Flavonoids are a class of polyphenolic compounds widely distributed in the plant kingdom, which display a variety of biological activities, including chemoprevention and tumor growth inhibition. Our aim was to investigate the effects of several polyphenols on the growth and metastatic potential of B16-BL6 melanoma cells in vivo. Intraperitoneal administration of quercetin, apigenin, (-)-epigallocatechin-3-gallate (EGCG), resveratrol, and the anti-estrogen tamoxifen, at the time of i.m. injection of B16-BL6 cells into syngeneic mice, resulted in a significant, dose-dependent delay of tumor growth, without toxicity. The relative descending order of potency was EGCG > apigenin = quercetin = tamoxifen > resveratrol > control. Furthermore, polyphenols significantly potentiated the inhibitory effect of a non-toxic dose of cisplatin. When tested for the ability to inhibit lung colonization, quercetin, apigenin, and tamoxifen (but not EGCG or resveratrol) significantly decreased the number of B16-BL6 colonies in the lungs in a dose-dependent manner, with quercetin and apigenin being more effective than tamoxifen. Interestingly, quercetin, apigenin, and tamoxifen (but not EGCG or resveratrol) significantly decreased the invasion of B16-BL6 cells in vitro, with quercetin and apigenin being more effective than tamoxifen. This suggests that anti-invasive activity is one of the mechanisms underlying inhibition of lung colonization by quercetin and apigenin. In conclusion, quercetin and apigenin inhibit melanoma growth and invasive and metastatic potential; therefore, they may constitute a valuable tool in the combination therapy of metastatic melanoma.

MATERIAL AND METHODS

Cells

The B16-BL6 cell line is a murine melanoma variant, highly metastatic to the lungs of syngeneic C57BL/6N mice (Talmadge and Fidler, 1982), selected from the parent B16 cell line (Hart, 1979). Tumor cells were grown as monolayers in DMEM (GIBCO, Paisley, UK) supplemented with 10% heat-inactivated FCS (GIBCO) and 2 mM glutamine. For injection, cells were harvested in growth phase. High-affinity estrogen-binding sites in B16-BL6 cells were assayed using the dextran-coated charcoal method. Furthermore, the presence of estrogen receptor proteins was assayed immunohistochemically by anti-estrogen receptor antibodies (Neomarkers, Union City, CA) in cytocentrifuged preparations of B16-BL6 cells. Both methods failed to reveal these receptors. Type II estrogen-binding sites were assayed by the hydroxyapatite method, as described (Piantelli et al., 1995).

Drugs and chemicals

Quercetin (3,3’,4’,5,7-pentahydroxylavone), apigenin (4’,5,7-trihydroxylavone), rutin (3-rhamnosylglucoside of quercetin), (-)-epigallocatechin-3-gallate (EGCG; [2R,3R]-2-[3,4,5-trihydroxyphenyl]-3,4-dihydro-2H-benzopyran-3,5,7-triol-3-[3,4,5-trihydroxybenzoate]), resveratrol (3,4’,5-trihydroxy-trans-stilbene), curcumin (1,7-bis[4-hydroxy-3-methoxylavone]-1,6-heptadiene-3,5-dione), tamoxifen (trans-2-[4-(1,2-diphenyl-1-butenyl)phenoxy]-N,N-dimethylamino)-amidine), and cisplatin (cis-diaminedichloroplatinum) were obtained from Sigma (Deisenhofen, Germany). Ipriflavone (isoflavanone) was a gift from Chiesi (Parma, Italy).

In vitro cell proliferation

Cells were plated at 10^4/cm^2 in 16 mm wells of 24-well plates (Falcon, Becton Dickinson, Oxnard, CA). After 18 hr, the medium was replaced with fresh medium containing the compounds to be tested. All compounds, except EGCG, were taken from an absolute ethanol stock solution, and control cells were treated with the same amount of vehicle. The final ethanol concentration did not exceed 0.5% (v/v), either in control or in treated samples. EGCG was dissolved in 1% ethanol.

