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The flavonoid quercetin induces changes in mitochondrial permeability by inhibiting adenine nucleotide translocase

Rosalba Ortega · Noemí García

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Abstract This study shows the effects of the flavonoid quercetin on diverse mitochondrial functions, among them membrane permeability. Our findings indicate that the addition of 50 μM quercetin did not produce reactive oxygen derived species; however, it inhibited the oxidative stress induced after the addition of Fe^2/H_2O_2 by about 38%. At this concentration, quercetin also promoted a fast calcium release, inhibited oxidative phosphorylation, stimulated oxygen consumption, and decreased membrane potential. In addition 50 μM quercetin inhibited the adenine nucleotide translocase (ANT) by 46%. These effects induced the opening of the permeability transition pore and release of cytochrome c, by its interaction with a component of the non-specific pore complex, fixed to the carrier in the conformation c, as carboxyatractyloside does. Quercetin-induced permeability transition pore opening was inhibited by 0.5 μM cyclosporin A, but, interestingly, the release of cytochrome c was not inhibited by the immunosuppressor, as quercetin was found to disrupt the outer membrane.

Keywords Flavonoids · Quercetin · Permeability transition · Mitochondria · Adenine nucleotide translocase · Cytochrome c · Calcium

Introduction

Quercetin is a flavonoid commonly found in fruits and vegetables and is readily absorbed after ingestion. Plants synthesize flavonoids as secondary metabolites, produced from the degradation of aromatic amino acids, such as phenylalanine and tyrosine, as a defense against oxidative stress damage (Winkel-Shirley 2002). It is known that quercetin is a potent antioxidant that scavenges several reactive oxygen species, including superoxides and hydroxyls, as well as other free radicals (Hu et al. 1995; Cano et al. 2002). However, the flavonoid is also a potent pro-oxidant, the strength of which varies depending on its concentration (Wätjen et al. 2005). Its potential as anti-oxidant is determined by three structural groups: i) the catechol moiety of the B-ring, ii) the 2, 3-double bond in conjunction with a 4-oxofunction of a carbonyl group in the C-ring, and iii) the presence of 3– and 5–OH-groups in the A-ring (Sekher et al. 2001). The pro-oxidant action is related to the degradation products of quercetin, such as o-semiquinone and o-quinone. These in turn form a radical that facilitates the formation of superoxide and the depletion of GSH (Metodiewa et al. 1999). These characteristics of quercetin have been the cause of some controversy. For example, flavonoids might have effects on lipid peroxidation and membrane permeability transition (Santos et al. 1998). Another report shows that quercetin may induce apoptosis by generating reactive oxygen species (ROS) (Wätjen et al. 2005). More recently, Dorta et al. (2005) reported that the flavonoids quercetin and galangin may induce opening of the permeability transition pore through a mechanism involving their uncoupling action and the consequent diminution of the ATP levels.

Mitochondrial permeability transition is a process that depends on the presence of high calcium concentrations, as well as on an inducing agent, such as heavy metals, i.e, Hg^{2+} (Chávez and Holguín 1988), Cd^{2+} (Zazueta et al. 2000; Belyaeva et al. 2004), Cu^{2+} (García et al. 2000), reactive oxygen-derived species (Kowaltowski et al. 1998; Petrosillo

R. Ortega · N. García (✉)
Departamento de Bioquímica, Instituto Nacional de Cardiología, Ignacio Chávez, Juan Badiano # 1 Col. Sección XVI, Mexico, DF 14080, Mexico
e-mail: ngarciar@salud.gob.mx

