wermer syndrome and Hutchinson−Gilford progeria syndrome are among these).

2.2.4. Hypertensive Clinical Effect. Hypertension is systolic blood pressure above 140 mm Hg and diastolic blood pressure over 90 mm Hg consistently, which is an important problem. Que may reduce blood pressure via nonendothelial mechanisms and is a promising agent in the treatment of hypertension.[211]

In a study by Gormaz et al.,[212] Que lowered blood pressure in hypertensive patients when administered for 28 days at a dose of 1 g/day. This effect might be due to the mediation of improved endothelial function via both increased nitric oxide release and decreased endothelin-1 production. In a randomized, double-blind, placebo-controlled, crossover study performed with human patients with stage 1 hypertension, administration of high-dose Que was shown to lead to a decrease in systolic, diastolic, and mean arterial pressure, and these results show that it can be used for the treatment of early-stage hypertension.[213]

2.2.5. Cardiovascular Preclinical and Clinical Effects. Cardiovascular disease is an important health issue especially in industrialized countries and are considered to be among the main reasons for morbidity and mortality.[99] Que is considered to be a promising agent due to its great potential in the prevention and treatment of chronic diseases such as cardiovascular problems.[79] For example, both Que and its metabolites can be beneficial in the early stages of atherosclerosis due to their involvement in monocyte recruitment. And atherosclerosis is known to be the leading cause of cardiovascular disease mortality.[214]

Que supplementation might reduce cardiovascular problems and prevent obesity-associated mortality though it was found to have no positive effect on body weight.[215] Nevertheless, it possesses important heart-related advantages such as inhibition of LDL oxidation, vasodilatory effects not dependent on endothelium, protective effect under oxidative stress on nitric oxide, and endothelial function.[216] It might also exert positive effects on the cardiovascular system by reducing inflammation,[217] and it is considered to possess antiatherogenic effect.[212]

2.2.6. Antioxidant Preclinical Effects. Oxidant compounds are known to lead to many important diseases in human body; therefore, antioxidant compounds have gained importance in the prevention of oxidation-associated diseases/disorders.

Que is an excellent antioxidant and probably the most potent scavenger of reactive oxygen species and reactive nitrogen species due to its two antioxidant pharmacophores for free-radical scavenging.[218] One of the oxidant activity-associated disorders is age-related macular degeneration (AMD) that leads to vision loss in the elderly.[219] Retinal pigment epithelial cells (RPEs) are quite susceptible to damage by reactive oxygen intermediates. Foods rich in antioxidant compounds might reduce the risk of the development of AMD, and since Que has cytoprotective effects, it is considered as a good candidate for the prevention of early pathologic changes in age-related macular degeneration. Not only in AMD but Que might also be beneficial in the inhibition of oxidative stress-mediated neuronal damage since oxidative stress is considered as one of the major reasons for the development of neurodegenerative disorders and vascular pathologies in the brain due to its radical-scavenging and metal-chelating activities.[110] It might also be an effective protector against neurodegenerative diseases caused by oxidative stress and apoptosis.[220]

2.2.7. Anti-inflammatory Preclinical Effect. Que is known to possess anti-inflammatory effect. It is effective in various inflammation models, and the analgesic activity of the compound is also considered to be linked to its anti-inflammatory property.[221] It also has beneficial effects as a topical product prepared for rheumatoid arthritis. Arthritic disorders are very common throughout the world, and this topical product containing Que in a nanoemulsion-based gel would be beneficial in the prevention of joint dysfunction and disability in adults.[222]

Respiratory diseases are widespread in the pediatric population, especially pneumonia. Lung fibroblasts undergoing inflammatory damage is seen as the occurrence and development of disease; therefore, Que might be effective against pneumonia since it can alleviate inflammatory damage by ameliorating lipopolysaccharide-originated inflammatory damage of WI-38 lung fibroblasts.[135]

2.2.8. Other Uses/Activities. Since Que is a multifaceted compound, it is indicated in other disorders and/or conditions as well. Some of them are summarized as follows:

