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# Myricetin and Quercetin Are Naturally-Occurring Co-substrates of Cyclooxygenases *In Vivo*[1]

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## Abstract

Bioflavonoids are ubiquitously present in the plant kingdom, and some of them are presently being sold as healthy dietary supplements around the world. Recently, it was shown that some of the dietary polyphenols were strong stimulators of the catalytic activity of cyclooxygenase I and II, resulting in increased formation of certain prostaglandin (PG) products *in vitro* and also in intact cells in culture. In the present study, we investigated the effect of two representative dietary compounds, quercetin and myricetin, on plasma and tissue levels of several PG products in normal Sprague-Dawley rats. We found that these two dietary bioflavonoids could strongly stimulate the formation of PG products *in vivo* in a time-dependent manner, and the stimulatory effect of these two bioflavonoids was dose-dependent with a unique biphasic pattern. At lower doses (<0.3 mg/kg b.w.), they strongly stimulated the formation of $PGE_2$, but at higher doses (>0.3 mg/kg b.w.), there was a dose-dependent reduction of the stimulatory effect. These results provide support for the hypothesis that some of the bioflavonoids are naturally-occurring physiological co-substrates for the cyclooxygenases *in vivo*.

### Keywords

Cyclooxygenase; Prostaglandin; Bioflavonoids; Co-substrates for cyclooxygenase

## INTRODUCTION

Cyclooxygenase (COX) I and II catalyze the metabolism of arachidonic acid, resulting in the formation of prostaglandins (PGs), thromboxanes, and hydroxyeicosateraenoic acids (HETEs) [1–4]. These autacoids exert a whole host of bological actions in the body through activation of specific membrane receptors [5–7]. Although inhibitors of COX I and II are effectively used to treat a number of medical conditions (such as chronic inflammation) where their activity is abnormally elevated, it is also known that abnormally-low levels of COX activity are associated with a number of severe pathological conditions, including gastrointestinal ulceration and bleeding [8–10] and cardiovascular diseases [11]. The important functional roles of COX in

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normal physiology sometimes are best exemplified by the deleterious side effects seen in patients taking nonsteroidal anti-inflammatory drug (NSAID) such as aspirin and ibuprofen [12,13]. These NSAIDs are nonselective inhibitors of COX I and II, and they not only inhibit PG biosynthesis at the inflammatory sites (mostly mediated by COX II), but also inhibit the constitutive PG biosynthesis (mostly mediated by COX I). Inhibition of the constitutive PG biosynthesis in the stomach and intestine by NSAIDs is directly responsible for causing severe gastric hemorrhage and ulceration because PGs produced by the constitutive COX I in the stomach and intestine exert important functions in maintaining the integrity of the mucosal epithelium [8–10]. Similarly, chronic use of selective COX II inhibitors (*e.g.*, rofecoxib) is associated with an elevated cardiovascular risk and mortality [11,14].

Therefore, it is evident that the basal levels of COX activity and ultimately the basal circulating and tissue levels of arachidonic acid-derived autacoids need to be maintained within a normal range in order to exert many of their normal physiological functions. Lower basal levels of the COX I and II activity are not always better or beneficial for optimal health. However, the physiological importance of maintaining normal levels of COX activity and PGs has not received much attention until very recently in light of the clinical observations of severe adverse effects seen in patients chronically receiving selective COX II inhibitors such as celecoxib and rofecoxib [8,11–13].

Recently, we found that some of the dietary polyphenols are powerful activators of the catalytic activity of COX I and II in the *in vitro* enzyme assays as well as in cultured cells, resulting in increased formation of various arachidonic acid metabolites [15]. In the present study, we studied the effect of two representative dietary compounds (quercetin and myricetin) on plasma and tissue levels of several PG products in an animal model. We found that these two dietary bioflavonoids could strongly activate the formation of PG products *in vivo*, thus provide support for the notion that some of the bioflavonoids are naturally-occurring physiological co-substrates for the COX enzymes.

## MATERIALS AND METHODS

### Chemicals and reagents

Myricetin and quercetin were purchased from Sigma-Aldrich (St. Louis, MO). Enzyme immunoassay (EIA) kits for $TXB_2$, $PGE_2$, $PGF_{2\alpha}$ and $PGD_2$ were obtained from Cayman Chemical (Ann Arbor, MI).