Several polyphenolic compounds are known as cancer chemopreventive agents (Kuroda and Hara, 1999). In particular, flavonoids are a class of natural polyphenolic compounds, widely distributed in the plant kingdom, that display a variety of biological activities, including tumor growth inhibition and chemoprevention (Formica and Regelson, 1995). We and others have shown that the flavonoid quercetin (3,3’,4’,5,7-pentahydroxylavone) inhibits the growth of human mammary, ovarian, colorectal, leukemic, and lung tumor cells (Markaverich et al., 1988; Scambia et al., 1990b; Ranelletti et al., 1992; Larocca et al., 1995; Caltagirone et al., 1997). We have also shown that quercetin inhibits the in vitro growth and clonogenesis of human melanoma cells, probably through type II estrogen-binding sites (Piantelli et al., 1995). However, other mechanisms should be taken into consideration. Flavonoids inhibit the activity of several enzymes that consider cell proliferation (Formica and Regelson, 1995), arrest cell-cycle progression (Yoshida et al., 1990a; Ranelletti et al., 1992; Lepley et al., 1996; Plaumann et al., 1996), and induce apoptosis (Wei et al., 1994; Plaumann et al., 1996; Ahmad et al., 1997). The anti-estrogen tamoxifen inhibits the proliferation of melanoma cells independently from its anti-estrogenic mechanism of action, probably by interacting with type II estrogen-binding sites (McClay et al., 1995; Piantelli et al., 1995). Moreover, clinical findings have indicated that addition of tamoxifen to combination chemotherapy regiments increases the response of melanoma patients (Del Prete et al., 1984; McClay et al., 1989; Cocconi et al., 1992; Gause et al., 1998). Our aim was to investigate the effects of several polyphenols, as well as of tamoxifen, on the growth and metastatic potential of the highly metastatic murine B16-BL6 melanoma in vivo.
dissolved in H2O. Treatments were repeated after 24 hr. Quadruplicate hemocytometric counts of triplicate cultures were performed after 72 hr of exposure to the compounds. The control value was 160,000 ± 10,000 cells/well. Closed triangles, quercetin; open squares, apigenin; closed circles, curcumin; closed squares, tamoxifen; inverted open triangles, EGCG; closed diamonds, resveratrol; open triangles, ipriflavone; open circles, rutin; open diamonds, hesperidin. Results from 3 experiments performed in triplicate are expressed as means ± SD.

### TABLE I – POLYPHENOLS AND TAMOXIFEN INHIBIT MELANOMA CELL GROWTH

<table>
<thead>
<tr>
<th>Treatments</th>
<th>IC50 (μM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apigenin</td>
<td>1.5</td>
</tr>
<tr>
<td>Quercetin</td>
<td>3.5</td>
</tr>
<tr>
<td>EGCG</td>
<td>8.9</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>2.8</td>
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<tr>
<td>Curcumin</td>
<td>3.6</td>
</tr>
<tr>
<td>Resveratrol</td>
<td>5.0</td>
</tr>
</tbody>
</table>

Results are expressed as mean of 3 experiments in triplicate. SDs were <10%.

receiving vehicle or daily i.p. treatments at the indicated doses. Quercetin, apigenin, resveratrol, curcumin, and tamoxifen were suspended by sonication in PBS containing 20% polyethylene glycol (PEG 400) and 2% Tween-80 (pH 7.2) (Gerritsen et al., 1995). EGCG and cisplatin were dissolved in H2O. Treatments were started on the day of tumor cell injection for all compounds except cisplatin. Cisplatin was administered i.v. 3 days after tumor cell injection at 3-day intervals for a total of 3 doses. Tumor growth was measured 3 times a week with a caliper, and tumor volume was estimated by the formula length × width2/2 (Giavazzi et al., 1986; Alessandri et al., 1987; Chirivi et al., 1994). The mean volume of the leg on the day of tumor cell injection was 0.05 ± 0.01 cm3. All animals were treated according to European Community guidelines.