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It can be used as a protective factor against some drugs in the treatment of schizophrenia. This disease is a severe, chronic psychiatric disorder and is thought to be associated with oxidative stress. Drug use in the treatment of this disease, for example, haloperidol, is associated with a risk of developing important side effects (i.e., movement disorder like drug-induced parkinsonism, akathisia, and dystonia). Que reduces lipid peroxidation of plasma exposed to haloperidol or amisulpride; therefore, it can be beneficial in the protection against antipsychotic drugs.[223]

Que might be used as a sunscreen, and it was demonstrated in a study that it was as effective as the compound homosalate, a common ingredient found in sunscreen products.[224]

Isoquercitrin was demonstrated to have antiviral effects against African historical and Asian epidemic strains of ZIKV in human hepatoma, epithelial, and neroblastoma cell lines. This study was performed as an *in vitro* study; however, it is an important disease and therefore it might be worth mentioning it here. This derivative prevents the internalization of virus particles into the host cell and therefore prevents their entrance into the cell. Therefore, it can be a promising antiviral compound in the prevention of Zika virus infection.[225]

Que might protect against dimethoate-induced oxidative stress. This compound is an organophosphate insecticide that acts by interfering with the functioning of cholinesterase (an enzyme required for the proper functioning of the nervous system) and therefore may lead to human poisonings. Que decreases lipid peroxidation and protein oxidation, increases superoxide dismutase and catalase activities in human lymphocytes, and hence protects against dimethoate-induced oxidative stress.[226]

Whitening cosmetics are very popular throughout the world due to their antimelanogenesis activities. Que has been tested for this effect in human trials. Though Que was found to be ineffective in hypopigmentation of human skin, its tested glycosides were found to be somewhat effective in concentration-dependent behavior.[227]

Que was tested in 12 healthy men for 7 days on bike riding performance via the measurement of VO_2 max and time to fatigue. Both these parameters were found to increase; therefore, it could be concluded that this flavonoid might increase the endurance capacity of the skeletal muscle.[228]

Eccentric exercises are involved in training programs of athletes, and they involve lengthening of the skeletal muscle while producing force. However, this produces a mechanical stress and induces breaking of contractile components and then the occurrence of an inflammatory phase that leads to secondary muscle damage. In a double-blind, placebo-controlled, randomized study with crossover design carried out on 12 moderately active men, Que promoted membrane stability by preserving excitation−contraction coupling in myocytes. Therefore, it can be said that Que might improve general physical fitness and even might improve performance.

2.3. Quercetin Bioavailability and Related Issues. Despite the immense benefits of Que, it is limited by poor aqueous solubility, poor permeability, instability in physiological medium (stomach and intestine), short biological half-life, and extensive first past metabolism in the liver before reaching the systemic circulation resulting in poor oral bioavailability,[229−231] which limits the application of Que pharmaceutically. Nevertheless, recent progress in the field of drug delivery has enabled the consequential development of alternative drug-delivery systems to counteract the poor bioavailability of Que and achieve better therapeutic results tailored to enhance its biological activity. Ideal delivery systems must protect Que in the upper gastrointestinal tract to avoid its instability while releasing it at colon with prolonged sustained release with enhanced bioavailability.[231]

2.3.1. Quercetin Nanoformulations: A Way to Overcome Bioavailability-Related Issues. Nanoparticles offer a promising platform to enhance Que bioavailability owing to their large surface area, ability to be customized for targeted delivery of drugs, improved bioavailability, protection against enzymes, and physiological conditions, and they provide a controlled release of medication from a single dose.[232]

Natural polymers have been extensively studied for Que delivery, such as chitosan, which is a natural polysaccharide that has been used for the preparation of Que nanoparticles. Que-loaded chitosan nanoparticles with enhanced encapsulation efficiency and sustained release with small size (<200 nm) were prepared by Baksi et al.,[233] which showed a significantly reduced IC_{50} value compared to free Que in cytotoxicity assay as well as a significant reduction of tumor volume in comparison to disease control groups in mice. Que-loaded chitosan nanoparticles were also investigated by encapsulating Que into pH-sensitive self-assembled amphiphilic chitosan nanoparticles; blank nanoparticles were nonantiproliferative, while Que maintains its metabolism inhibition against MCF-7 cells after encapsulation.[234] Zein was also used for Que loading, which provided high and sustained levels of the drug in plasma and higher relative bioavailability with enhanced anti-inflammatory action.[235]

