Hibiscus, Rooibos, Yerba Mate in Glycoxidation and Neurodegeneration

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The well-known food safety associated with the consumption of hibiscus, rooibos, or yerba mate, and the acceptance of these herbs linked to pleasant taste, have elicited great interest in defining their nutraceutical potential. These plants produce several bioactive metabolites, have a pleasant taste, and a long-lasting history as safe foods. These plants produce several bioactive metabolites, have a pleasant taste, and a long-lasting history as safe foods. The literature on hibiscus, rooibos, and yerba mate teas in the context of nutritional strategies for the attenuation of oxidative stress-related glycoxidation and neurodegeneration was reviewed, and, here, Alzheimer's Disease is approached as an example. The focus is given to mechanisms of glycation inhibition, as well as neuroprotective in vitro effects, and, in animal studies, to frame interest in these plants as nutraceutical agents related to current health concerns.

Keywords: herbal teas ; oxidative stress ; glycoxidation ; neurodegeneration

1. Antioxidant and Anti-Glycation Effects of Hibiscus, Rooibos, and Yerba Mate

The brain, the liver and other organs appear to be sensitive to oxidative stress [1][2][3]. Some body of work has addressed the potential of hibiscus, rooibos, and yerba mate crude extracts in the mitigation of ROS production, as well as anti-glycation, both in vitro (**Table 1**) and in vivo (**Table 2**), approaching major biomarkers as glutathione, SOD, CAT, and the formation of autofluorescent AGEs. In vitro studies on neuroblastoma cell culture (SH-SY5Y) demonstrated that hibiscus ethanolic extracts (100 µg/mL) reduced ROS production, and more significantly lipid peroxidation, when compared to cells exposed to H_2O_2 stress, which is supposed to contribute to cell membrane lipid layer maintenance [4]. Under in vivo conditions, such antioxidant potential was translated as increased engagement of CAT and SOD enzymes in the brain of diabetic male Sprague-Dawley rats who orally received 25 mg/kg body weight of hibiscus aqueous extract [5].

The effect of rooibos was similar over SOD and CAT, as observed in immobilization-induced oxidative stress Sprague-Dawley animals receiving a supplement of rooibos, in a 4-week study. The intake of rooibos aqueous extract (10 mg/mL) was demonstrated to result in greater activity of both enzymes in comparison to animals under stress but not receiving rooibos supplementation [6]. In consequence, in this same study, rooibos was associated with lower brain lipid oxidation. Rooibos is considered to act over DAF-16/FOXO signaling pathway, which mediates SOD, CAT, and GST levels, modulating life span [7].

Table 1. In vitro antioxidant and anti-glycation effects of rooibos, hibiscus, yerba mate extracts.

Assay	Species [Extract]	Measure	Dose or EC_{50}	Reference
Antioxidant	*H. sabdariffa* [Ethanolic]	Lipid peroxidation (SH-SY5Y cells)	Control: 800% Extract (100 µg/mL): 300%	[4]
		ROS production (SH-SY5Y cells)	Control: 130% Extract (100 µg/mL): 100%	
	H. sabdariffa [Methanolic]	Malondialdehyde	EC_{50} 22 µg/mL	[8]
		Monoamine Oxidase	EC_{50} 44 µg/mL	
		ATPase activity	EC_{50} 22 µg/mL	

Assay	Species [Extract]	Measure	Dose or EC_{50}	Reference
Anti-glycoxidation	*A. linearis* [Aqueous]	AGE formation inhibition (Fluorescence 340/420 nm) Glucose in BSA system	Control (aminoguanidine): 45% Green extract (200 µg/mL): 45% Fermented extract (200 µg/mL): 55%	[9]
	H. rosa-sinensis [Aqueous]	AGE formation inhibition (Fluorescence 340/420 nm) Fructose in BSA system	Control (Aminoguanidine): IC_{50} 6 µg/mL Extract: IC_{50} 67 µg/mL	[10]
	I. paraguariensis [Aqueous]	AGE formation inhibition (Fluorescence 340/420 nm) Fructose in BSA system	Control (Fructose): 4000 a.u. Extract (2.5 µg/mL): 3000 a.u.	[11]
		AGE formation inhibition (Fluorescence 340/420 nm) Methylglyoxal in BSA system	Control (green tea): 65 a.u. Extract (20 µg/mL): 42 a.u.	[12]

BSA: bovine serum albumin.