### *In vivo* animal experiments

All procedures involving the use of live animals were approved by the Institutional Animal Care and Use Committee (IACUC) of our university, and the NIH guidelines for humane treatment of animals were strictly followed. Male Sprague-Dawley rats (4 to 5-week-old, specific pathogen-free) were obtained from Harlan Laboratories (Indianapolis, IN), and maintained at the central animal facility of the University of Kansas Medical Center (KUMC). After arrival, the animals were allowed to acclimatize for one week prior to being used in the experiments. The animals were housed under constant conditions of temperature (20 ± 1°C) and a 20-h light/20-h dark cycle, and had free access to food and water. The rats were 8 weeks old at the time when they were used in the experiments.

In *Experiment-I*, the animals were divided into five groups (with 4 rats in each group). On the day of the experiment, myricetin and quercetin (at 0.1 and 0.3 mg/kg b.w., dissolved in 100 μL normal sterile saline containing 5% ethanol) were injected *i.v.* into each animal. Animals in the control group were injected *i.v.* 100 μL vehicle only. The blood samples were collected from the tail vein for up to 6 h. The plasma was immediately separated by centrifugation, and

indomethacin was added at a 10-μM final concentration to the plasma. The concentrations of several PGs, including $PGD_2$, $PGE_2$, $PGF_{2\alpha}$ and $TXB_2$, were quantified using the EIA kits provided by Cayman Chemical (Ann Arbor, MI).

In *Experiment-II*, the animals were divided into eleven groups (with 3 rats in each group). On the day of the experiment, myricetin and quercetin (at 0.05, 0.1, 0.3, 1 and 5 mg/kg b.w., dissolved in 100 μL normal sterile saline containing 5% ethanol) were injected *i.v.* into each animal. Animals in the control group were injected *i.v.* 100 μL vehicle only. The blood samples were collected from the tail vein at 4 h after injection. The plasma was prepared and the concentrations of $PGE_2$ (a representative PG) were quantified as described above.

In *Experiment-III*, the male rats were divided into three groups (with 6 rats in each group). Myricetin and quercetin (10, and 50 mg/kg b.w., dissolved in 500 μL of 1% methyl cellulose) were given orally. The control animals were given vehicle only. The blood samples were collected for preparation of plasma, and the concentrations of $PGE_2$ were quantified by using the EIA kit.

In *Experiment-IV*, the male rats were divided into five groups (with 4 rats in each group). Myricetin and quercetin (0.1 mg/kg b.w., dissolved in 100 μL of 0.9% NaCl and 5% ethanol) were given *i.v.* The control animals were injected *i.v.* 100 μL vehicle alone. The animals were then sacrificed at 4 h after injection. The blood samples were collected for preparation of plasma, and the liver, kidney, stomach, lung and small intestine were removed and perfused through the artery with ice-cold saline, and a part of the tissue was frozen in liquid nitrogen and then kept at −80°C. The plasma levels of $PGE_2$ were analyzed using EIA as described above. For analysis of the tissue levels of $PGE_2$, tissues were thawed and then homogenized with a polytron-type homogenizer in a 100 mM Tris-HCl, pH 7.4 (5 mL/g of tissue), containing 1 mM EDTA and 10 μM indomethacin. The homogenates were centrifuged at 12000 g for 30 min at 4°C. The supernatants were then used for measurement of $PGE_2$ levels by using the EIA kit as described above.

### Statistical analysis of the data

Data were expressed as the mean ± S.D. Statistical difference in PG levels between different treatment groups was determined using the Student's *t*-test and analysis of variance (ANOVA). Differences were considered statistically significant at $P < 0.05$.

## RESULTS

### Effect of myricetin and quercetin on plasma levels of PGs

In the present study, we first determined the plasma levels of several PG products in male Sprague-Dawley rats following a single *i.v.* injection of myricetin or quercetin at two very low doses: 0.1 and 0.3 mg/kg b.w. (approximately 25 or 75 μg/rat, respectively). The reason that the route of *i.v.* administration was used was to minimize some of the confounding factors in these initial experiments that sought to determine whether or not some of the bioflavonoids that were identified as strong activators of the COX-mediated formation of various PG products *in vitro* [15] were also activators *in vivo*. Using $PGE_2$ as an example (one of the major PG products detected in our *in vitro* study [15]), we determined the time dependence for the changes in its plasma levels. We found that both quercetin and myricetin at the two very low doses markedly increased the plasma levels of $PGE_2$ in a time-dependent manner (Fig. 1A, 1B). The effect elicited by quercetin at the 0.1 and 0.3 mg/kg b.w. doses was similar, and the formation of $PGE_2$ reached a plateau at ~1 h after quercetin administration. In comparison, the plasma levels of $PGE_2$ in animals after receiving an *i.v.* injection of 0.1 and 0.3 mg/kg b.w. of myricetin reached plateau in 6 and 2 h, respectively. It appeared that myricetin had a relatively