Synthetic polymers were also used for the formulation of Que delivery systems. Que nanoparticles using synthetic poly(lactide-*co*-glycolide) (PLGA) nanoparticles were formulated in several studies. One study utilized Que-loaded PLGA nanoparticles using pluronic as a stabilizer, and conjugation with transferrin (Tf-QrPLGA) showed significant antiproliferative and cytotoxic effects on metastatic cell lines as well as apoptosis and cycle cell arrest.[236] Lou et al.[237] prepared gold Que loaded into PLGA nanoparticles that induced cell autophagy and apoptosis in human neuroglioma cells as well as suppressed tumor growth through activation LC3/ERK/Caspase 3 and suppression AKT/mTOR signaling. The antidiabetic action of Que was also reported using PLGA nanoparticles, involving the emulsion−diffusion−evaporation method, which showed enhanced antioxidant properties as well as increased oral bioavailability (523%) of Que with sustained plasma concentration for 6 days *in vivo*, suggesting a reduced dosing frequency of the nanoformulations.[238]

Polymeric micelles have also been utilized in the synthesis of quercetin nanoparticles. Chen et al.[57] developed a lecithin-based nanomicelle (LMPM) delivery system, which improved the solubility of Que as well as achieved sustained release and higher bioavailability as well as enhanced cytotoxicity against MCF-7 breast cancer cells with no toxic effects. Tan et al.[239] utilized nanomicells for preparing Que from diblock copolymer of poly(ethylene glycol) (PEG)-derivatized phosphatidylethanolamine (PE) as oral anticancer dosage forms, which showed enhanced bioavailability and stability in simulated gastric fluid as well as enhanced antitumor activity using the A549 cancer cell line and murine xenograft model with no apparent toxicity.[240]

Metallic nanoparticles were also used in Que nanoparticle formulation. One study used phenylboronic acid (PBA)-conjugated zinc oxide nanoparticles (PBA-ZnO) loaded with

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Que.[241] The presence of PBA moieties over the nanoparticle surface facilitates targeted delivery of Que to cancer cells. Moreover, Que-loaded PBA-ZnO nanoparticles showed pH-responsive drug-release behavior and induced apoptotic cell death in human breast cancer cells (MCF-7) via enhanced oxidative stress and mitochondrial damage. Braga et al.[242] incorporated Que and silver nanoparticles (AgNPs) into poly(vinyl chloride) (PVC) matrix, which demonstrated significant antimicrobial activity against food pathogens (*Escherichia coli*, *Salmonella Typhimurium*, and *Listeria monocytogenes*) and considerable effect in inhibiting bacterial growth, indicating a possibility of the prevention of microbial dissemination in foods with a significant antioxidant effect. Another study prepared Que/CdSe/ZnS nanoparticles (QCZ NPs), which showed antibacterial activity against drug-resistant *E. coli* and *Bacillus subtilis* as well as anticancer activities by affecting cell proliferation and migration in BGC-823 cells.[243] Que-loaded silica nanoparticles synthesized using the oil-in-water microemulsion method act as antioxidants and anti-inflammatory agents. The prepared nanoparticles showed superoxide radical scavenging effects as well as higher cell viability and lower amounts of proinflammatory cytokines produced by macrophages.[244] Another study focused on loading of Que on silica nanoparticles and investigated its effect on MCF-7 breast cancer cell lines, which showed cell cycle arrest, apoptosis, and reduced cell vitality and growth rate, thereby offering a promising approach in breast cancer prevention.[245]

