LICORICE: ABSORPTION, DISTRIBUTION, METABOLISM
AND CANCER CHEMOPREVENTION

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ABSTRACT

This is a comprehensive chapter describing the bioavailability and metabolism, as well as dose tolerance of 18-β-Glycyrrhetic acid (GA), an active component of licorice roots. In recent years, attention has been focused to consider licorice as a possible cancer chemopreventive agent. Results summarized in this report suggest that 18-β-GA and carbenoxolone are effective chemopreventive agents against carcinogen-induced preneoplastic lesions in mouse mammary gland organ culture. Moreover, both carbenoxolone and GA inhibited chemically-induced mammary carcinogenesis in rats. Further studies also have shown that while GA induces estrogen receptor modestly, it dramatically down-regulates progesterone receptors in uterus and mammary glands. Since there was a potent inhibition of progesterone receptors by GA, it may have effects toward other physiological events related to progesterone receptors.

INTRODUCTION

Licorice, the root of *Glycyrrhiza galba* (Leguminosae), has been traditionally used in Chinese herbal medicine for hundreds of years. Ethnomedical information suggests that it has been used for a variety of purposes
including contraception, liver disfunction, dysmenorrhea, cough, and cancer. A large number of compounds have been isolated from licorice which includes carbohydrates, coumarins, lignans, lipids, flavonoids, triterpenes, etc. The biological effects include, but are not limited to antibacterial, analgesic, antimutagenic, antispasmodic, antihelcer, anti-inflammatory, anti-immunomodulatory and antifungal. Such a broad scope of activity and chemical composition makes licorice a unique edible material. In order to selectively understand properties of the chemical components of licorice, considerable attention has been directed to pentacyclic triterpene β-glycyrrhetic acid (3-hydroxy-11 oxo-18β-olean-12-en-30-oic acid) (GA) and its glucoside glycyrrhizin (GL). Glycyrrhizin is a principal component of licorice and is ingested orally as a sweetener. When administered orally to humans, R-glycyrrhetic acid, an aglycon of GL, is detected in the serum. Since GA and its synthetic analog carbenoxolone (3-O-β-carboxypropionyl-GA) have been used clinically, and often pseudo-aldosteronism is associated as a side effect of carbenoxolone, attention has been focused towards understanding the absorption, distribution and dose tolerance of GL, GA and carbenoxolone in experimental models. The chemical structures of these agents are shown in Fig. 27.1.

β Glycyrrhetic Acid  \( R = \text{OH} \)

Carbenoxolone \( R = \text{COOH} \)

\[
\begin{align*}
\text{Glycyrrhizin} & \quad R = \end{align*}
\]

![Chemical Structures](image)

**FIG. 27.1. CHEMICAL STRUCTURES OF SELECTIVE COMPONENTS FROM LICORICE ROOT**

In addition to numerous activities attributed to licorice root, in recent years its possible use in cancer prevention has been explored. The demonstration of a cancer-prevention strategy requires that the active chemopreventive agent, at a totally nontoxic concentration, either prevent initiation of transforma-
Licorice and Cancer Prevention

Licorice (Glycyrrhiza glabra) is a plant native to parts of the Middle East and the Mediterranean region. It has been used for centuries in traditional medicine for its various health benefits, including anti-inflammatory, anti-cancer, and anti-microbial properties. Licorice root contains numerous compounds, including triterpenoids, flavonoids, and lignans, which are responsible for its therapeutic effects.

The primary active compound in licorice root is glycyrrhizin (GL), a glycoside of glycyrrhetic acid. GL is metabolized to licorice acid (LA), which is responsible for the characteristic taste of licorice. GL and LA are known to possess anti-inflammatory, anti-microbial, and anti-tumor properties.

The mode of action of licorice and its compounds is multifaceted. They have been shown to inhibit tumor promotion, angiogenesis, and cell proliferation. GL and LA can also induce apoptosis in cancer cells, making them promising candidates for chemoprevention and treatment of cancer.

The effectiveness of licorice and its compounds in cancer prevention has been studied in various preclinical and clinical trials. Several studies have reported that licorice and its metabolites can reduce the risk of cancer development and progression in several types of cancer, including stomach, colon, breast, and liver cancer.

Licorice has been shown to inhibit the production of tumor promoting agents, such as reactive oxygen species and reactive nitrogen species. It also inhibits the activation of nuclear factor-κB (NF-κB), a transcription factor that plays a crucial role in the regulation of cellular proliferation and survival.

In addition to its anti-cancer properties, licorice has also been shown to have anti-inflammatory effects, which are believed to play a role in the chemoprevention of cancer. The anti-inflammatory effects of licorice compounds can help reduce the inflammation that is associated with cancer.