et al. 2004; García et al. 2005; Zorov et al. 2006), uncoupling agents, such as fatty acids (Wiechowski and Wojtczak 1998; García et al. 2005), oxidant agents, such as phenylarsine oxide (Schweizer et al. 2004: García et al. 2007), and inhibitors of the adenine nucleotide translocase (ANT), such as carboxyatractyloside (Chávez et al. 1991). The permeability transition pore has a diameter of 2–3 nm that allows crossing of molecules of up to 1,500 Da (Bernardi 1999; Zoratti et al. 2005). Recently, we reported that mitochondrial DNA fragments can exit the matrix through this pore (García et al. 2007). On the other hand, proteins localized in the intermembrane space, such as endonuclease G (Davies et al. 2003) and cytocrome c (Brutaite et al. 2001), can exit mitochondria by two possible mechanisms: the first involves breaking the outer membrane by osmotic lysis (Weiss et al. 2003) and the second involves the formation of Bax pores during the apoptotic process (Schlesinger and Saito 2006; García-Sáez et al. 2007). The permeability transition pore complex is formed mainly by three different proteins: the adenine nucleotide translocase (ANT) localized in the inner membrane, the voltage-dependent anionic channel (VDAC), localized in the outer membrane, and cyclophilin D, localized in the matrix. This pore is regulated by the immunosuppressor cyclosporin A (Zoratti et al. 2005). Recently, the study of permeability transition has gained relevance due to its close relationship with apoptosis, since transition permeability regulates cytochrome c release that triggers the mitochondrial pathway of apoptosis (Borutaite et al. 2003; Correa et al. 2007).

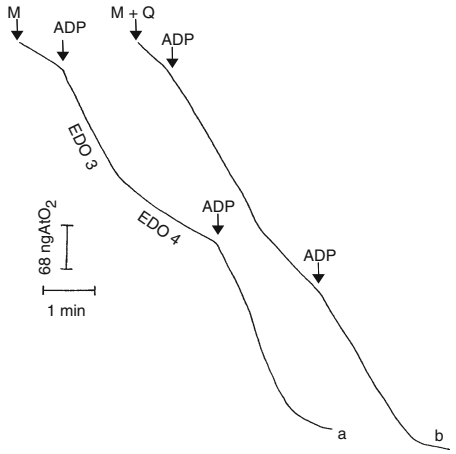
The results from the present work indicate that quercetin induces permeability transition by directly interacting with the adenine nucleotide translocase and inhibiting its activity. An interesting point is that this flavonoid induces the release of cytochrome c through a mechanism that is insensitive to cyclosporin A.

Materials and methods

Mitochondria were isolated from rat kidney cortex by homogenization of the tissue in 0.25 M sucrose-1 mM EDTA, buffered to pH 7.3 with 10 mM Tris, following the standard centrifugation pattern. The final pellet was suspended in free EDTA-sucrose-Tris medium. Mitochondrial protein was determined by the method of Lowry et al. (1951). Oxygen consumption was assayed polarographically by using a Clark type electrode. Mitochondria were incubated in 1.5 ml of a basic medium containing 125 mM KCl, 10 mM HEPES, 10 mM succinate, 3 mM phosphate, and 5 μg rotenone, pH 7.3; 0.2 mM ADP was added to induce state 3 respiration. Calcium movements were determined following the change in absorbance at 675–685 nm using the external metallochromic indicator Arsenazo III (Scarpa et. al. 1978) and using $^{45}CaCl_2$ (specific activity 500 cpm/nmol). Two mg of mitochondrial protein were added to 3 ml of basic medium containing 125 mM KCl, 10 mM succinate, 10 mM HEPES, 0.2 mM ADP, 5 μg rotenone, and 50 μM Ca^2. After 10 min of incubation, aliquots of 0.2 ml were withdrawn and filtered through a 0.45-μm pore diameter filter, and the mitochondrial radioactivity retained in the filter was measured. Transmembrane potential was analyzed by measuring the changes in absorbance at 511–533 nm according to Akerman and Wikström (1976), using the dye saphranine. Membrane lipid peroxidation was analyzed by measuring the generation of thiobarbituric acid-reactive substances (TBARS) as reported by Ohkawa et al. (1979). Mitochondrial protein (1 mg) was added to 1 ml of basic medium supplemented with 5 μg rotenone, 50 μM Ca^{2+} and 400 μM Fe^{2+}/citrate (1:1); 20 min after incubation, TBARS were measured, after extraction with butanol, in a spectrophotometer at 532 nm, and their concentration was calculated using a tetraetoxypropane curve. The adenine nucleotide translocase activity was measured as follows: mitochondrial protein (1 mg) was incubated for 20 s with 30 μM [^{3}H] ADP (specific activity 1,300 cpm/nmol) and then an aliquot was filtered through a 0.45-μm filter and washed with 0.1 M KCl. Cytochrome c release was analyzed after 10 min of incubation at 25°C of 2 mg of mitochondria protein in the basic medium, described above, with added quercetin. Cytochrome c content was evaluated using a primary monoclonal antibody against cytochrome c (1:1,000 dilution) and an alkaline-phosphate-conjugated secondary antibody.