slower onset of effect than quercetin, but the former was more efficacious than the latter for increasing the plasma levels of $PGE_2$. The maximal increase in $PGE_2$ plasma levels following administration of myricetin and quercetin was approximately 10- and 8-fold, respectively, over the basal levels in vehicle-treated animals (Fig. 1A, 1B).

We also compared the plasma levels of three other PGs ($PGD_2$, $PGF_{2\alpha}$ and $TXB_2$) at a selected time point (4 h) post injection of quercetin or myricetin. The levels of all these arachidonic acid metabolites were increased. $TXB_2$, a metabolite of $TXA_2$, was increased by approximately 5-fold in the plasma following administration of myricetin or quercetin, and it became the quantitatively-predominant arachidonic acid metabolite detected (Fig. 1E). The basal plasma levels of $PGD_2$ and $PGF_{2\alpha}$ were very low in untreated animals, and treatment with myricetin or quercetin significantly increased their levels (Fig. 1C, 1D).

Next we determined the dose dependence for the stimulatory effect of quercetin and myricetin on plasma $PGE_2$ levels in male Sprague-Dawley rats by including a wide dose range, *i.e.*, at 0.05, 0.1, 0.3, 1 and 5 mg/kg b.w. (single *i.v.* injection). Our data showed that the stimulatory effect of these two bioflavonoids on COX-mediated formation of $PGE_2$ was clearly dose-dependent and followed a unique biphasic pattern (Fig. 2). At lower doses (<0.3 mg/kg b.w.), these two bioflavonoids strongly stimulated the formation of $PGE_2$ in a dose-dependent manner. However, at higher doses (>0.3 mg/kg b.w.), myricetin and quercetin started to show a dose-dependent reduction of their stimulatory effect, and it almost reverted to the original basal levels when 5 mg/kg b.w. myricetin or quercetin was injected. The maximal increase in $PGE_2$ plasma levels following administration of myricetin or quercetin was seen with the 0.3 mg/kg b.w. dose (Fig. 2). Notably, the biphasic pattern of regulation of $PGE_2$ plasma levels closely resembled the curve patterns for their stimulation of the formation of $PGE_2$ *in vitro* catalyzed by COX I or COX II or in intact cells in culture [15].

In the present study, we also determined the plasma levels of $PGE_2$ in male Sprague-Dawley rats following a single oral administration of quercetin (at 10 and 50 mg/kg b.w.). Using $PGE_2$ as an example, we determined the time dependence for the changes of PG plasma levels. Our data showed that quercetin increased the plasma levels of $PGE_2$ in a time-dependent manner at the doses of 10 and 50 mg/kg b.w. (Fig. 3). The formation of $PGE_2$ reached a plateau at approximately 6 h following administration of quercetin, and the maximal increase was approximately 3-fold (Fig. 3).

### Effect of myricetin and quercetin on tissue levels of PGs

In a separate experiment, we sought to determine the tissue levels of various PG products ($PGE_2$, $PGD_2$, $PGF_{2\alpha}$ and $TXB_2$) in animals that received a single *i.v.* injection of 0.1 mg/kg b.w. of myricetin or quercetin 4 h earlier (data shown in Fig. 4). As summarized in Fig. 4A, the basal levels of these PG products were very different in different tissues. For instance, while comparable levels of $PGE_2$ were present in rat liver, brain and lung, its level in the small intestine was unusually high, approximately 30 times higher than that in the kidney. $PGD_2$ had its highest level in the small intestine, followed by lung, brain, and liver. In the blood, $PGE_2$ and $TXB_2$ were the two quantitatively-predominant PGs, whereas $PGD_2$ and $PGF_{2\alpha}$ were present at rather low levels.

