THE FLAVONOID LUTEOLIN CONTRIBUTES TO MITOCHONDRIAL FUNCTION IN VARIOUS ORGANS AND TISSUES

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Abstract

Mitochondria are involved in intracellular Ca^{2+} buffering and signal transduction. In most cells, cell death occurs when RTR switches to an open state as a result of the toxic accumulation of Ca^{2+} ions in the mitochondria.

At the same time, in non-neuronal cells, through RTR, Ca^{2+} ions are released in mitochondria and participate in physiological signal transmission, and control of various bioenergetic processes. Based on this, we investigated the effect of different concentrations of the flavonoid isorhamnetin on RTR status in mitochondria. A concentration of 10 μM of Ca^{2+} ions was used as an inducer. According to the results of the study, an increase in the number of mitochondria was observed in the presence of Ca Ca^{2+} ions in the incubation medium. In the experiments, the effect of isorhamnetin flavonoid on the RTR of mitochondria was determined. In this case, isoramnetin at a concentration of 50 μM inhibited RTR opening by 23.9% compared to the control. A concentration of 100 μM of this flavonoid inhibited RTR opening by 44.7% and at a concentration of 150 μM, 74,

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Introduction

The obtained results show that isoramnetin has an inhibitory effect on Ca^{2+}-dependent RTR in liver mitochondria. The half-maximal inhibitory (IC50) concentration of liver mitochondria PTP of flavonoid isorhamnetin was IC50=103.7±4.5 μM. It is known that changes in the RTR of liver mitochondria are observed in various pathological conditions. In this case, a decrease in the number of adenine nucleotides in the mitochondria directly leads to a decrease in the inhibitory properties of RTR. In this case, the study of the effect of flavonoids with antioxidant properties as inhibitory agents of PTP shows that In a previous study [15], we showed that a number of natural flavonoids, depending on their antioxidant properties, protect against the occurrence of MPT, therefore, they have the ability to act as cytoprotectors against necrosis and apoptosis, although the data are recent. [16,17] have shown that some flavonoids can promote apoptosis due to prooxidant/MPT induction. In this context, disruption of apoptosis by cells is associated with tumor initiation, progression, and metastasis [18,19], and flavonoids are considered as promising anticancer agents [20]. In this study, we reviewed the energetic aspects of isolated rat liver mitochondria exposed to the flavonoids quercetin, tachyfolin, catechin, and galangin, taking into account the double bond 2,3/3-OH group and 4-we yield (Fig. 1). Oxofunction in the C-ring and o-di-OH in the B-ring of their structures, as well as mitochondrial mechanisms potentially involved in cell necrosis and apoptosis.

2. Materials and methods

2.1. Chemical substances

Flavonoids were purchased from Sigma/Aldrich. All materials used are of the highest commercial grade. The amount of dimethyl sulfoxide used to solubilize the flavonoids did not affect the reactions. All solutions were made using glass distilled deionized water (2 mM contaminant Ca^{2+}).

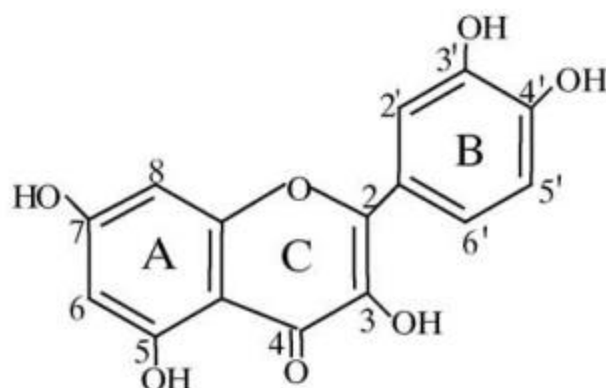
2.2. Protection of rat liver mitochondria

Mitochondria were isolated using a standard differential centrifuge [21]. Wistar rats weighing approximately 0.15 kg were euthanized; livers (15–20 g) were immediately removed, cut into a 40 mL medium containing 200 mM sucrose, 2 mM EGTA, and 15 mM HEPES-KOH, pH 7.15, and homogenized three times for 16 s at 60 s intervals with Potter. Homogenates were centrifuged at 480×g for 6 min, and the resulting supernatant was centrifuged at 10,200×g for 15 min. Pellets were suspended in a 15 ml medium containing 200 mM sucrose, 0.4 mM