Results

Figure 1 shows the effect of quercetin on mitochondrial respiration. Panel A shows two representative traces of respiration without quercetin (trace a) and with 50 μM quercetin (trace b). In both traces, 200 μM ADP had been added to stimulate oxidative phosphorylation. It was found that quercetin diminished the respiratory control from 3.25± 0.22 to 1.87±0.20; representing an inhibition of 42%. This indicates that quercetin uncoupled oxidative phosphorylation, depending on the concentrations used in the assays, which were 30 μM, 40 μM, 45 μM, and 50 μM. At lower concentrations, this effect was not observed. However, it should be noted that in fact, at lower concentrations the membrane electric gradient collapsed, as observed in Fig. 2 panel A, where the addition of 50 μM Ca^2 had no effect, and the potential was decreased in the presence of 1 μM CCCP (trace a). After the addition of 5 μM quercetin, the transmembrane potential collapsed (trace b), and this effect was increased when 30 μM quercetin was added (trace c).



Quercetin	Respiratory Control ± SD	% oxygen consumption EDO 3 ± SD	% oxygen consumption EDO4 ± SD
0	3.25 ± 0.22	100	100
30	2.32 ± 0.36*	103.5 ± 14.3	133 ± 8.7***
40	2.31 ± 0.44*	100 ± 6.0	143 ± 21****
45	1.99 ± 0.34*	85.3 ± 6.2**	139 ± 15**
50	1.87 ± 0.20*	81.2 ± 5.0***	143 ± 21****

Quercetin vs control
*p > 0.05, ** p > 0.02, *** p > 0.01, **** p > 0.03

Fig. 1 Effect of quercetin on mitochondrial respiration. Mitochondrial protein (1 mg) was added to 1.5 ml of basic medium, pH 7.3; plus 5 μg rotenone, 0.2 mM ADP, and 30 μM, 40 μM, 45 μM, and 50 μM quercetin (*Q*). Trace a shows the characteristic respiration without quercetin and trace b in the presence of 50 μM quercetin. The table in the figure shows the respiratory control, the percentage of oxygen consumed in state 3, and percentage of oxygen consumed in state 4. Statistics (1-way ANOVA) was applied to three differents assay

Figure 2, panel B, shows the effect of quercetin on the transmembrane potential in the absence of calcium. These results indicate that quercetin did not need calcium to disrupt the transmembranal potential gradient. In this respect, Dorta et al. (2005) and Trumbeckaite et al. (2006) reported that the flavonoid acts as an uncoupler for the induction of the permeability transition pore.

Figure 3 shows the effect of quercetin on calcium retention, as an indication of permeability transition pore opening. Figure 3a shows the effect of different concentrations of quercetin added to the medium. Trace a shows the calcium retention without addition of quercetin, and trace b shows that the addition of 30 μM quercetin induced calcium release. The rate of calcium release was increased in parallel with increasing concentrations of the flavonoid, i.e., from 40 (trace c), 45 (trace d), to 50 μM (trace e). The addition of 50 μM quercetin also decreased calcium retention and increased the rate of release. The addition of lower quercetin concentrations (2 μM, 10 μM, 15 μM, and 20 μM) did not have any effect on calcium retention, as shown in Fig. 3b. The presence of 0.5 μM cyclosporin A inhibited the effect of 50 μM quercetin, as shown in Fig. 3c, trace b. The effect of quercetin on the opening of the permeability transition pore is clear, as the previous results were inhibited by CSA. The presence of albumin (BSA) in the medium also inhibited the reaction (Fig. 3c, trace c), which may indicate that quercetin might be solubilized in the lipid milieu of the membrane probably modifing its fluidity. In order to evaluate the possible modification of membrane fluidity, the calcium release reaction to the flavonoid was assayed at different temperatures 4°C, 10°C, 15°C, 25°C, 30°C, 35°C, and 40°C. The results shown in Fig. 4 indicate that calcium was released