Treatment of animals with myricetin and quercetin differentially increased the levels of these PG products in different tissues. Myricetin and quercetin increased the levels of $PGE_2$ by ~5-fold in liver, 3-fold in kidney, and less than 2-fold in small intestine, lung and brain. Similarly, these two dietary compounds also increased the levels of $PGD_2$ in these tissues. For $PGF_{2\alpha}$, the major increase was observed in kidney (5-fold), followed by lung and small intestine, and the increase in liver and brain was rather small. For $TXB_2$, a major increase (approximately 5-fold) was observed in liver, followed by small intestine, and its increase in kidney, brain and

lung was relatively small. In this experiment, we also determined the blood levels of PGs (shown in Fig. 4G), and the data matched the observations of the other experiments (Fig. 1).

## DISCUSSION

Recently, we found that some of the dietary bioflavonoids are powerful direct stimulators of the catalytic activity of COX I and II *in vitro*, resulting in increased formation of various PGs, thromboxanes, and hydroxyeicosateraenoic acids (HETEs) from arachidonic acid as substrate [15]. The present study was designed to determine whether bioflavonoids at physiologically-relevant doses could exert similar stimulatory effects *in vivo*. Our results showed that the plasma and tissue levels of several PG products in male SD rats following a single *i.v.* injection of very low doses of myricetin or quercetin (*i.e.*, 0.1 and 0.3 mg/kg b.w.; approximately 25 or 75 μg/rat, respectively) were markedly increased in a time-dependent manner. In addition, when quercetin was administered orally (at 10 or 50 mg/kg b.w.), it also significantly increased the plasma levels of $PGE_2$ (a representative PG product measured) in male SD rats in a time dependent manner, although the effect was less efficacious compared to *i.v.* administration. We also found that the stimulatory effect of these two bioflavonoids on COX-mediated formation of $PGE_2$ was dose-dependent and followed a unique biphasic pattern. This biphasic pattern of $PGE_2$ plasma levels closely resembled the curve patterns for their stimulatory effect *in vitro* catalyzed by COXs or in cultured intact cells as reported recently [15].

A number of earlier studies have reported an inhibitory effect of dietary bioflavonoids on COX-mediated PGs formations in lipopolysaccharide-induced animal model [16–18], but little information is available concerning the effect of these dietary compounds on COX-mediated PG formation *in vivo*. To our knowledge, this is the first report on a stimulatory effect of dietary bioflavonoids on PG formation *in vivo* at physiologically relevant doses in intact animals. It has been estimated that the combined daily dietary intake of various bioflavonoids in men is approximately one gram from food sources [19,20]. Generally, rodents have a much faster rate of metabolic disposition of dietary phenolic compounds than humans. However, even if we simply assume that the bioavailability of bioflavonoids in humans is as low as rodents, then the estimated effective oral dose for men according to the rodent effective oral dose (at 10 mg/kg b.w.) would still be readily attainable. Therefore, it is believed that bioflavonoids would be biologically-effective stimulators of COX I and II-mediated formation of various PG products in humans.

Bioflavonoids are known to have diverse beneficial effects in the body. In the capillary, they increase its plasticity, decrease its fragility, and ultimately reduce capillary bleeding [23]. In the blood, bioflavonoids reduce the aggregation of red blood cells and platelets [24]. In the immune system, they act to strengthen the body's natural defense against viruses and infections, and can also serve as natural anti-inflammatory agents [25]. In addition, bioflavonoids can also help with hypertension, allergies, wound healing, and peptic ulceration [26,27]. It is of interest to suggest that the unique ability of bioflavonoids to modulate the COX I and II activity and particularly the levels of various prostaglandin products in circulation and tissues appears to provide the mechanistic underpinnings for some of the beneficial biological effects known to be associated with bioflavonoids. In this context, it is also of note that our data showed that the levels of different PG products are differentially affected in different tissues by bioflavonoids, which may provide the basis for the differential biological effects of bioflavonoids in these tissues.

In summary, the results of our present study showed that myricetin and quercetin (two representative dietary bioflavonoids) have a powerful direct stimulatory effect on the COX's catalytic activity *in vivo*. Given the large amount of pre-existing information in the literature concerning the inhibitory effect of bioflavonoids on the COX activity, our finding is rather

intriguing, and it also suggests that bioflavonoids may function as naturally-occurring, physiological co-substrates/stimulators of the COX I and II.