Lipid-based nanoparticles were also utilized in Que encapsulation. Solid lipid nanoparticles were formulated to encapsulate Que with sustained release till 48 h, showing enhanced cytotoxic effect and a lower IC_{50} than free Que in MCF-7 breast cancer cells.[246] Hatahet et al.[247] tested three approaches to improve Que delivery to skin—liposomes, lipid nanocapsules (LNC), and smart Crystals—and concluded that Que smart Crystals enabled the superficial deposition of Que on top of the skin. On the other hand, LNC seems to allow Que delivery to viable epidermis that holds the promise for skin inflammatory disorders such as psoriasis, while liposomes showed the least favorable characteristics in terms of encapsulation efficiency and particle size. Vijayakumar et al.[248] prepared solid lipid nanoparticle (SLN) dispersion containing Que using tripalmitin and lecithin as lipid core, and then the surface was coated with chitosan, which showed enhanced *in vitro* release and cellular uptake of Que using Caco-2 cells. Que-loaded cationic nanostructured lipid carriers consisting of glycerol monostearate, medium chain triglycerides, and soy lecithin were found to exhibit a slower release *in vitro* during the digestion compared to those of Que suspended in 0.5% (w/v) sodium carboxymethylcellulose aqueous solution.[249]

The poor bioavailability of flavonoids limits their biological effectiveness, which has been influenced by several factors.[188,228] One of the more critical points is that in an aqueous solution, its solubility varies from 0.00215 g/L at 25 °C to 0.665 g/L at 140 °C. However, it shows high solubility at 25 °C in organic solvents such as ethanol (2 g/L) and dimethylsulfoxide (30 g/L).[250] Then, as a consequence, the poor solubility and instability of this flavonol in aqueous intestinal fluids and the quick metabolism reduce its efficacy and oral bioavailability;[218,251−253] which is almost 1% in humans.[254] Nevertheless, Que is a druglike compliant with Lipinski's rule of five without any violation (Figure 2), which predicts that a compound with ≤5 hydrogen-bond donors, ≤10 hydrogen-bond acceptors, molecular weight ≤500, and log $P \leq 5$ more probably presents a high bioavailability.[255]



Figure 2. Lipinski's rule-of-five quercetin-like properties.

Different studies have demonstrated that Que circulated as types of conjugates in the blood. Thereafter, quercetin-3-*O*-*β*-D-glucuronide (Q3GA), a major metabolite of Que, and quercetin-3′-*O*-sulfate are distributed throughout the body where they may exert beneficial functions in target tissues.[228,256] Hydrophilic Q3GA has been found to be deconjugated into hydrophobic Que aglycone at injured sites which, in turn, may improve the pathological conditions.[228,257] Other Que-related compounds such as the Que monoglucosides present higher bioavailability,[258] and isoquercetin (quercetin-3-*O*-*β*-D-glucopyranoside) exhibited a better pharmacokinetic profile in particular.[259] However, it should be noted that nonconjugated aglycones, including methylquercetins, are scarcely detected in the human plasma.[260]

Alongside with this characteristic, of a BCS class II drug, a moderately short half-life after intravenous injection of Que was also observed.[261,262] These drawbacks, which can limit the clinical administration of Que, demand urgent solutions to maintain free Que levels in blood and other tissues for a prolonged period.[263] In this sense, nanoformulations have been strongly recommended as an alternative to Que therapy.

2.3.2. Nanodelivery Systems for Quercetin. Several biocompatible, biodegradable, affordable, and versatile nanoparticles are currently available for formulating bioactive compounds for health promotion and prevention. Nanoparticles can increase the solubility and stability of Que, enhancing its absorption, cellular uptake, and protection from premature degradation in the body, resulting in decreased toxicity.[264]

Numerous studies highlight that nanoencapsulation may elevate the bioactivities of Que, improving its sustained release.[265−267] During an *in vivo* critical evaluation of Que as an antileishmanial agent through the use of different vesicular delivery systems, the nanoencapsulated Que was found to be the most potent in reducing the parasite burden in the spleen, with a better reduction of hepatotoxicity and renal toxicity compared to free drug or drug in other vesicular forms.[264] Also, the gastro protection mediated by nanoencapsulated Que was better than by free Que, by preventing mitochondrial damage and regulation of key enzymes.[267] The oral administration of Que-loaded poly(lactide-*co*-glycolide) nanocapsules containing triphenylphosphonium increased brain uptake and remarkable mitochondrial localization after cerebral ischemia reperfusion in young and aged rats.[268] Besides, the encapsulation of Que in lipid-core nanocapsules of poly(*ε*-