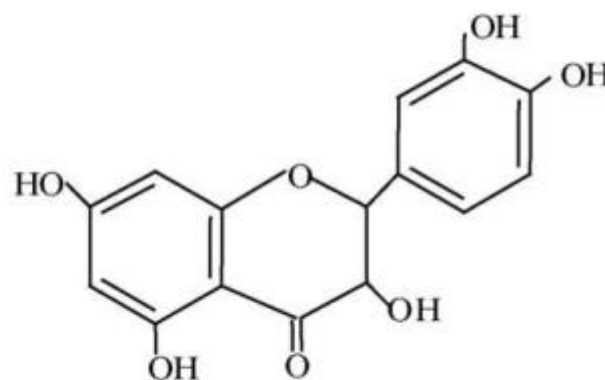
EGTA, and 15 mM HEPES-KOH, pH 7.15, and centrifuged at 3300 × g for 16 min. The final mitochondrial pellet was suspended in a 2 ml medium containing 200 mM sucrose and 15 mM HEPES-KOH, pH 7.15, and used within 180 min.

2.3. Standard incubation process

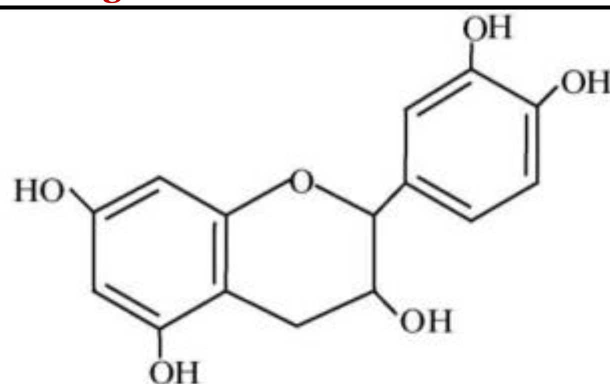
Mitochondria supplemented with 5 mM potassium succinate (+ 2.5 M rotenone) in a standard incubation medium containing 120 mM sucrose, 60 mM KCl, and 15 mM HEPES-KOH, pH 7.2, were incubated at 30°C in vitro.



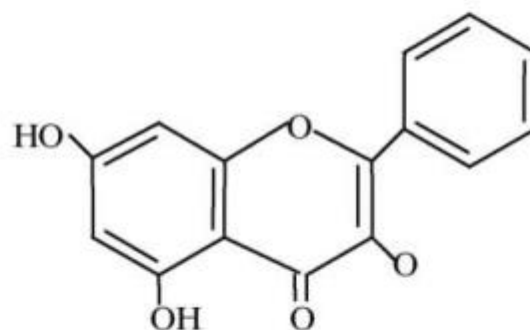
3, 3', 4', 5, 7-pentahydroxyflavone
Quercetin
(Quer)



3, 3', 4', 5, 7-pentahydroxyflavanone
Taxifolin
(Tax)



3, 3', 4', 5, 7-pentahydroxyflavanol
Catechin
(Cat)



3, 5, 7-trihydroxyflavone
Galangin
(Gal)

Fig. 1. Flavonoids structures.

2.4. Evaluation of the interaction of flavonoids with the mitochondrial membrane and their effect on fluidity.

Incorporation of 1,6-diphenyl-1,3,5-hexatriene-4-trimethylammonium trimethylammonium tosylate (TMA-DPH) [22] into membranes induces a fluorescence response (F), whose static quenching is described by the Stern-Volmer equation. : F0/F = 1 + KSV [Q], where F0 and F are the fluorescence intensity in the absence and presence of quencher, respectively, and KSV, the Stern-Volmer constant. To assess the interaction of flavonoids with the mitochondrial membrane, mitochondria (0.4 mg protein) were incubated with 0.56 μM TMA-DPH in a standard incubation medium at 30 °C before the addition of different amounts of flavonoids. 2 ml. Fluorescence was measured with an F-

2500 spectrofluorometer at excitation and emission wavelengths of 362 and 432 nm, respectively. Membrane fluidity was assessed by steady-state fluorescence polarization (P) of TMA-DPH under the experimental conditions described above. P, i.e., the membrane-to-fluid ratio (1/P), was calculated from the fluorescence intensity measured parallel (I1) and perpendicular (I2) to the plane of excitation light according to the following equation: $P = I1 - (G)I2/I1 + (G)I2$, where G is the instrument polarization correction factor [23].