### Lung-colonization assay

Mice were injected with 5 × 104 tumor cells in 0.1 ml PBS in the lateral tail vein. Treatments were administered i.p. daily, starting 1 hr before tumor cell injection. Mice were killed by cervical dislocation 14 to 18 days after tumor cell injection. Lungs were fixed in Bouin’s solution, and black tumor cell colonies were counted by 2 different operators.

### Organ-distribution assay

Cultures of B16-BL6 cells were pre-labeled with 5-[35S]-iododeoxyuridine (Amersham, Aylesbury, UK) at 0.3 mcg/ml for 24 hr. Labeled tumor cells, at a concentration of 5 × 103 in 0.1 ml PBS, were injected i.v. in mice receiving vehicle or i.p. treatment 1 hr before cell injection. At 10 min and 2, 4, 8, and 24 hr after tumor cell injection, mice were killed and the lungs removed and washed with 3 changes of 70% ethanol. Radioactivity in lungs, liver, spleen, kidneys, blood, and bladder urine was determined using a gamma-counter (Fidler, 1970)

### Tumor growth assay

Female C57BL/6N mice (6 to 8 weeks old) were obtained from Charles River (Calco, Italy). Animals were age- and weight-matched in each experiment. Tumor cells (5 × 105), in 0.1 ml PBS, were injected i.m. into the gastrocnemius muscle of mice, which were randomized into experimental groups of 6 to 8 animals}

**Figure 1** – Polyphenolic compounds inhibit the growth of B16-BL6 melanoma cells in vitro. Cells were plated at 103/cm² in 16 mm wells of a 24-well plate. After 18 hr, the medium was replaced with fresh medium containing the compounds to be tested. Treatments were repeated after 24 hr. Quadruplicate hemocytometric counts of triplicate cultures were performed after 72 hr of exposure to the compounds. The control value was 160,000 ± 10,000 cells/well. Closed triangles, quercetin; open squares, apigenin; closed circles, curcumin; closed squares, tamoxifen; inverted open triangles, EGCG; closed diamonds, resveratrol; open triangles, ipriflavone; open circles, rutin; open diamonds, hesperidin. Results from 3 experiments performed in triplicate are expressed as means ± SD.

**TABLE I – POLYPHENOLS AND TAMOXIFEN INHIBIT MELANOMA CELL GROWTH**

<table>
<thead>
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<th>Treatments</th>
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<tbody>
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<tr>
<td>EGCG</td>
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<td>Curcumin</td>
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<tr>
<td>Resveratrol</td>
<td>5.0</td>
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</tbody>
</table>

Results are expressed as mean of 3 experiments in triplicate. SDs were <10%.

Post hoc comparisons were then performed by Scheffe’s test, at a significance level of 5%, to compare the efficacy of treatments. Two-tailed Student’s t-test for unpaired comparisons was used to assess the significance of the effects of treatments on the formation of tumor colonies in the lungs and on B16-BL6 invasive activity.

### Statistical analysis

The effects of treatments on intramuscular tumor growth were evaluated by ANOVA with repeated measures. Post hoc comparisons were then performed by Scheffe’s test, at a significance level of 5%, to compare the efficacy of treatments. Two-tailed Student’s t-test for unpaired comparisons was used to assess the significance of the effects of treatments on the formation of tumor colonies in the lungs and on B16-BL6 invasive activity.

### RESULTS

**Polyphenolic compounds inhibit the growth of B16-BL6 melanoma cells in vitro**

The in vitro growth of B16-BL6 melanoma cells in the presence of a series of polyphenolic compounds (10⁻¹⁰ to 10⁻⁵ M) was evaluated. Quercetin, apigenin, EGCG, resveratrol, curcumin, and tamoxifen inhibited the growth of B16-BL6 cells in a concentration-dependent manner (Fig. 1). The concentrations needed to
inhibit cell growth by 50% (IC50) are reported in Table I. In contrast, rutin, hesperidin, and ipriflavone were ineffective (Fig. 1). The inhibitory effect of tamoxifen could not be reversed by addition of exogenous estrogens (data not shown). In agreement with this observation, we found that B16-BL6 cells were estrogen receptor-negative. The compounds that inhibited cell growth also inhibited B16-BL6 DNA synthesis, as assessed by thymidine incorporation, with IC50 values similar to those observed to reduce cell numbers (data not shown).