Licorice has been widely used in traditional medicine for its medicinal properties. It is well tolerated and generally safe, although some side effects, including fluid retention and sodium retention, have been reported.

Recent studies have also shown that licorice and its compounds can be effective in combination with other cancer therapies. This may lead to more effective treatment regimens for cancer patients.

In conclusion, licorice and its compounds have promising potential for cancer prevention and treatment. Further research is needed to fully understand the mechanisms of action and the optimal use of licorice in cancer prevention and treatment.

Absorption and Distribution of GL and GA

Experiments in the literature on the subject of absorption and tissue distribution of licorice components, especially GL and GA, are largely incomplete. During the past few years, extraction and HPLC procedures have been developed to separate GL, GA, and their metabolites in the serum, urine, bile, or organ tissues. Recently, a complete distribution comparison of GL and GA has been reported. Ichikawa et al. injected 100 mg/Kg GL or 60 mg/Kg GA in male Wistar rats. Urinary bladder, bile duct and femoral artery were cannulated for collecting samples. Bile, urine and blood were collected for 24 h period, whereas other organs were collected 1 h after the intravenous injection with the licorice components. HPLC analysis was carried out to separate GL and GA. The half-lives of elimination for GL were 50 min, whereas for GA it was 80 min. GL was largely concentrated to GA in the liver and kidney. GA on the other hand was retained in the brain, liver, kidney and skin. However, the concentration in liver was significantly lower than GL. The majority of GL was
secreted in bile, whereas a negligible amount of GA was present in bile or urine. These results suggested that although GL remains intact in the rat, GA is readily metabolized. The results from Ichikawa et al. are summarized in Table 27.1. In a separate study Sakiya et al. have shown that following a bolus injection of GL, no GA was detected in the serum indicating that the conversion of GL to GA occurs in the small intestine. The results are consistent with those of Ichikawa, in that GA is rapidly metabolized, whereas GL is distributed in various organs. Recently, a comparison was made between the absorption of GL and GA in germ-free rats versus conventional rats. Results showed that orally-administered GL was poorly absorbed from the gut and is hydrolyzed by the intestinal bacteria. No GA was detected for up to 17 h after the administration of GL in germ-free rats; whereas GA was detected in conventional rats after 4 h of oral treatment with GL.

**TABLE 27.1**

**TISSUE DISTRIBUTION OF GLYCYRRHIZIN AND GLYCYRRHETINIC ACID IN RATS**

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Glycyrrhizin Recovered (%)</th>
<th>Glycyrrhetic acid Recovered (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>5.0</td>
<td>13.8</td>
</tr>
<tr>
<td>Brain</td>
<td>0.0</td>
<td>2.4</td>
</tr>
<tr>
<td>Liver</td>
<td>24.5</td>
<td>9.0</td>
</tr>
<tr>
<td>Kidney</td>
<td>11.1</td>
<td>7.9</td>
</tr>
<tr>
<td>Skin</td>
<td>6.7</td>
<td>10.0</td>
</tr>
</tbody>
</table>

Adopted from Ichikawa et al. (12).

**Metabolism of GL and GA**

The consumption of licorice as a sweetener, or its components and analogues, such as GA and carbenoxolone, is almost always by the oral route. Therefore metabolism of GL and GA has been studied in the intestine or by the intestinal flora. Hattori and colleagues reported on the incubation of intestinal bacterial mixture, prepared from human feces, with either glycyrrhizin or β glycyrrhetinic acid for 48 h. Metabolites were separated and identified using silica gel thin-layer chromatography and mass spectral analysis. Results indicated that glycyrrhizin is initially metabolized to its aglycone form 18-β-glycyrrhetinic acid and then transformed by epimerization to 3-epi-18-β-glycyrrhetinic acid. This epimerization of β-glycyrrhetinic acid was reversible via an intermediate,
3-hydro-18-β-glycyrrhetinic acid. Hattori subsequently identified, *Ruminococcus* sp., the strains of bacteria responsible for the hydrolysis of glycyrrhizin to glycyrrhetinic acid and the reduction of 3-dehydroglycyrrhetinic acid to GA. However, *Clostridium innocuum* was responsible for the conversion of 3-dehydro-GA to 3-epi-GA. A mixture of both bacterial strains completed the entire metabolic spectrum.\(^7\)