## Abbreviations used

| | |
|---|---|
| COX I and COX II | cyclooxygenase I and II, respectively. |

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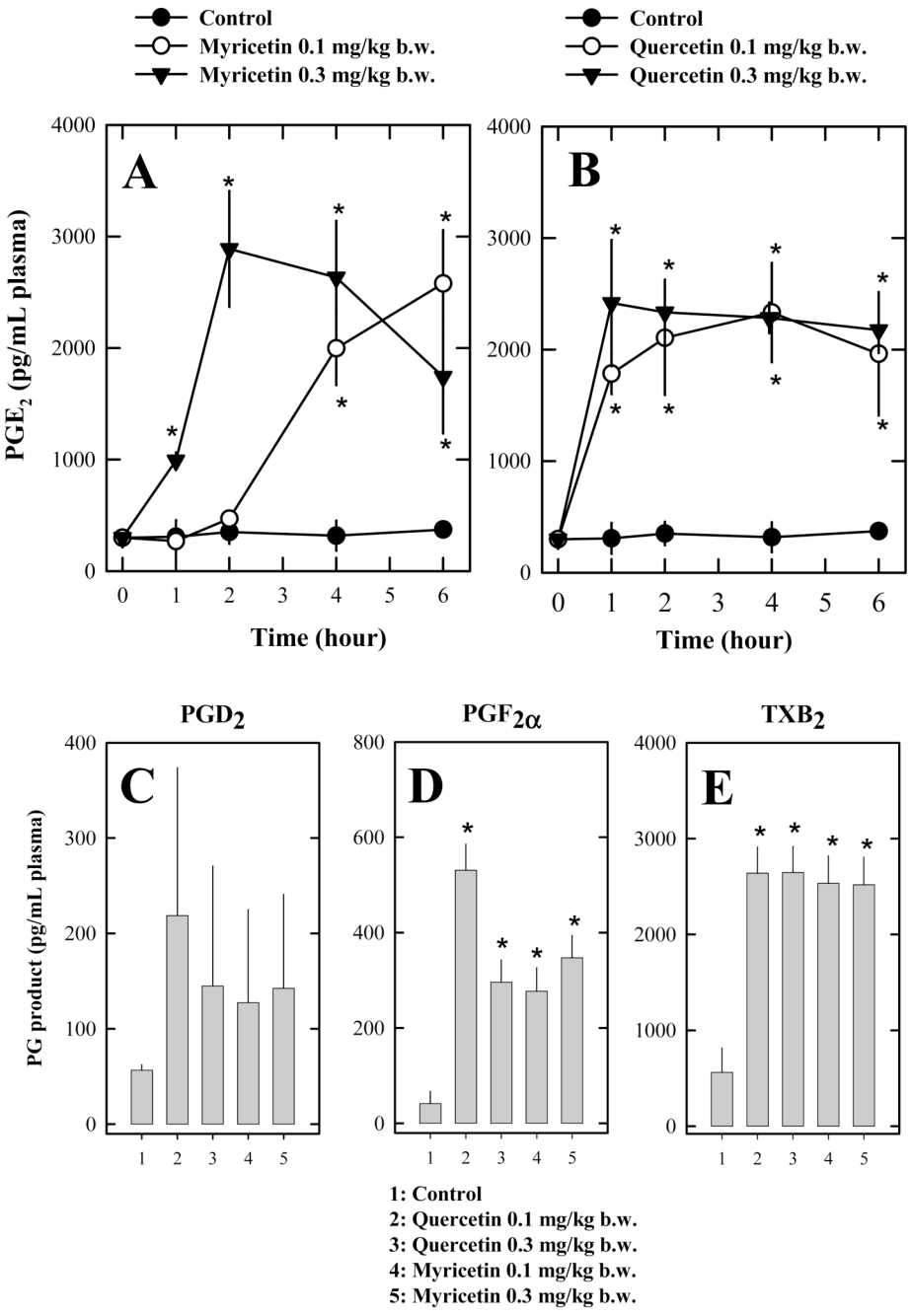


**FIGURE 1.**

The plasma levels of $PGE_2$ in rats injected *i.v.* with 0.1 or 0.3 mg/kg b.w. of myricetin or quercetin. The blood samples were collected from the tail vein for up to 6 h. The plasma was immediately prepared and stored at −80°C for measurement of PGs ($PGD_2$, $PGF_{2\alpha}$, and $TXB_2$) by using EIA kits. Data represent mean ± S. D. ($n = 4$). * $P < 0.05$ compared to the corresponding values of the control group.