Oxidative stress and inflammation are interconnected mechanisms that play roles in chronic disease progression [13]. Hibiscus was also demonstrated to attenuate the effect of markers on the interface between oxidative stress and inflammation. COX-2 is a mediator in inflammatory action, while monoamine oxidase (MAO) plays a major role in the outer mitochondrial membrane, regulating the metabolism of monoaminergic neurotransmitters [14][15]. Compelling evidence involves both biomarkers in the progression of ROS-related inflammation in major metabolic disorders [16][17]. Oboh et al. (2018) reported that roselle methanolic extract reduced MAO expression in vitro (EC_{50} = 43.69 µg/mL), while diabetic Wistar albino mice had decreased COX-2 activity toward the inversion of oxidative stress [18].

Glutathione (GSH) is a powerful mechanism in animal cell redox control [19]. It has been demonstrated that aging neurons have lower levels of the reduced form (GSH) which is converted into the oxidized version (GSSG) [20]. Oral supplementation of rooibos (10 mg/mL) and yerba mate (200 mg/mL) extracts showed effects on the increase of the GSH/GSSH ratio. Such behavior attributed to yerba mate was also observed in synaptosomal/mitochondrial P2 fractions [21], as well as in brain homogenates of chronic immobilized rats [22], which suggests that synaptosomal cells are key in GSH control in rats.

Rooibos, hibiscus, and yerba mate provide an important phytochemical repertoire with anti-glycoxidation activity. Reactive saccharides, such as glucose, fructose, and ribose, as well as carbonyl compounds, such as glyoxal, and methylglyoxal, have been described as important precursors of AGEs [23]. Therefore, in the search for anti-glycation molecules, different glycation precursors are investigated. Several glycation derivatives, including protein cross-links, are auto-fluorescent and can be detected at excitation/emission wavelengths of 335/385 nm, for total AGE estimation, and 485/520 nm for cross-link estimation [24][25]. This characteristic is explored in vitro for bioassays on the inhibition of AGE formation. Caffeic and chlorogenic acid were found to be major components in *I. paraguariensis* extracts. Along with the study of the inhibition of AGEs, based on fluorescence measures, caffeic acid showed the most significant effect (90%) in a methylglyoxal-BSA system compared to aminoguanidine (60%) control [26]. Chlorogenic acid, on the other hand, showed similar EC_{50} to aminoguanidine, 10 mM and 8 mM, respectively, in fructose/inhibition in the ovalbumin system [27]. When it comes to the crude extracts of yerba mate (2.5 µg/mL), a reduction of 25% occurred in the formation of fluorescent AGEs [11], while rooibos non-fermented extract (200 µg/mL) was shown to limit fluorescence up to 45%, equivalent to the aminoguanidine control [10]. In vivo, elevated glucose levels in diabetic patients have been correlated to the occurrence of glycated hemoglobin [28]. These polyphenols, as well as rutin and quercetin (also part of the phytochemical composition of these plants), act mainly by the inhibition of Amadori product formation in the early stage of the Maillard Reaction [29][30]. In addition, they may also contribute to glucose homeostasis by insulin resistance reduction, decreasing circulating AGEs, and lipid peroxidation in diabetic rats. Hibiscus tisane was demonstrated to play a role in circulating glucose and AGE reduction, while reducing the incidence of glycated hemoglobin [31].

Table 2. In vivo antioxidant and anti-glycation effects of rooibos, hibiscus, yerba mate extracts.

Target Effect/Organ	Species [Extract]	Concentration	Animal Model	Measure	Effect	Tendency	Reference
Antioxidant/Brain	*A. linearis* [Aqueous]	1 g/100 mL	Immobilization-induced oxidative stress Sprague Dawley rats	CAT	Control (Stress): 2 unit/mg Extract: 3 unit/mg	↑	[6]
				FFA	Control (Stress): 700 µg/mL Extract: 650 µg/mL	↓	
				GSH/GSSG	Control (Stress): 7.5 Extract: 9	↑	
				HIAA	Control (Stress): 400 mg/g tissue Extract: 350 mg/g tissue	↓	
				Lipid peroxidation	Control (Stress): 50 nmol/g tissue Extract: 40 nmol/g tissue	↓	
				SOD	Control (Stress): 1 unit/mg Extract: 1.7 unit/mg	↑	
	H. rosa-sinensis [Aqueous]	25 mg/kg body weight	STZ induced diabetic Male Sprague-Dawley	CAT	Control (Diabetic): 5 U/mg Extract: 10 U/mg	↑	[5]
				SOD	Control (Diabetic): 7 U/mg Extract: 15 U/mg	↑	
	H. sabdariffa [Aqueous]	200 mg/kg body weight	Male Swiss albino mice	MDA	Control (STZ): 3 nmol/g White hibiscus extract: 0.5 nmol/g Red hibiscus extract: 0.5 nmol/g	↓	[18]
				MPO	Control (STZ): 75 µg/mg tissue White hibiscus extract: 20 µg/mg tissue Red hibiscus extract: 20 µg/mg tissue	↓	
				Cox-2	Control (STZ): 4 (fold change) White hibiscus extract: 1 (fold change) Red hibiscus extract: 1 (fold change)	↓	