**Tolerance of GA and Carbenoxolone**

In addition to its therapeutic use, licorice has been extensively used as a sweetener. A high intake of licorice can cause hyper-mineralocorticoidism with potassium loss and sodium retention.\(^{19}\) As a result increased blood pressure and deregulation of aldosterone effects may be noticed. This makes it imperative to evaluate the tolerance of a maximum nontoxic dose of licorice for human consumption. Stormer *et al.* in a review\(^9\) indicated that if one assumes that 0.2% of glycyrrhizin acid is present in licorice root, then 50 g of licorice root will generate 100 mg of glycyrrhizin acid. This amount will be sufficient to produce adverse effects in a sensitive individual. Generally people consuming approximately 400 mg glycyrrhizin acid demonstrate the side effects of the agent. Since 100 mg glycyrrhizin acid is found to be the lowest concentration with measurable side effects, 10% of that concentration or 10 mg of glycyrrhizin acid (5 g of licorice roots) per day may be considered to be a safe dose.\(^{19}\)

A dose tolerance study for determining the maximum tolerated dose of GA and carbenoxolone in rats was conducted in our laboratory. Rats were divided in six groups and fed increasing dose levels of GA and carbenoxolone mixed with AIN 76A diet for six weeks. The concentration of these agents in the test diet ranged from 625 mg/kg diet to 10,000 mg/kg (1%). Animals were weighed twice a week. Results showed that there was no difference in the body weights between control and the 2,500 mg/Kg GA dose. At the 5,000 or 10,000 mg/Kg dose level, there was a significant reduction in the body weight gain. These results are summarized in Table 27.2. Since 2,500 mg/kg was the maximum non-toxic tolerated dose for β glycyrrhetinic acid, carcinogenesis experiments were conducted using 80% of the maximum tolerated dose (2g/kg diet). An identical dose tolerance pattern was observed for carbenoxolone. Carbenoxolone also affected body weight at 5,000 mg/kg diet.

In a separate toxicity study with glycamil (ammonium glycyrrhizinate) it was observed that the LD\(_{50}\) for rats and mice was >5,000 mg/kg of oral dose, whereas for guinea pigs it was >3,000 mg/kg in an acute toxicity study. In a subchronic study of eight weeks with 700 mg/kg of glycamil, it was also found to be non-toxic in terms of its effects of body weight, hepatic function, electrolyte balance and organ weights. Similar results have been obtained in a chronic study with rats and mice with a 90 mg/kg dose level.
Chemoprevention of Mammary Carcinogenesis by GA and Carbenoxolone

Several reports in the literature have appeared, which strongly suggest chemopreventive activity of components of licorice root in a two-stage skin carcinogenesis model. Nishino et al.\textsuperscript{69} reported that 18-β-GA inhibited 7,12 dimethylbenz[a]anthracen (DMBA)-induced and 12-O-tetradecanoylphorbol-13-acetate promoted skin cancer incidence by more than 50\%. This inhibitory effect was more prominent when teleocydin was used as a promoter. We have been evaluating potential chemopreventive agents in a variety of \textit{in vivo} and \textit{in vitro} carcinogenesis models. Chemically-induced \textit{in vivo} carcinogenesis in urinary bladder, lung, pancreas, prostate, skin and mammary gland have been extensively employed.\textsuperscript{20} On the other hand, we have utilized an \textit{in vitro} approach in which the effectiveness of a suspect chemopreventive agent is identified using a mouse mammary gland organ culture model.\textsuperscript{21} Once the compound is considered effective in the organ cultures, then the potential chemopreventive agent is further evaluated in a carcinogen-induced \textit{in vivo} rat mammary carcinogenesis model. This approach was employed for the evaluation of β-GA and carbenoxolone as chemopreventive agents.

Mammary Gland Organ Culture (MMOC)

Based upon the concept that the mammary gland responds to growth promoting protein and steroid hormones to alter morphology and functional state of the organ in animals and humans, an organ culture model was established.\textsuperscript{22,23}
It was found that organ tissue not only responds to hormones in culture to induce differentiation, but also responds to the carcinogen. Under appropriate hormonal conditions, the organ culture tissue develops preneoplastic mammary lesions (ML), which would form adenocarcinoma upon transplantation in syngeneic mice.\textsuperscript{24} We have further modified this model system to determine if the chemopreventive agents would suppress the development of these ML (Fig. 27.2). Results have consistently shown that the compounds that suppress the development of ML also inhibit carcinogen-induced incidence or multiplicity of mammary tumors.\textsuperscript{22,23} We examined effects of 18-\textgamma-\textgreek{G}A and carbenoxolone on the development of DMBA-induced ML in organ culture.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig27.2.png}
\caption{Experimental design for the induction of mammary lesions in organ cultures.}
\end{figure}