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caprolactone) safely increased its oral efficacy in experimental cutaneous leishmaniasis.[269]

The potentiality of nano-Que as a promising adjuvant vehicle for chemotherapy has been demonstrated.[270] In this sense, size, charge, and retention reached by a nanoform of Que in combination with anticancer drugs like adriamycin and mitoxantrone may solve multidrug resistance.[271] Co-delivery of doxorubicin with phytosomes increased the efficacy of the drug in tumor microenvironment.[272] Also, co-delivery of doxorubicin in a nanosized system based on gold nanocages increased the intracellular accumulation and could maximize the antitumor effect on malignant cells.[273] Lately, co-loading of Que and vincristine through lipid polymeric nanocarriers exhibited the best *in vitro* and *in vivo* antitumor efficacy, showing a synergistic effect to overcome chemoresistant lymphoma.[274]

Chitosan has been used to design promising delivery systems capable of offering excellent protection and controlled released of Que. In this sense, micelles of a chitosan/polycaprolactam nanocomplex containing folic acid and Que efficiently inhibited breast cancer cells.[275] Recently, the encapsulation of anticancer drugs into the nanomicelles of the Que−chitosan conjugate demonstrated that it could display a sustained-release profile in gastrointestinal simulation fluid and promote cellular uptake.[276]

Other polymers have allowed the preparation of biocompatible hybrid nanomaterials. To this effect, Que loading into nanosized polymeric micelles of methoxy poly(ethylene glycol)−cholesterol conjugate might be a potential formulation for the controlled and targeted drug delivery to tumor in a pH-sensitive manner.[277] Likewise, conjugating Que into the backbone of poly(β-amino esters) guaranteed a uniform release and retention of its antioxidant activity.[278] The synthesis of hybrid nanocomposite structures based on silica and PEG entrapping Que showed positive outcomes on the biocompatibility toward tested cell lines.[279] Recently, a nanoplatform of poly-D-L-lactide-*co*-glycolide decorated with chitosan and PEG was suitable for the delivery of Que increasing its anticancer potency.[280]

Other therapeutic nanosystems containing Que have been reported as successful applications of nanotechnology to solve the problems of hydrolysis and short half-life. In this sense, new Que conjugated to gold nanoparticles was successfully evaluated for the first time against leishmanial macrophage infections, indicating its future application in the chemotherapy of wild- and resistant-type visceral leishmaniasis.[281] Of note, solubility and bioavailability of Que were improved by a nanoliposomal presentation, which enhanced the cellular uptake and effectively displayed antioxidant protection.[282]

Moreover, the synthesis of a synergistic nanocomposite by conjugating Que and acetylcholine to the surface of Se nanoparticles enhanced the antibacterial activity against Methicillin-resistant *Staphylococcus aureus*.[283] Que-loaded nanolipidic carriers/solid lipid nanoparticles offered better drug loading and controlled release to brain with appreciable stability, with improvement of Que *in vitro* antioxidant performance.[284] Que inclusion into silk fibroin nanoparticles conserved the antioxidant activity in comparison to the equivalent amount of free drug, being successfully transported and delivered gastrointestinally.[285] Que-loaded phytosome nanoparticles were prepared using the thin-film hydration method, whose enhanced therapeutic efficacy over free Que was associated with better absorption.[286]

It stands out that the formulation of Que-loaded nanomicelles (Soluplus) improved the bioavailability of the drug and enhanced its antidiabetic effect.[287] Lately, nano-Que significantly reduced the toxicity of the food mutagen 2-amino-3-methylimidazo[4,5-*f*]quinolone, which was higher than bulk Que.[288]

The previous observations raise the possibility of further studies using Que, in combination with existing clinically approved drugs to evaluate the synergism or using nanotechnology-related strategies.