2.5. Continuous monitoring analysis

Experiments were carried out on purebred white rats weighing 180-200 g. Rat liver mitochondria were separated by differential centrifugation. Composition of separation medium: 250 mM sucrose, 10 mM Tris-HCl, 1 mM EDTA, pH 7.4. The amount of protein in mitochondria was determined by the biuret method. Staining of mitochondria was performed photometrically at a wavelength of 540 nm. The Fe^{2+}/ascorbate system was used to study the process of LPO in the mitochondrial membrane. Under the influence of this system, the mitochondrial membrane loses its barrier function, resulting in the LPO process. IM composition: KCl – 125 mM,tris-HCl - 10 mM, pH 7.4; Concentrations: $FeSO_4$ - 20 μM, ascorbate - 400 μM; the amount of protein in mitochondria was 0.3-0.4 mg/ml. In experiments, the effect of afzelin (kaempferol-3-rhamnoside) flavonoid on the LPO process induced by inducers of the Fe^{2+}/ascorbate system in the mitochondrial membrane was studied. Afzelin flavonoid inhibited the LPO process by 14.7% at a concentration of 25 μM, by 36.8% at a concentration of 50 μM, and by 55.4 and 71.2%, respectively, at the concentrations of 75 and 100 μM, the inhibition of mitochondria by inducers. Further studies investigated the effect of kaempferol, another glycoside of kaempferitrin, on the LPO process in mitochondria. In this case, kaempferitrin induces the LPO process in mitochondria induced by the Fe^{2+}/ascorbate system by 33.2% at a concentration of 50 μM, At the concentration of 100 μM, 63.4% and at the concentration of 150 μM, 78.1% inhibition was determined. As can be seen from the obtained results, it was shown that the studied glycosides of kaempferol exert weaker antioxidant properties compared to kaempferol (up to 10 μM).