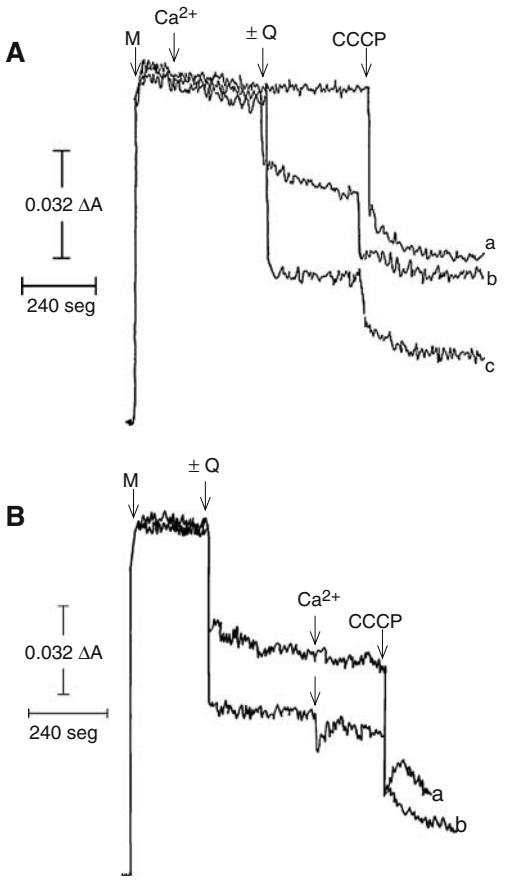


Fig. 2 Effect of quercetin on membrane potential. Mitochondrial protein (2 mg) was added to 3 ml of the basic medium, as described under Materials and Methods. In addition, the medium contained 5 μg rotenone, 0.2 mM ADP, 50 μM Ca^2, 10 μM saphranine, and quercetin (*Q*) at different concentrations. Panel A trace a shows control mitochondria with the addition of 1 μM CCCP; trace b shows the effect of 5 μM quercetin and trace c shows the effect of 30 μM quercetin. Panel B trace a shows the effect of 5 μM quercetin without Ca^2 and trace b shows the effect of 30 μM quercetin without Ca^2. Where indicated, 2 mg mitochondrial protein, 50 μM Ca^2 and 1 μM CCCP were added

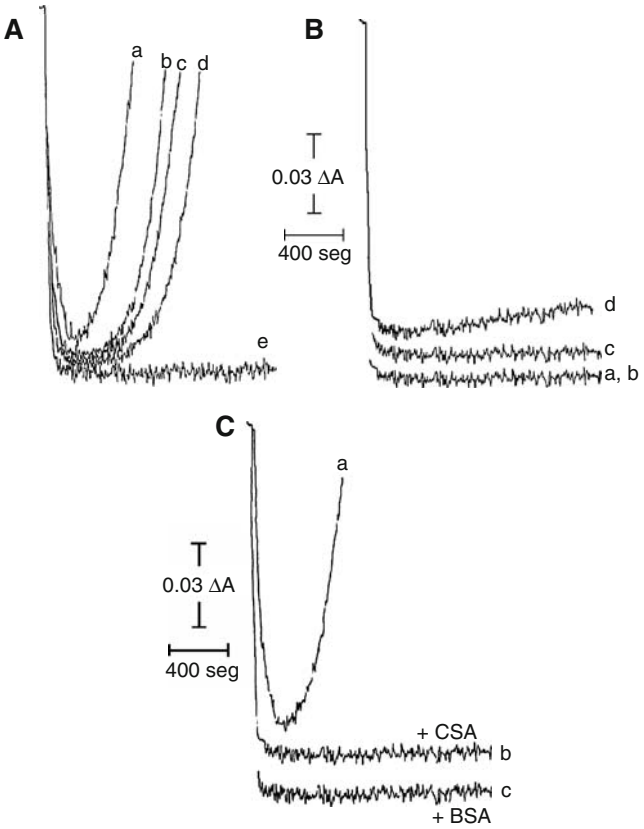


Fig. 3 Effect of quercetin on calcium retention. Mitochondrial protein (2 mg) was added to 3 ml of basic medium, as described under Materials and Methods. In addition, the medium contained 5 μg rotenone, 0.2 mM ADP, 50 μM Ca^2, 50 μM Arsenazo III, and quercetin at different concentrations. Panel **a** shows the calcium released in the presence of 50, 45, 40, 30 μM quercetin (trace a, b, c, and d, respectively). Trace e shows the calcium retention without quercetin. Panel b, shows the effect of 2 μM, 10 μM, 15 μM, and 20 μM quercetin (a, b, c and d respectively). Panel c, trace a, shows calcium release in the presence of 50 μM quercetin; trace b, in the presence of 50 μM quercetin plus 0.5 μM cyclosporine A; and trace c, in the presence of 50 μM quercetin plus 1 mg albumin