Target Effect/Organ	Species [Extract]	Concentration	Animal Model	Measure	Effect	Tendency	Reference
Anti-glycoxidation	*H. sabdariffa* [Ethanolic]	500 mg/kg body weight	Cypermethrin oxidative stress male mice (*Mus musculus*)	AChE	Control (Cypermethrin): 0.5 µmol/min/mg Extract: 2.5 µmol/min/mg	↓	[32]
				CAT	Control (Cypermethrin): 0.04 µmol/min/mg Extract: 0.06 µmol/min/mg	↓	
				H_2O_2	Control (Cypermethrin): 1.2 µmol/mg Extract: 0.3 µmol/mg	↓	
				MDA	Control (Cypermethrin): 2 µmol/mg Extract: 0.5 µmol/mg	↓	
	I. paraguariensis [Aqueous]	200 mg/mL	Chronic immobilization stress male Wistar rats	GSH/GSSG	Control: 0.48 Extract: 0.50	→	[22]
				Lipid peroxidation	Control: 2.1 TBA/mg Extract: 1.3 TBA/mg	↓	
		200 mg/mL	Male Wistar rats	GSH/GSSG	Control: 4.7 Extract: 16.6	↑	[21]
				Lipid peroxidation	Control: 1.3 MDA eq/mg Extract: 0.3 MDA eq/mg	↓	
		50 mg/kg BW	PTZ-induced seizure male Wistar rats	CAT	Control (PTZ): 5 mmol/min/mg Extract: 9 mmol/min/mg	↑	[33]
				SOD	Control (PTZ): 15.50 U/mg Extract: 23 U/mg	↑	
				Sulfhydryl protein	Control (PTZ): 0.09 nmol DTNB/mg Extract: 0.31 nmol DTNB/mg	↑	
	H. rosa-sinensis [Ethanolic]	25 mg/kg BW	STZ induced diabetic Male Sprague-Dawley	Glycated hemoglobin	Control: 13% Extract: 6%	↓	[5]
	H. sabdariffa [Methanolic]	200 mg/kg BW	STZ induced diabetic Male Sprague-Dawley	Serum glucose	Diabetic control: 400 mg/dL Extract: 100 mg/dL	↓	[31]
				AGE levels	Diabetic control: 4.5 mg/mL Extract: 3 mg/dL	↓	

STZ: streptozotocin.

2. Neuroprotective Effects of Hibiscus, Rooibos, and Yerba Mate

Several studies have shown that plant metabolites, such as flavonoids, anthocyanins, and phenolic acids, are active components with neuroprotective properties [34]. Complementary in vitro and in vivo assays demonstrated that *H. sabdariffa* led to the inhibition of AChE and butyrylcholinesterase (BChE), both related to the hydrolysis of acetylcholine [8][18] (**Table 3**). So far, more prolific research on this issue is found over hibiscus tisane. **Table 3** exemplifies the investigation of different organic extractions of *H. sabdariffa*. Data from PC12 cells, a cell model for neural crest neuroblastic cells, demonstrated that hibiscus ethanolic extract (60 µg/mL) allowed the reduction of apoptotic cell counts [35].

Table 3. In vitro neuroprotective effect of aqueous, ethanolic, and methanolic H. sabdariffa extracts.

Extract	Measure	Dose or EC50	Reference
Aqueous	**AChE inhibition**	**Control (galantamine): IC_{50} 7 µg/mL White hibiscus extract: IC_{50} 123 µg/mL Red hibiscus extract: IC_{50} 106 µg/mL**	[18]
Ethanolic	**PC12 cells Inhibition of cell apoptosis**	**Control (SGD): 65 apoptotic cells Extract (60 µg/mL): 30 apoptotic cells**	[35]
Methanolic	**AChE inhibition**	**IC_{50} 46.96 µg/mL**	[8]
	BChE inhibition	**EC_{50} 40.38 µg/mL**	