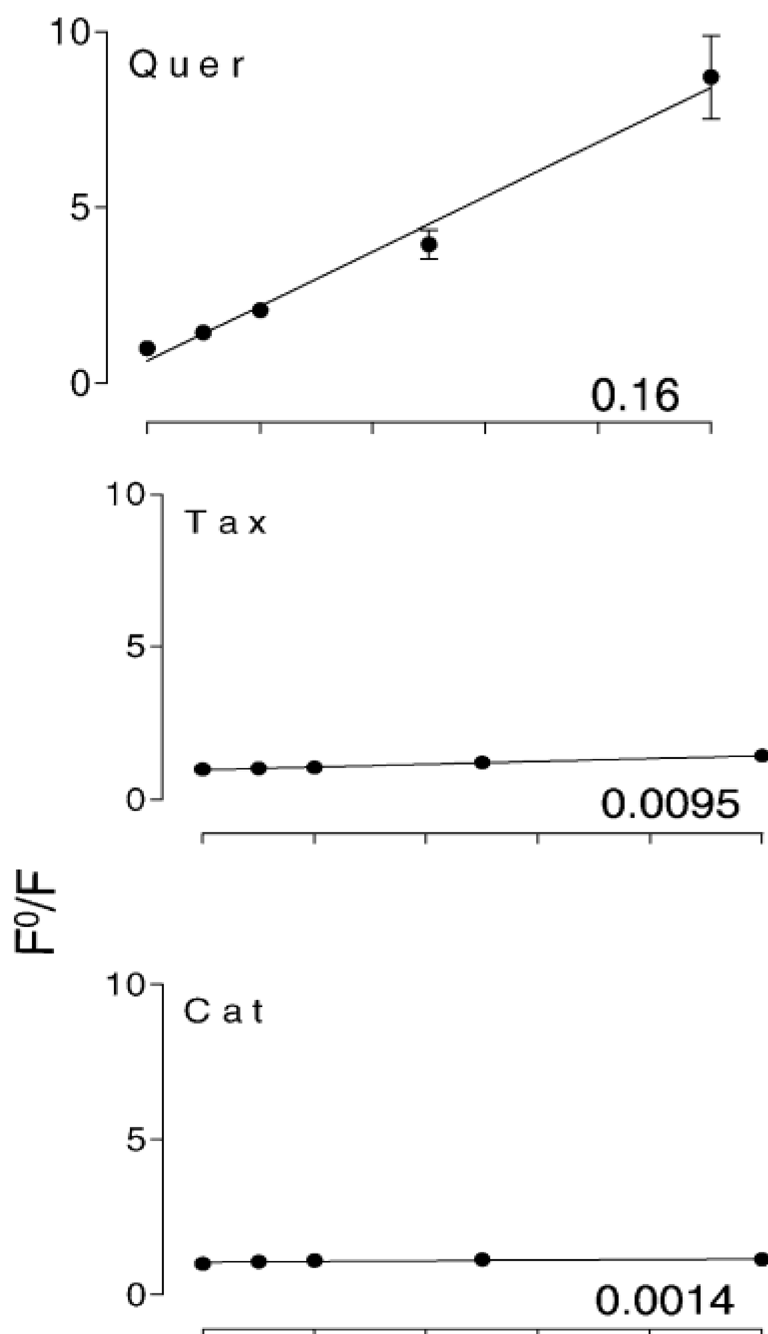
2.6. Determination of ATP

ATP was detected by the hot luciferin-luciferase assay system [26]. The mitochondrial suspension (2 mg protein/ml) was centrifuged at 8000 × g for 4 min at 5°C, and the pellet was treated with 2 ml of ice-cold 1 M $HClO_4$. After

centrifugation at 13,000 × g for 6 min at 4°C, 90 ml aliquots of the supernatants were neutralized with 80 ml of 2 M KOH, 800 mM TRIS-HCl, pH 7.7 (final volume, 2 ml) and centrifuged again. Bioluminescence was measured in the supernatant with a Sigma/Aldrich assay kit using an AutoLumat LB953 Luminescence photometer (PerkinElmer Life Sciences, Wilbad, Germany) according to the manufacturer's instructions.

2.7. Statistical analysis

Statistical analysis was performed by analysis of variance and Dunnett's test.



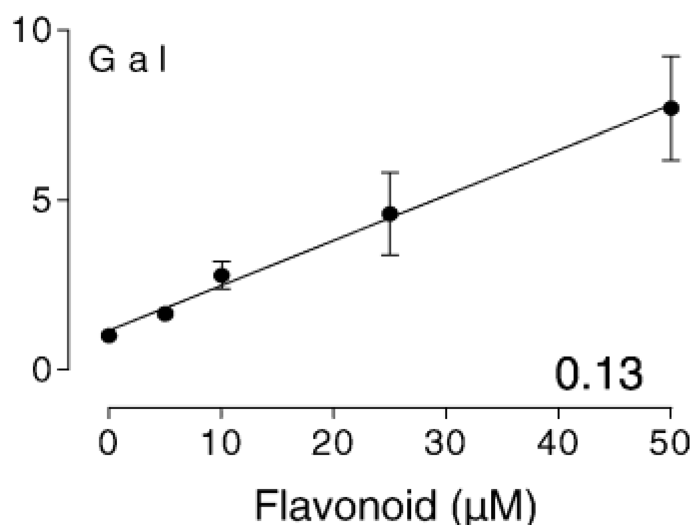


Figure 2. The interaction of flavonoids with the mitochondrial membrane was assessed by quenching the fluorescence of the TMA-DPH-labeled mitochondrial membrane (0.4 mg protein) incubated in a standard medium (125 μM 5M10 μM) at 30°C. mM HEPES-KOH, pH 7.4), in a final volume of 1 ml, showing the corresponding Stern-Volmer constants. Values ± SEM are relative to the results of three experiments using different mitochondria preparations and the control in the absence of flavonoids.