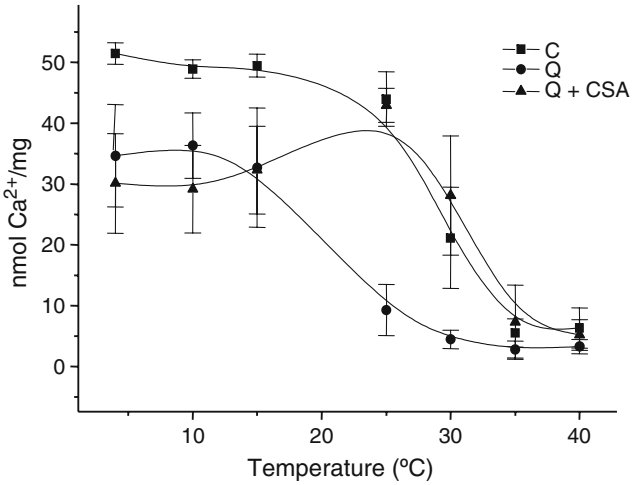


Fig. 4 Effect of temperature on calcium release induced by quercetin. Mitochondrial protein (2 mg) was added to 3 ml of basic medium plus 5 μM rotenone, 0.2 mM ADP, 50 μM $^{45}Ca^2$, and then incubated for 10 min. After incubation, an aliquot was filtered through a 0.45-μm filter. The calcium content in mitochondria with or without quercetin was quantified at different temperatures (10°C, 15°C, 25°C, 30°C, 35°C, and 40°C)

when the temperature reached 25°C. At lower temperatures, quercetin diminished the rate of calcium uptake.

On the other hand, there are several reports indicating that quercetin acts as antioxidant or pro-oxidant, depending on its concentration (Wätjen et al. 2005; Robaszkiewicz et al. 2007). In this respect, experiments were carried out to explore the ability of quercetin to induce or inhibit oxidative stress. Figure 5 reveals the presence of malondialdehyde in mitochondria with or without quercetin under conditions of permeability transition after the addition of 50 μM calcium, and under conditions of oxidative stress (i.e., after the addition of Fe^{2+}/H_2O_2). The presence of quercetin alone did not induce generation of malondialdehyde. However, when oxidative stress was present, quercetin inhibited the production of malondialdehyde by about 38%. This indicates that quercetin, under the conditions used in this study may act as an antioxidant.

Figure 6 shows the adenine nucleotide translocase activity in the presence of quercetin. The exchange of adenine nucleotides was inhibited by 46% in the presence of 50 μM quercetin. This could indicate that quercetin may interact with the translocase, or be a regulator of the permeability transition pore.

The permeability transition pore induces cytochrome c release. Figure 7 a shows the release of cytochrome c after

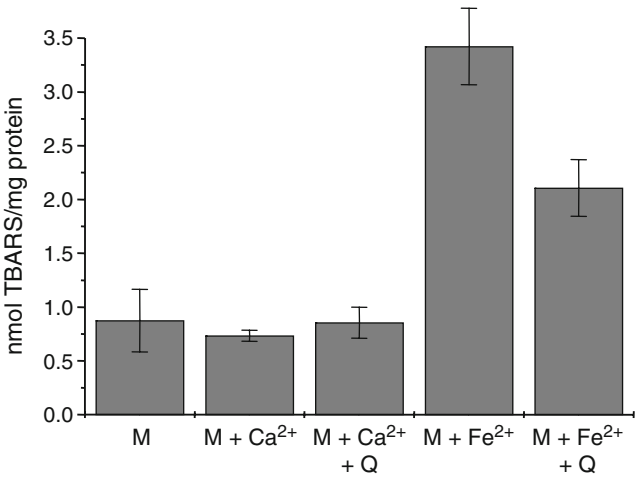


Fig. 5 Effect of quercetin on lipid peroxidation. Mitochondrial protein (1 mg) was incubated for 10 min in 1 ml of basic medium plus 5 μM rotenone, 0.2 mM ADP; thiobarbituric acid reactive species (TBARS) were measured as indicated under Materials and Methods. Where indicated, 50 μM Ca^2, 50 μM quercertin, 400 μM/3 mM Fe^2/H_2O_2 were added