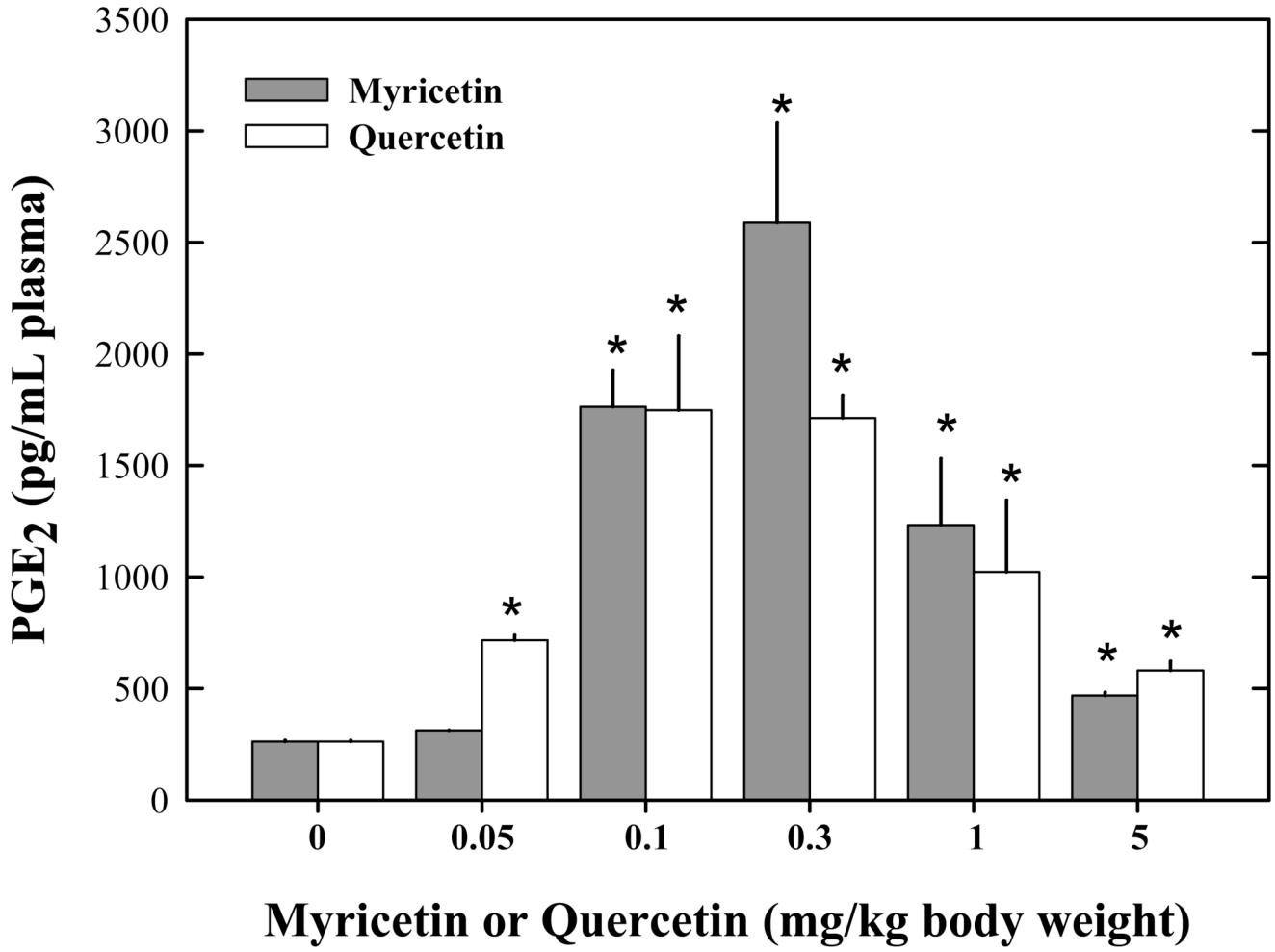


**FIGURE 2.**

The dose-dependent effect of myricetin or quercetin on the levels of plasma $PGE_2$ in rats. Myricetin or quercetin was injected *i.v.* into each animal, and animals in the control group were injected *i.v.* with the vehicle only. The blood samples were collected for preparation of plasma from the tail vein at 4 h after injection, and the $PGE_2$ levels were measured by using an EIA kit. Data represent mean ± S. D. ($n$ = 3). * $P < 0.05$ compared to the levels at 0 h.