3. Results

3.1. Interaction of flavonoids with the mitochondrial membrane

The inner membrane probe TMA-DPH enters the hydrophobic core of membranes oriented parallel to the axis of the lipid acyl chain and has fluorescence, whose quenching by chemicals reflects changes in the membrane structure. The Stern-Volmer constant values for quenching this fluorescence reaction in the presence of flavonoids (Fig. 2) show that quercetin and galangin are very effective in interacting with the mitochondrial membrane compared to tachyfolin and catechin. The fluorescence polarization (P) of TMA-DPH represents the order of motion in the hydrophobic core of the membrane lipid bilayer, which is inversely related to the membrane fluidity (1/P). Thus, we also estimated 1/P for mitochondria exposed to flavonoids (results not shown), consistent with the above results, we observed that only quercetin and galangin were highly effective in reducing mitochondrial membrane fluidity. In the experiments, the effect of flavonoids was studied in the de-energized state of the inner membrane of mitochondria about Na+ and H+ in a nitrate isoosmotic medium. In the conducted experiments, the passive ion permeability of the inner

membrane of the liver mitochondria was studied in the isoosmotic dienergized environment of NH_4NO_3 under the influence of luteolin flavonoid. It was found that the passive conductivity of protons increased by 1.3 times under the influence of a 10 μM concentration of luteolin a flavonoid. Under the influence of flavonoid concentration of 20 μM, the passive conductivity of protons in the NH_4NO_3 isoosmotic medium increased by 1.5 times compared to the control. under the influence of flavonoid concentrations of 30, 40, and 50 μM, it was shown that the passive ion permeability of the inner membrane of mitochondria increases by 2.1, 2.6, and 3.0 times, respectively. Continuing the research, the effect of luteolin flavonoid on the passive ion permeability of the inner membrane of liver mitochondria in the NaNO3 isoosmotic medium was studied. As a result of the effect of luteolin flavonoid concentration of 10 μM, it was shown that the passive ion permeability of liver mitochondria increased by 1.6 times compared to control parameters. Under the influence of 20 μM, 30 μM, 40 μM and 50 μM concentrations of flavonoid, the passive ion permeability for $Na^{(+)}$ ions of the inner membrane of rat liver mitochondria, compared to the control, was 2.2, 2.8, 3.3, respectively. 3, It was found to increase 7 times. As can be seen from the obtained results, it was found that the flavonoid luteolin increases the passive ion permeability of the inner membrane of liver mitochondria of monovalent cations in de-energized conditions.

3.2. Effects of flavonoids on mitochondrial respiration/ΔPS

At a concentration of 40 M, only quercetin significantly inhibited the stimulation of state 3 respiration of mitochondria by succinate, a substrate of respiratory chain II, or glutamate + malate, substrates of site I (Figure 3). At 24 M, inhibition of state 3 respiration was insignificant for the evaluated flavonoids, except for quercetin, which showed rate values close to those observed at 50 5 concentration.