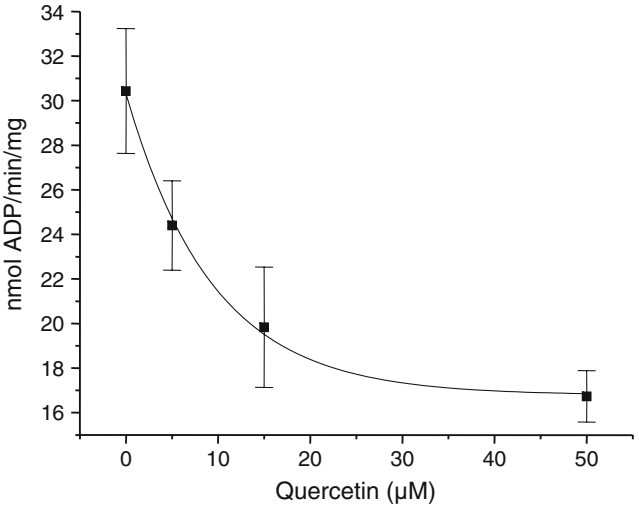


Fig. 6 Effect of quercetin on adenine nucleotide exchange. Mitochondrial protein (1 mg) was incubated in a basic medium, as described under Materials and Methods. In addition, 30 μM [^{3}H]-ADP (sp. act. 1,300 cpm/nmol) and quercetin at different concentrations (5 μM, 15 μM, and 50 μM) was added. After 30 s of incubation, at 25°C, an aliquot of 0.2 ml was withdrawn and filtered through a 0.45-μm pore diameter filter. The radioactivity retained in the filter was measured

addition of quercetin. As illustrated, the flavonoid induced the release of cytochrome c from mitochondria. The presence of 1 μM cyclosporin A did not inhibit the quercetin-induced cytochrome c release. Based on these results, we evaluated the integrity of the outer membrane, since, cyclosporin A was able to inhibit the quercetin-induced calcium release reaction as demonstrated in Fig. 3b. The outer membrane integrity was evaluated by following the presence of monoamine oxidase by means of a western blot. As shown in Fig. 7, the presence of quercetin induced disruption of the outer membrane in such a way that indicated that cytochrome c must be released through a mechanism that is insensitive to cyclosporin A.

Discussion

There are a number of reports about the effect of flavonoids on mitochondrial function. These reports indicate that these compounds effectively protect heart mitochondria from undergoing ischemia-reperfusion damage (Brookes et al. 2002). In addition, flavonoids avoid the oxidative damage induced by mercurials in brain mitochondria (Franco et al. 2007), and protect against uncoupling and inhibition of mitochondrial ATP synthesis (Trumbeckaite et al. 2006; Dorta et al. 2005). Nevertheless, there is a growing controversy in relation to the effect that flavonoids have on mitochondrial functions, because flavonoids may act as either protectors or inducers of damage. The controversy is based on the characteristics exhibited by flavonoids as antioxidants and pro-oxidants (Cano et al. 2002; Sekher Pannala et al. 2001; Robaszkiewicz et al. 2007). The results of this study indicate that quercetin may induce inhibition of mitochondrial oxygen consumption at concentrations above 30 μM. On the other hand, it induces a drop in the transmembrane electric gradient at concentrations of 5 μM and 30 μM, with or without calcium, as observed in Fig. 2. Lower concentrations of quercetin (2 μM, 10 μM, 15 μM and 20 μM) have no effect on calcium release; this would indicate that the collapse of the transmembrane potential does not suffice to induce the opening of the permeability transition pore, for the same reason that the presence of calcium does not increase the drop of the membrane potential. At concentrations above 30 μM, quercetin induced calcium release by opening the permeability transition pore. In this respect, Dorta et al. (2005) reported that quercetin-induced changes in permeability transition might be due to its uncoupling effect. However, this effect was not clear because, in the absence of calcium, quercetin induced a drop in the transmembrane electric gradient.