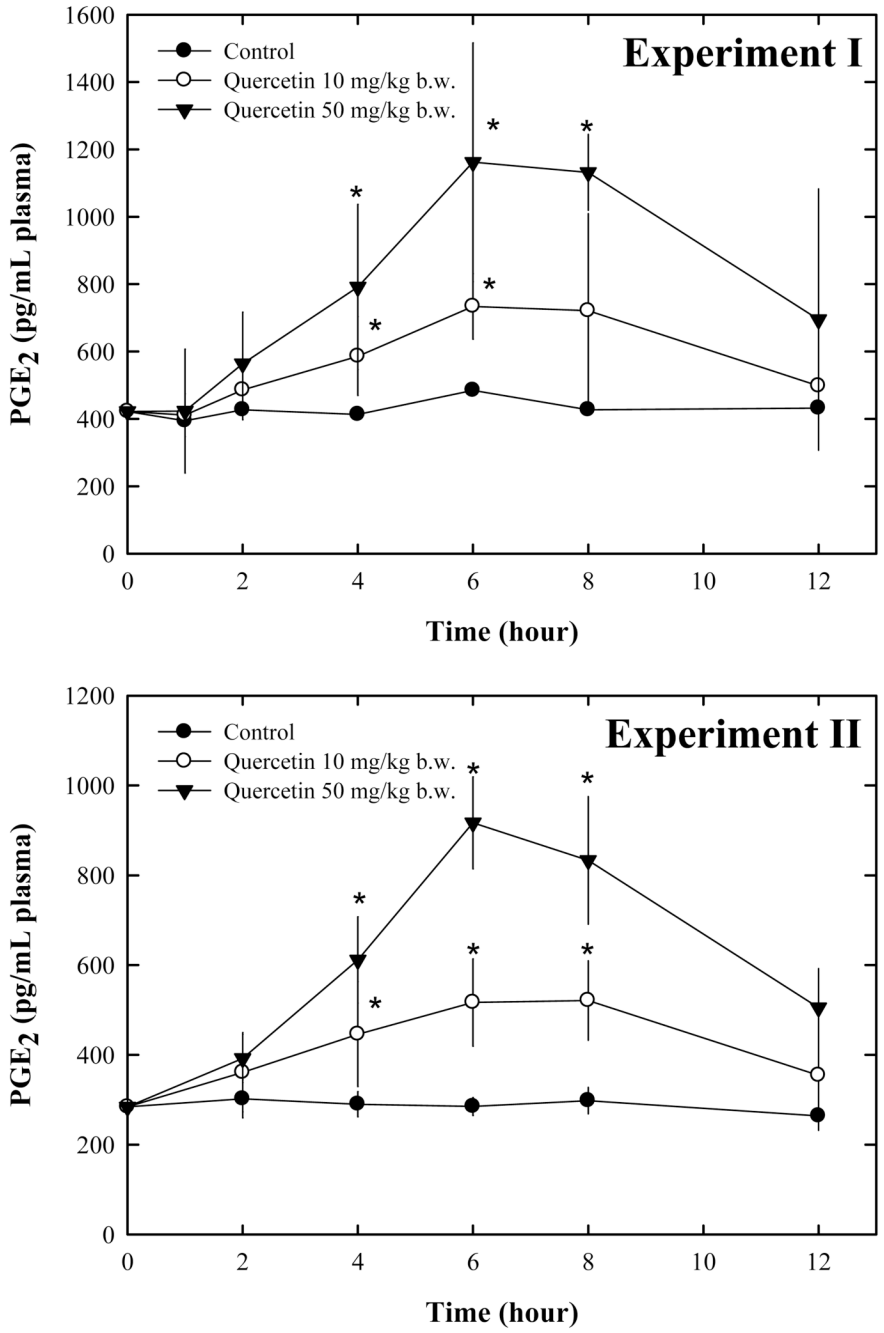


**FIGURE 3.**

Effect of oral administration of quercetin on the levels of plasma $PGE_2$ in rats. Quercetin (10 and 50 mg/kg b.w.) was administrated orally, and animals in the control group were given the same volume of vehicle only. The blood samples were collected for preparation of plasma, and the levels of $PGE_2$ were measured by using an EIA kit. Data represent mean ± S. D. (For experiment *I*, $n = 3$, and for experiment *II*, $n = 6$). * $P < 0.05$ compared to the corresponding values of the control group.