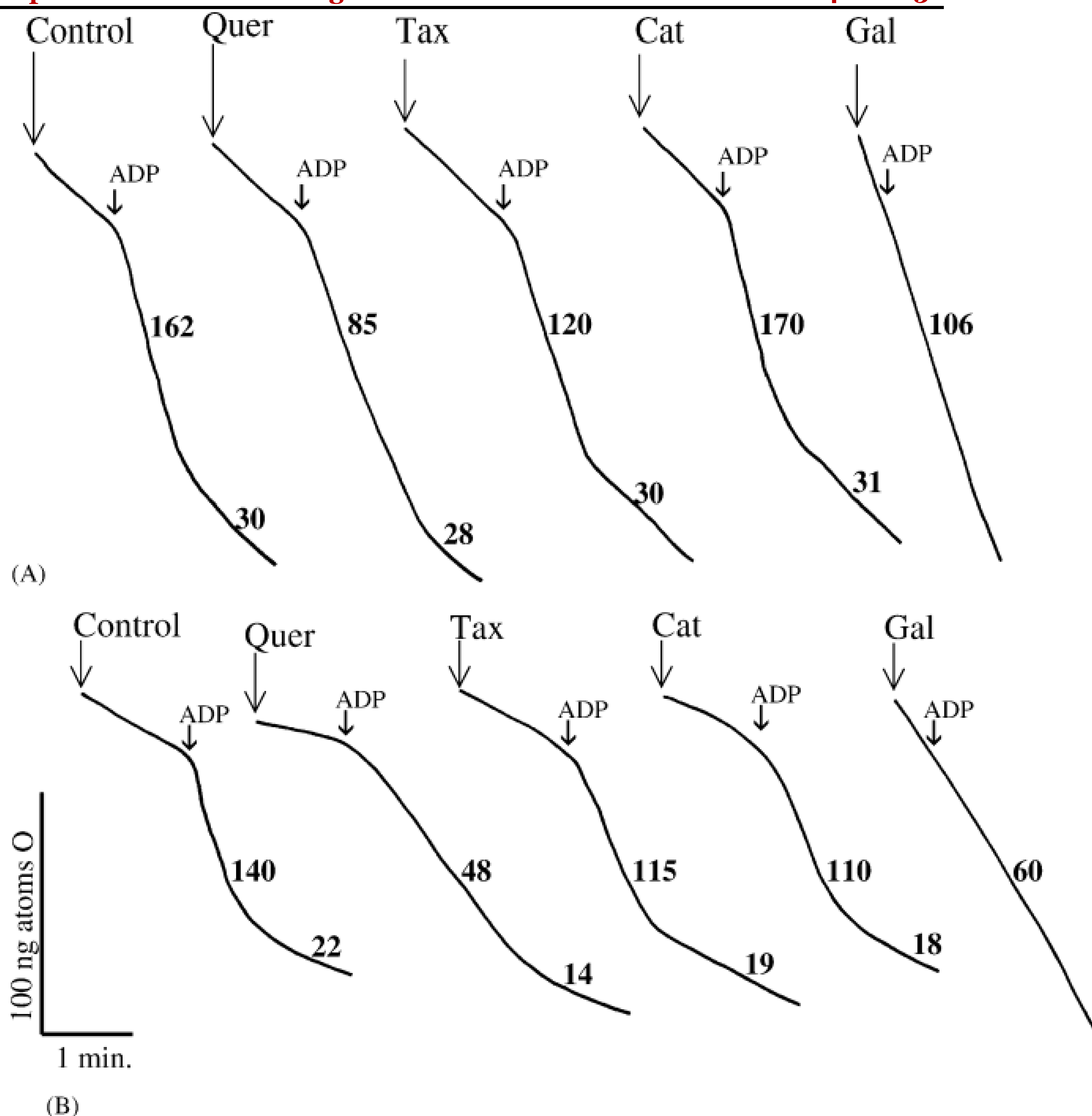


Figure 3. Effect of 40 M flavonoid on state 3 and state 4 respiration of isolated rat liver mitochondria (1.5 mg protein) incubated with 4 mM succinate + 2.5 M rotenone (A) or 2.5 M at 30°C. malate (B), in the presence of 0.5 mM EGTA and 10 mM K_2HPO_4 in the standard medium described in the legend to Fig. 2, in a final volume of 1.5 ml. State 3 respiration was initiated with 0.4mmol ADP. Tracings are representative of three experiments using different mitochondria preparations. Values are state 3 and state 4 respiration rates given as ng atoms O min^{-1}.