On the other hand, it is well known that inducers, such as carboxyatractyloside (Gunter and Pfeiffer 1990; Haworth and Hunter 2000) and fatty acids, i. e., oleate and agaric

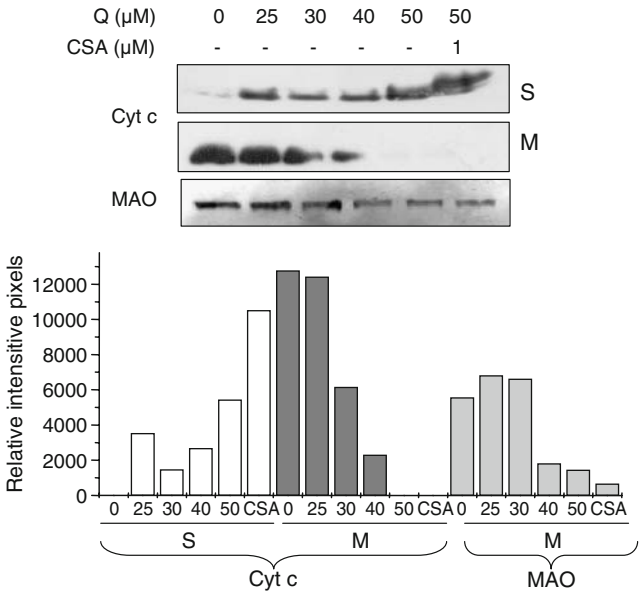


Fig. 7 Induction of cytochrome c release by quercetin. Mitochondrial protein (2 mg) was added to 3 ml of basic medium, as described under Materials and Methods. In addition, the medium contained 5 μg rotenone, 0.2 mM ADP, 50 μM Ca^2 and 0.5 μM cyclosporin A, where indicated. Before adding mitochondria, quercetin was added, and then the mitochondria were added and incubated at 25°C for 10 min. After incubation, mitochondrial suspensions were centrifuged at 14 0000×*g* for 10 min. The contents of cytocrome c (*cyt c*) and monoamine oxidase (*MAO*) were measured in mitochondria (*M*) and supernatants (*S*). The graph shows the pixels measured by western blot

acid (García et al. 2005) promote permeability transition by inhibiting the adenine nucleotide translocase. In this regard, the present results indicate that quercetin inhibited the adenine nucleotides exchange in the presence of 50 μM quercetin by 46%. This seems to indicate that quercetin induced permeability transition by interacting with the adenine nucleotide translocase, a component or regulator of the permeability transition pore (Brustovetsky and Klingenberg 1996; Halestrap 2004; Kokoszka et al. 2004). The action of quercetin would be similar to that of carboxyatractyloside in fixing the adenine nucleotide translocase on the cytosol side of the inner membrane (Pebay-Peyroula et al. 2003) to induce permeability transition.

At the same time, we cannot ignore the fact that quercetin has the property of being a pro-oxidant, at high concentrations, due to its structure (Wätjen et al. 2005; Metodiewa et al. 1999). For this reason, quercetin could induce changes in permeability through the generation of reactive oxygen species (Petrosillo et al. 2004; García et al. 2005). However, the results shown here indicate that the flavonoid did not induce generation of free radicals, but rather inhibited them when the production of free radicals was induced with Fe^2/H_2O_2. In this sense, quercetin is an antioxidant, as has been reported before (Saija et al. 1995; Park et al. 2003; Chow et al. 2005; Franco et al. 2007).

In addition, it is known that apoptosis is generally associated with activation of caspase cascades and the family of Bcl–2 proteins (Finucane et al. 1999). In addition, apoptosis is accompanied by mitochondrial dysfunction signs, including loss of the inner membrane potential and the release of cytochrome c (Correa et al. 2007). Our results indicate that quercetin induced cytochrome c release from mitochondria. Interestingly, the presence of cyclosporin A was not able to inhibit its release, the way it inhibited calcium release, since the flavonoid ruptured the outer membrane, releasing cytochrome c.

In conclusion, we can say that quercetin induces the opening of the permeability transition pore through inhibition of the adenine nucleotide translocase, and that this produces cytochrome c release that is insensitive to cyclosporin A. This effect could explain why this flavonoid is both a damage inducer and/or a protector.

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