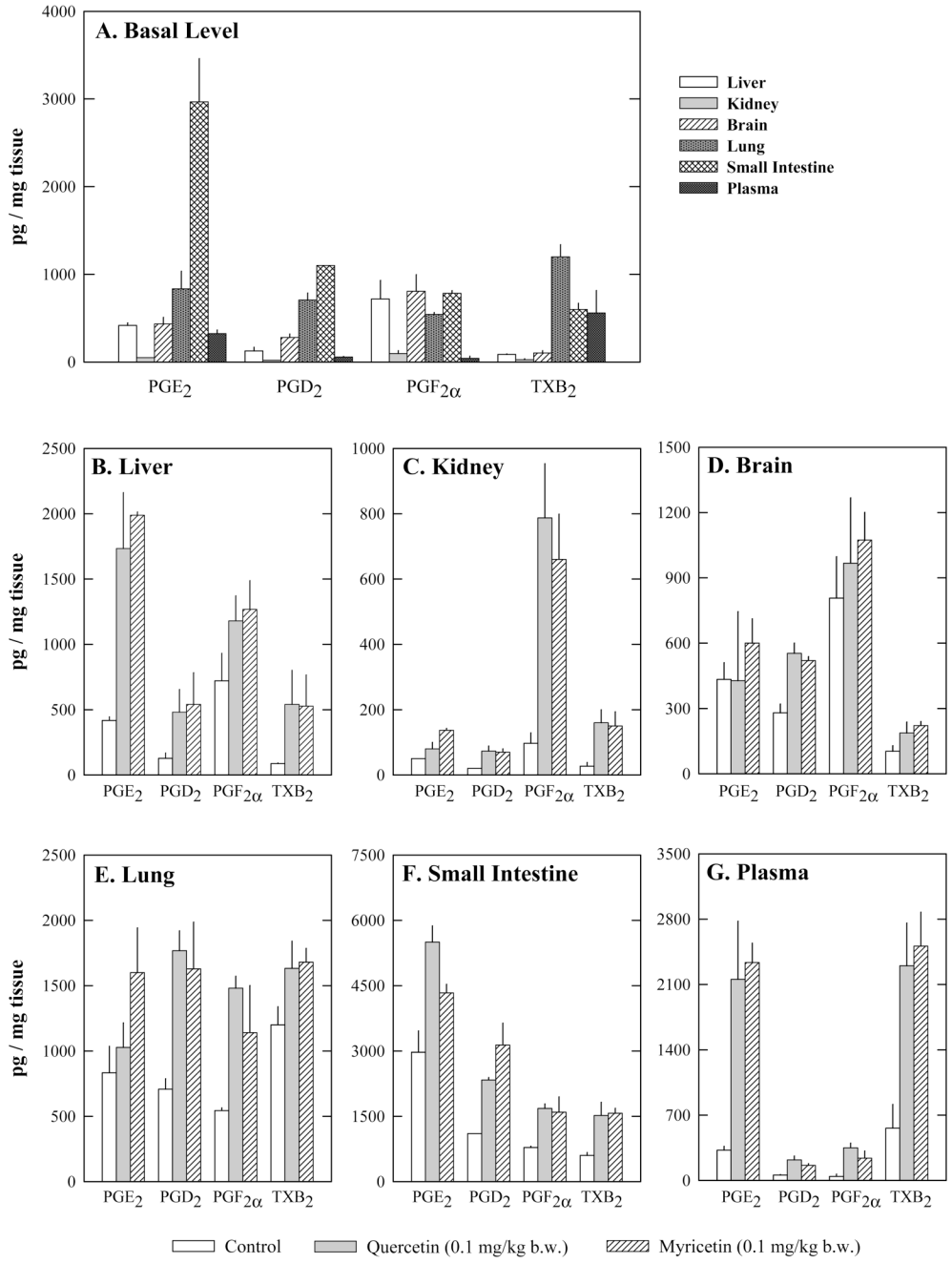


**FIGURE 4.**

The effect of quercetin and myricetin on the tissue levels of $PGE_2$, $PGD_2$, $PGF_{2\alpha}$ and $TXB_2$ in rats. Myricetin and quercetin (0.1 mg/kg b.w.) were injected *i.v.* into the animals, and the control animals were injected *i.v.* with 100 μL vehicle. The animals were sacrificed 4 h later. The blood samples were collected for preparation of the plasma. Liver, kidney, stomach, lung and small intestine were also removed, quickly frozen in liquid nitrogen, and then kept at −80° C. The levels of $PGE_2$, $PGD_2$, $PGF_{2\alpha}$ and $TXB_2$ in these tissues were measured by using the EIA kits. Data represent mean ± S. D. ($n$ = 4).