When it comes to in vivo assays (**Table 4**), a diet enriched with hibiscus anthocyanins was able to downregulate several aspects of Alzheimer's Disease, such as neuroinflammation. The aggregation of Aβ-peptides in the brain is a source of oxidative stress and was demonstrated to lead to lipid peroxidation [36]. In addition, Aβ-peptides play a role as a RAGE ligand, which account for a factor in oxidative stress in astrocytes and cerebral endothelial cells, as reported by [37]. In non-transgenic Alzheimer's Disease model mice, Aβ-42 accumulation was reduced following γ-secretase, APH1a, and BACE1 activity [18]. *C. elegans* is a simple nematode, with an approximately 83% genome similar to humans, which means it is extremely useful in human physiological studies [38]. Yerba mate extract was able to downgrade neuro-oxidative biomarkers, such as Aβ-42 expression and ROS levels, in *C. elegans*. Most importantly, such effects were correlated to increased worm lifespan, suggesting that yerba mate extract can help to slow down aging [39].

In addition to these findings, some data on animal behavior shed light on the neuroprotective effects of hibiscus and yerba mate teas. Some strategies are used for neuronal damage perception, such as behavioral assay associated with anxiety-related, cognitive and spatial learning, and aversive memory. Respectively, elevated plus maze, Morris water test, and step-down avoidance tasks are behavioral tests able to estimate such cognitive impacts [40][41][42]. The Morris water maze test evaluates mice spatial reference. Regarding this issue, El-Shiekh et al. (2020) demonstrated that hibiscus flower extracts (both red and white flowers) (200 mg/kg) were able to restore mice spatial capacities compared to STZ-induced Alzheimer's Disease model mice. Hibiscus was suggested to attenuate neuroinflammation and amyloidogenesis in the treated animals. In anxiety and memory assessment, it has been demonstrated that yerba mate hydroethanolic extract (300 mg/kg body weight) increased anxiolytic-like behavior in mice, which was suggested to be due to the bioactivity of yerba mate extracts over the cholinergic system, together with the levels of caffeine in this plant. On the other hand, scopolamine-induced deficit was prevented by ilex extract [43].

Table 4. In vivo neuroprotective effects of rooibos, hibiscus, yerba mate extracts.

Species [Extract]	Concentration	Animal Model	Measure	Effect	Tendency	Reference
***A. linearis* [Aqueous]**	**100 mg/mL**	**Zebrafish larvae**	**Monoamine oxidase**	**Control (Clorgyline): 100% Extract: 60%**	↓	[44]
			Cell viability	**Control: 100% Extract: 40%**	↓	
	12.5 µg/mL	**Zebrafish larvae**	**ROS production**	**Control: 600% (120 min) Extract: 200% (120 min)**	↓	

Species [Extract]	Concentration	Animal Model	Measure	Effect	Tendency	Reference
H. sabdariffa [Aqueous]	200 mg/kg BW	Male Swiss albino mice	Moris water test	Control (STZ): 20 sExtract: 30 s	↑	[18]
			BACE1	Control (STZ): 5 (fold change) White hibiscus extract: 2 (fold change) Red hibiscus extract: 2 (fold change)	↓	
			Aβ-42	Control (STZ): 250 mg/mg tissue White hibiscus extract: 100 mg/mg tissue Red hibiscus extract: 100 mg/mg tissue	↓	
			γ-secretase	Control (STZ): 3.5 (fold change) White hibiscus extract: 1 (fold change) Red hibiscus extract: 1 (fold change)	↓	
H. sabdariffa [Ethanolic]	500 mg/kg BW	Swiss albino mice	AChE activity	Control (Scopolamin): 44 nM/min/g tissue Extract: 33 nM/min/g tissue	↓	[45]
I. paraguariensis [Aqueous]	10.5 mg/L	*Caenorhabditis elegans*	Aluminum induced oxidative stress	Control: 0.6 μM/h/mg Extract: 0.4 μM/h/mg	↓	[46]
	4 mg/mL	*C. elegans*	Aβ-42 expression	Control: 1 a.u. Extract: 0.6 a.u.	↓	[39]
			AChE activity	Control: 100% Extract: 50%	↓	
			Lifespan	Control: 15 days Extract: 17 days	↑	
			ROS production	Control: 100% Extract: 50%	↓	
I. paraguariensis [Ethanolic]	500 mg/kg	Male C57Bl/6 mice	Catalepsy	Control (reserpine): 120 s Extract: 60 s	↓	[47]
	300 mg/kg BW	Male Swiss mice	Elevated Plus Maze	Control: 17% Extract:40%	↑	[48]
			AChE	Control: 4.5 mmol/min/mg Extract: 8.0 mmol/min/mg	↑	
			Step-down avoidance task	Control: 170 s Extract: 70 s	↓	

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