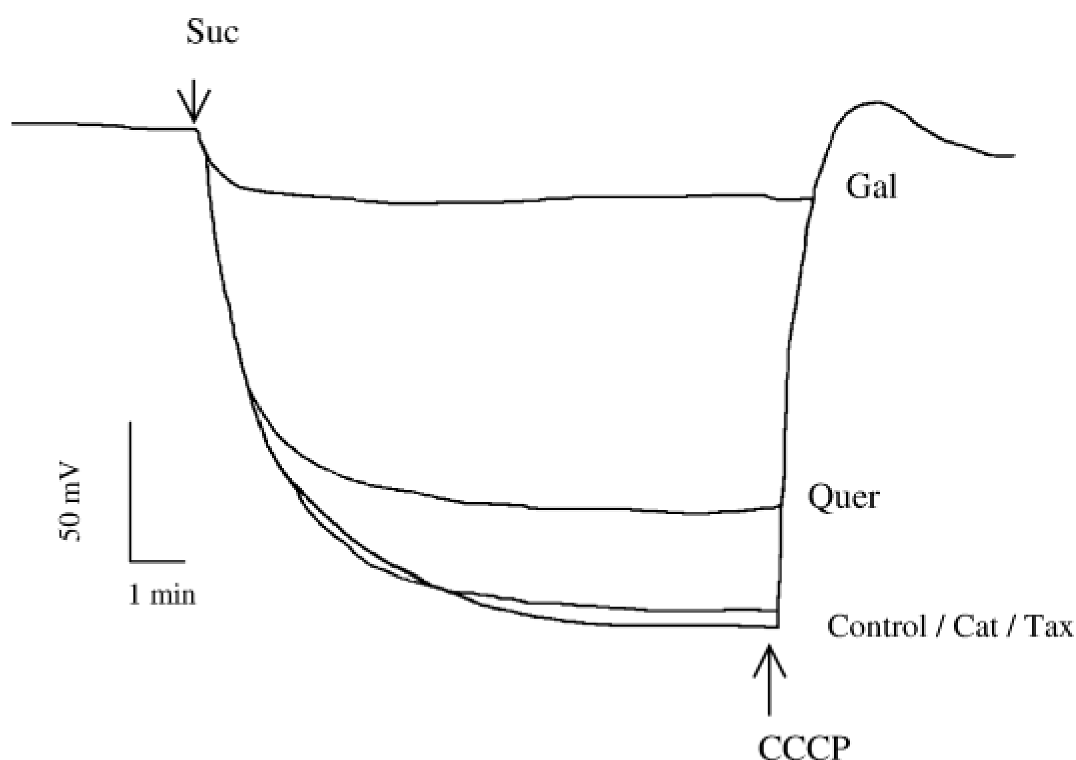


Figure 4. Effect of 40mM flavonoids on ps of succinate-stimulated isolated rat liver mitochondria incubated under the conditions described in the legend to Figure 3.

4. Discussion and Conclusion

This study examines the energetic aspects of isolated mitochondria exposed to the flavonoids quercetin, tachyfolin, catechin and galangin. The 2,3 double bond / 3-OH group and 4-oxo function on the C-ring, as well as the o-di-OH structure on the B-ring, were taken into account. These structural features determine the important properties of flavonoids, particularly their antioxidant activity in biological systems [14]. The 2,3 double bond structure gives the C-ring high rigidity and keeps it in a flatter position compared to the A-ring; The 3-OH group interacts with the B-ring via a hydrogen bond, placing it practically in the same plane as the A and C-rings [27,28]. Because this conformation important.

Since the order of high lipid packing and rigidity of membrane structures and the energetic processes of mitochondria are particularly sensitive to the organization of the inner membrane of the organelle, we evaluated the interaction of flavonoids with the mitochondrial membrane using the internal T-MA flux. Our results are consistent with the notion that the rigidity imparted to the flavonoid structure by the 2,3 double bond/3-OH group favours the interaction of these compounds with membranes, as well as a previous report showing that some flavonoids modulate

the liposome. membrane fluid [29]. Regarding the higher effect of quercetin/galangin compared to assays using DPH/TMA-DPH, these flavonoids are probably partitioned to the hydrophobic core of the mitochondrial membrane, then helps to reduce its fluidity. In this regard, previous reports have linked the restriction of lipid fluidity caused by the interaction of some flavonoids with membranes to the protection provided by these compounds against oxidative stress by reducing the kinetics of free radical reactions [29,30].

Quercetin and galangin, the only flavonoids that significantly interacted with/reduced mitochondrial membrane fluidity, were the compounds that inhibited or significantly promoted mitochondrial respiration. Therefore, the presence of a 2,3 double bond / 3-OH group in the C-ring, in connection with the o-di-OH structure in the B-ring, has an inhibitory effect, as in the case of quercetin. Effect on mode 3 of mitochondrial respiration, indicating interference in the respiratory chain or ATP synthase. On the other hand, since flavonoids are weak acids with hydrophobic properties, they may be among the substances that can cause mitochondrial uncoupling [31,32], although due to such properties, specific structural features have not yet been determined. Our results show that galangin, which presents a 2,3 double bond/3-OH group/4-oxo function in the C-ring but lacks an o-di-OH structure in the B-ring, is in the 4-state stimulates respiration and distributes, this structural feature favours protonophoretic cleavage activity in mitochondria, which occurs as a result of the diffusion of the uncharged form of the molecule through the mitochondrial membrane.