Polyphenolic compounds inhibit the growth of B16-BL6 melanoma cells in vivo

The effect of the compounds which inhibited in vitro cell growth was evaluated in vivo on i.m. melanoma growth at doses of 50, 25, and 12.5 mg/kg. No mortality or body weight changes were observed at doses up to 50 mg/kg. For all compounds, at concentrations higher than 50 mg/kg, body weight loss was observed (data not shown). In a typical experiment, tumors in control mice grew to an initial size of 1.35 ± 0.20 cm3 (mean ± SD) within 2 weeks of the injection and then to 3.46 ± 0.41 cm3 after 5 more days (Fig. 2). Quercetin at 25 and 50 mg/kg; apigenin at 25 and 50 mg/kg; and EGCG, resveratrol, and tamoxifen at 50 mg/kg significantly delayed tumor growth (p < 0.0001). At 50 mg/kg, the ranking order of potency was EGCG > apigenin = quercetin = tamoxifen > resveratrol > control.

Figure 2 – Polyphenolic compounds inhibit the growth of B16-BL6 melanoma cells in vivo. B16-BL6 cells (5 × 104) were injected into the gastrocnemius muscle. Mice were treated i.p. each day with the compounds to be tested or vehicle (control). Results are expressed as means ± SD (n = 8 mice/group) and represent 3 experiments. (a) Closed circles, control; open squares, 25 mg/kg apigenin; open triangles, 50 mg/kg apigenin; closed squares, 25 mg/kg quercetin; closed triangles, 50 mg/kg quercetin. (b) Closed circles, control; open diamonds, 50 mg/kg resveratrol; open squares, 50 mg/kg tamoxifen; open triangles, 50 mg/kg EGCG. ANOVA of the data showed that both the treatments and the time of treatments (days) had a significant effect on tumor volume (p < 0.0001). The interaction “days × treatments” was significant (P < 0.0001). Post hoc comparisons by Scheffe’s test showed that quercetin at 25 and 50 mg/kg; apigenin at 25 and 50 mg/kg; and EGCG, resveratrol, and tamoxifen at 50 mg/kg significantly delayed tumor growth (p < 0.0001). At 50 mg/kg, the ranking order of potency was EGCG > apigenin = quercetin = tamoxifen > resveratrol > control.

Figure 3 – Apigenin increases the inhibitory effect of cisplatin on B16-BL6 melanoma cell growth in vivo. The experiment was performed as described in Figure 2. Cisplatin was administered i.v. 3 days after tumor cell injection at 3-day intervals, for a total of 3 doses. Results are expressed as mean ± SD (n = 8 mice/group) and represent 3 experiments. Closed circles, control; open squares, 25 mg/kg apigenin; open diamonds, 2 mg/kg cisplatin; open triangles, 25 mg/kg apigenin + 2 mg/kg cisplatin. ANOVA of the data showed that both the treatments and the time of treatments (days) had a significant effect on tumor volume (p < 0.0001). The interaction “days × treatments” was significant (p < 0.0001). Post hoc comparisons by Scheffe’s test showed that both apigenin and cisplatin alone significantly affected tumor volume (p < 0.0001) and that the combination of apigenin and cisplatin was significantly more effective than cisplatin or apigenin alone (p < 0.0001).

Figure 4 – Quercetin inhibits lung colonization of B16-BL6 cells. Cells (5 × 104) were injected in the lateral tail vein of 6 mice. Quercetin was given i.p. each day at 50 mg/kg. Lungs from mice treated with vehicle (upper row) and quercetin (lower row). Scale bar = 1 cm.
Summary of the document:

**TABLE II** — **QUERCETIN AND APIGENIN INHIBIT LUNG COLONIZATION OF B16-BL6 CELLS**

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Control</th>
<th>Quercetin (mg/kg)</th>
<th>Apigenin (mg/kg)</th>
<th>Tamoxifen (mg/kg)</th>
<th>EGCG (mg/kg)</th>
<th>Resveratrol (mg/kg)</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Quercetin (mg/kg)</td>
<td>Apigenin (mg/kg)</td>
<td>Tamoxifen (mg/kg)</td>
<td>EGCG (mg/kg)</td>
<td>Resveratrol (mg/kg)</td>
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<td>1</td>
<td>86 ± 19</td>
<td>65 ± 12</td>
<td>32 ± 4</td>
<td>61 ± 13</td>
<td>34 ± 4</td>
<td>73 ± 15</td>
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<td></td>
<td>(50)</td>
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<td>(34)</td>
<td>(71)</td>
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</tr>
<tr>
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<td>123 ± 19</td>
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<td>91 ± 12</td>
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<td>(77)</td>
<td>(34)</td>
<td>(74)</td>
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<td>(85)</td>
</tr>
<tr>
<td>3</td>
<td>77 ± 16</td>
<td>61 ± 6</td>
<td>30 ± 4</td>
<td>58 ± 8</td>
<td>34 ± 6</td>
<td>66 ± 10</td>
</tr>
<tr>
<td></td>
<td>(100)</td>
<td>(79)</td>
<td>(39)</td>
<td>(75)</td>
<td>(44)</td>
<td>(86)</td>
</tr>
</tbody>
</table>

*Experiments were performed as described in Figure 4. Colonies were counted by 2 different operators 14 days after tumor cell injection. Results are expressed as means ± SD and % of control (in parentheses). p < 0.05. p < 0.001.

**Quercetin and apigenin potently inhibit lung colonization of B16-BL6 cells**

The compounds which inhibited B16-BL6 tumor growth were tested for their ability to inhibit lung colonization. The macroscopic appearance of the lungs from untreated and treated mice clearly showed that 50 mg/kg quercetin reduced the number of lung metastases after i.v. injection of B16-BL6 cells (Fig. 4). When the effects of treatments were quantitatively evaluated, we found that quercetin and apigenin, at both 50 and 25 mg/kg, significantly decreased the number of colonies, while tamoxifen was effective only at the highest dose (Table II). In addition, in each of the 3 experiments shown in Table 2, quercetin and apigenin at 50 mg/kg were significantly more effective than tamoxifen at the same dose (p < 0.05). The inhibitory activities of quercetin and apigenin were similar and dose-dependent, being more effective at 50 than at 25 mg/kg (p < 0.001). Both compounds were ineffective at 12.5 mg/kg. EGCG and resveratrol were ineffective even at the highest doses used. The distribution of radiolabeled B16-BL6 cells in lungs, liver, spleen, kidneys, blood, and bladder urine of mice was not modified by any of the polyphenolic compounds or by tamoxifen.

**Quercetin and apigenin potently inhibit invasion of B16-BL6 cells in vitro**

Quercetin, apigenin, EGCG, resveratrol, and tamoxifen (10−5 M) were examined for their effect on invasion of B16-BL6 cells in vitro. Quercetin, apigenin, and tamoxifen, but not EGCG or resveratrol, significantly (p < 0.001) inhibited cell invasion (Fig. 5). Quercetin and apigenin were significantly (t = 12.024, p < 0.001) and t = 9.052, p < 0.001, respectively) more effective than tamoxifen, displaying similar potency with an inhibition of cell invasion of 96% and 90%, respectively.