3. CONCLUSIONS

There is an extraordinary attention to naturally occurring bioactive molecules, and Que is a great example of phenomenal therapeutic applications. The multitude of preclinical studies have allowed more in-depth studies, including the development of increasingly specific and targeted clinical studies. Apart from the several pharmacokinetic limitations of Que, the distinct techniques developed and currently applied have opened the possibility to overcome most of the previously identified gaps, thus allowing Que use under multiple preparations, for multiple purposes and even for different applications. Thus, the clinical applications and effectiveness of Que are remarkable. Nonetheless, as most of modern problems come from a wide variety of triggering agents, it would be of extreme importance to pay attention to the use of Que for preventive purposes, as well as in combination with multiple drugs to determine their abilities to potentiate or synergistically interact with these chemical agents, consequently reducing their side effects and related toxicity, at the same time increasing their overall efficacy and safety (as is the case of antitumor drugs).

AUTHOR INFORMATION

Corresponding Authors

Javad Sharifi-Rad − *Phytochemistry Research Center, Shahid Beheshti University of Medical Sciences, Tehran 1991953381, Iran;* orcid.org/0000-0002-7301-8151; Email: javad.sharifirad@gmail.com

Shahira M. Ezzat − *Department of Pharmacognosy, Faculty of Pharmacy, Cairo University, Cairo 11562, Egypt; Department of Pharmacognosy, Faculty of Pharmacy, October University for Modern Sciences and Arts (MSA), 6th October 12566, Egypt;* Email: shahira.ezzat@pharma.cu.edu.eg

Natália Martins − *Faculty of Medicine and Institute for Research and Innovation in Health (i3S), University of Porto, Porto 4200-319, Portugal*; Email: ncmartins@med.up.pt

Miquel Martorell − *Department of Nutrition and Dietetics, Faculty of Pharmacy, and Centre for Healthy Living, University of Concepción, Concepción 4070386, Chile; Universidad de Concepción, Unidad de Desarrollo Tecnológico, UDT, Concepción 4070386, Chile*; Email: mmartorell@udec.cl

William C. Cho − *Department of Clinical Oncology, Queen Elizabeth Hospital, Kowloon, Hong Kong*; Email: chocs@ha.org.hk

Authors

Bahare Salehi − *Student Research Committee, School of Medicine, Bam University of Medical Sciences, Bam 44340847, Iran*

Laura Machin − *Institute of Pharmacy and Food, University of Havana, Havana, Cuba*

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Lianet Monzote − *Parasitology Department, Institute of Medicine Tropical Pedro Kouri, Havana, Cuba*
Mohamed A. Salem − *Department of Pharmacognosy, Faculty of Pharmacy, Menoufia University, Menoufia 32511, Egypt*
Rana M. Merghany − *Department of Pharmacognosy, National Research Centre, Giza 12622, Egypt*
Nihal M. El Mahdy − *Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, October University for Modern Sciences and Arts (MSA), 6th of October 12566, Egypt*
Ceyda Sibel Kılıç − *Department of Pharmaceutical Botany, Faculty of Pharmacy, Ankara University, Ankara 06100, Turkey*
Oksana Sytar − *Department of Plant Biology Department, Institute of Biology, Taras Shevchenko National University of Kyiv, Kyiv 01033, Ukraine; Department of Plant Physiology, Slovak University of Agriculture, Nitra 94976, Slovak Republic*
Mehdi Sharifi-Rad − *Department of Medical Parasitology, Faculty of Medicine, Kerman University of Medical Sciences, Kerman 7616913555, Iran*
Farukh Sharopov − *Department of Pharmaceutical Technology, Avicenna Tajik State Medical University, Dushanbe 734003, Tajikistan*

Complete contact information is available at: https://pubs.acs.org/10.1021/acsomega.0c01818

Author Contributions

All authors contributed equally to the manuscript. J.S.-R. involved in the conceptualization; validation of resources, data curation, and writing were performed by all authors; J.S.-R., S.M.E., M.M., W.C.C., and N.M reviewed and edited the manuscript. All of the authors read and approved the final manuscript.

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