The respiratory chain inhibitory activity of several flavonoids is often related to the oxidation potentials of these compounds, which are generally in the same range as mitochondrial redox centres; The values of the oxidation potentials of quercetin, tachyfolin, catechin and galangin are +0.39, +0.46, +0.45 and +0.59 V, respectively [33,34]. Such redox activity leads to the generation of reactive oxygen species [33,35], so flavonoids with these properties are potential prooxidants in mitochondria and therefore potential MPT inducers. In this context, we failed to detect a significant increase in H_2O_2 generation/accumulation in mitochondria incubated with flavonoids under MPT assay conditions, this is assessed with dichorodihydro fluorescein or homovanillic acid (data not shown). Furthermore, we found that quercetin, which significantly inhibited state 3 respiration, did not significantly induce MPT, suggesting that there is probably a respiratory chain between the MPT-inducing ability and the inhibition of mitochondrial respiration by flavonoids. showed a clear inverse correlation. Accordingly, catechin and tachyfolin, which did not

significantly inhibit state 3 respiration, induced MPT in almost all concentration ranges tested. Therefore, these results suggest in principle that flavonoids are potential MPT inducers, except in cases of inhibition of the mitochondrial respiratory chain. Deenergization of mitochondria due to inhibition of the respiratory chain can prevent organelles from absorbing Ca^{2+}, which is necessary for the initiation of this process. In the same context, our results showing the lack of ability to induce MPT by galangin are to be expected because, as an uncouple, it does not allow mitochondria to retain the Ca^{2+} required to trigger MPT. These aspects indicate that quercetin, which significantly inhibits the respiratory chain and does not significantly induce MPT, releases mitochondrial Ca^{2+} and galangin is not secreted as MPT. consistent with the results of mitochondrial Ca^{2+} release. a very effective inducer of Ca^{2+} release from mitochondria. Ca^{2+} signals are essential for cell function, injury, and death, and mitochondria, together with the endoplasmic reticulum, play an important role in regulating the content of this cation in the cell. It is known that disruption of intracellular Ca^{2+} distribution can induce cytotoxicity leading to necrotic or apoptotic cell death. Mitochondrial Ca^{2+} efflux may promote cell necrosis, specifically by lowering mitochondrial matrix Ca^{2+} levels, which inhibit Ca^{2+}-stimulated mitochondrial dehydrogenases, deplete ATP, or inhibit Ca^{2+}-dependent enzymes and efflux enzymes. by stimulating cell apoptosis. phospholipases [8-10]. Thus, our results suggest that some flavonoids have a clear potential to induce Ca^{2+}-mediated cell death through necrosis or apoptosis. Pathways that induce Ca^{2+} release by CsA may consist of MPT in the case of tachyfolin, or uncoupling in the case of galangin, or some other mechanism, such as a Na+-independent current.

Despite the above-suggested potential of flavonoids evaluated in this study, it should be taken into account that most of the research on the properties of flavonoids has focused on the aglycone form of these compounds, although these are the main forms currently present in the human diet. glycoside form that is inactive by itself. The extrapolation of the effects of flavonoids produced in the aglycone form to in vivo conditions in humans is not well understood [42]. In addition, there is little information on the absorption and bioavailability of flavonoids in humans, although it is generally assumed that these compounds are absorbed in the form of aglycones after hydrolysis of the glycosides along the digestive tract. Also, flavonoids are extensively metabolized mainly by conjugative and oxidative enzymes. In the small intestine, flavonoids are substrates of several enzymes, which change metabolism in the liver. Potential molecular sites for metabolic modifications of flavonoids include methylation at

the B-ring catechol group and glucuronidation/sulfation of the A-ring of their structures [43,44].

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