**Discussion**

Although flavonoids have received extensive attention because of their anti-carcinogenic activity (Formica and Regelson, 1995; Kuroda and Hara, 1999), their in vivo potential as anti-cancer agents has been largely unexplored (Hofmann et al., 1990; Record et al., 1997; Carbo et al., 1999). Following previous findings by our group in human melanoma cells in vitro (Piantelli et al., 1995), we show here that flavonoids are effective in various aspects of tumor formation in the B16-BL6 mouse melanoma model in vivo. This model was chosen on the basis of the aggressive behavior and high metastatic potential of this cell line (Hart, 1979; Talmadge and Fidler, 1982). Intraperitoneal administration of the flavonoids quercetin, apigenin, and EGCG, at the time of the i.m. injection of tumor cells, resulted in a significant, dose-dependent delay in tumor growth. The anti-estrogen tamoxifen inhibits B16-BL6 tumor growth with a potency similar to that of quercetin, apigenin, and EGCG. Resveratrol, a polyphenolic compound, has been identified as an anti-carcinogenic and anti-proliferative agent (Jang et al., 1997; Mbonyebi et al., 1998; Carbo et al., 1999; Hsieh and Wu, 1999). It is active in melanoma growth, albeit with a lower potency than the above-mentioned flavonoids. A definite assessment of the relative efficacy of these compounds, however, will
require further studies on their bioavailability and pharmacodynamics. We have observed that not all molecules that inhibit i.m. tumor growth also inhibit metastatic potential. Quercetin and apigenin administered in vivo reduce the number of tumor colonies in the lungs, with a similar potency, in a dose-dependent manner, whereas EGCG and resveratrol are ineffective. Cell matrix invasion is one of the phases involved in the multistep metastatic process (Westermann and Kahari, 1999). Interestingly, quercetin and apigenin, but not EGCG or resveratrol, display potent anti-invasive activity on B16-BL6 cells in vitro, suggesting that the anti-invasive activity is one of the mechanisms underlying quercetin and apigenin inhibition of lung colonization. Tamoxifen reduces the metastatic potential of B16-BL6 cells in vivo. In agreement with previous data (Dewhurst et al., 1997), we have found that it also inhibits melanoma cell invasion in vitro. However, in both cases, it is significantly less potent than quercetin and apigenin. The anti-tumoral effects of flavonoids and tamoxifen do not depend on the presence of estrogen receptors, which are not expressed by B16-BL6 cells, and could be mediated in part by type II estrogen-binding sites, which are expressed by these cells (data not shown). Clearly, other mechanisms could be considered. Flavonoids indeed interfere with a variety of cellular enzymes, such as tyrosine kinase, phosphatidylinositol kinase, protein kinase C, and calmodulin (Cushman et al., 1991; Ferry et al., 1996; Nishioka et al., 1989; Singh et al., 1995; Agboola et al., 1997; Darbre et al., 1984; O'Brian et al., 1988; Formica and Regelson, 1995) with an arrest of the cell cycle (Ranelletti et al., 1992; Yoshida et al., 1990; Lepley et al., 1996; Plaumann et al., 1996). In addition, apigenin, EGCG, and other diet-derived flavonoids (Liu et al., 1986; Cao and Cao, 1999; Fotis et al., 1997) able to inhibit cell proliferation inhibit angiogenesis, which is essential for the growth of solid tumors (Folkman, 1995). Also, in vitro pre-treatment of melanoma cells with 20 µM genistein, a molecule which is isomeric to flavonoids, impairs the ability of these cells to colonize the lungs (Yan and Han, 1997). Interestingly, this inhibitory activity involves suppression of tyrosine phosphorylation of the focal adhesion kinase (Yan and Han, 1997). Furthermore, inhibition of calmodulin can mediate a decrease in melanoma cell invasiveness (Dewhurst et al., 1997). Clearly, much more research is needed to define the mechanisms of action of polyphenols on cancer cells in vivo. Whatever the mechanism, flavonoids are capable of reverting the phenotype of multidrug resistance and interact in a synergistic manner with cisplatin in different tumor cell types (Scambia et al., 1991; Hofmann et al., 1990). Here, we have demonstrated that flavonoids co-operate positively with cisplatin in inhibiting melanoma growth in vivo. In conclusion, quercetin and apigenin potently inhibit melanoma growth and invasive and metastatic potential; therefore, they may constitute a valuable tool in the combination therapy of metastatic melanoma and in the prevention of melanoma metastases. These potential applications are supported by a study performed on healthy volunteers (Gugler et al., 1975) and by a phase I clinical trial (Ferry et al., 1996), which has shown that quercetin has low toxicity in humans.

ACKNOWLEDGEMENTS

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