The detailed procedure of MMOC has been described elsewhere.\textsuperscript{22-25} Briefly, the glands were incubated with growth-promoting hormones for 10 days followed by the withdrawal of hormones for an additional 14 days. The carcinogen, DMBA (2\,	extmu g/ml) was included in the medium for 24 h between 72 and 96 h of the incubation. Fifteen glands per group were incubated with five concentrations of 18-\textgamma-\textgreek{G}A or carbenoxolone during the growth-promoting phase of the first 10 days of culture. At the end of the study, glands were fixed and evaluated for the presence or absence of the lesions. Results are shown in Fig. 27.3. Both 18-\textgamma-\textgreek{G}A and carbenoxolone inhibited ML development in a dose-responsive manner. \textgreek{G}A at 10\textsuperscript{\textgreek{M}} showed reduced effectiveness. This was attributed to the toxic effect of \textgreek{G}A at that concentration. Carbenoxolone was less...
effective than GA, however, no toxicity was associated with carbenoxolone in MMOC. These results suggest a possible chemopreventive activity of the licorice-derived agents β-GA and carbenoxolone in a mammary carcinogenesis model.

FIG. 27.3. INHIBITION OF DMBA-INDUCED MAMMARY LESIONS BY β GLYCYRRHETINIC ACID AND CARBENOXOLONE

Mammary lesions were induced in the mammary glands in organ cultures as described in the text. β Glycyrrhetinic acid (---■---) and carbenoxolone (---□---) were included in the medium between days 0-10 of the growth promoting phase. Percent inhibition was calculated by normalizing the data for the incidence in the control group of glands.
Effects of GA and Carbenoxolone in Carcinogen-Induced Mammary Carcinogenesis Model

There are two widely used in vivo mammary carcinogenesis models: one utilizes DMBA as a carcinogen, whereas the other one utilizes N-methyl-N-nitrosourea (MNU) as a carcinogen. We have extensively used both of these models in our laboratory.\textsuperscript{20,26} For the present study, the MNU-induced mammary carcinogenesis model was employed. The detailed procedure has been described previously.\textsuperscript{26} Typically, 50-day-old female Sprague Dawley rats are treated with a single intravenous injection of 50 mg/Kg body weight of MNU. Animals are fed the AIN 76A semi-purified diet as a basal diet. The chemopreventive agents are included in the diet by thoroughly mixing them with the basal diet. Normally the chemopreventive agents are mixed at 40 and 80\% of the maximum tolerated dose level, to ensure that the effect observed with the test agent is not related to the toxicity of the agent. As discussed above, the maximum tolerated non-toxic dose for both GA and carbenoxolone was 2,500 mg/Kg diet. Thus, the carcinogenesis experiments were carried out at 1,000 and 2,000 mg/kg dose levels. Both GA and carbenoxolone did not affect the tumor incidence during a 100-day experiment. At the 2,000 mg/kg of GA dose level, the tumor multiplicity was significantly reduced by 59\% (6.2 tumors/rat in control vs 2.6 tumors/rat). At the reduced dose level of GA, 1 g/kg, the effect was 48\% inhibition. At 2,000 mg/kg, carbenoxolone also inhibited multiplicity by 49\% (6.9 control vs 3.5 tumors/rat). Both GA and carbenoxolone increased tumor latency and the tumor weights were reduced (unpublished).

The effect of GA and carbenoxolone has been evaluated in a variety of experimental carcinogenesis systems. In addition to skin and mammary carcinogenesis models, carbenoxolone was found effective against liver and lung carcinogenesis; however, carbenoxolone was ineffective against colon\textsuperscript{27,28} and buccal pouch (unpublished) carcinogenesis.

Effects of Licorice Root Extract (LRE) on Steroid Receptors

Although the effect of licorice in mineralocorticoid, metabolism, has been recognized for a long time, only recently has the mechanism of its action been understood. Briefly it has been postulated that licorice, and specifically GA, inhibits 11\beta hydroxysteroid dehydrogenase.\textsuperscript{29} This enzyme inactivates corticosterone and cortisol and converts them to dehydrocortisone and cortisone. Aldosterone is not metabolized by this enzyme. Thus, in cells with high concentration of 11\beta hydroxysteroid dehydrogenase, the native glucocorticoids are inactivated leaving aldosterone as the steroid to regulate electrolyte balance. Inhibition of this enzyme activity by licorice would elevate the levels of corticosterone and cortisol resulting in increased mineralocorticoid activity.
The other major functional property of licorice has been reported to be its antiestrogenic activity.\textsuperscript{10,11} Although the steroid receptor modulation by licorice is highly relevant to cancer prevention research, it has not been investigated. We investigated the effects of dietary licorice root extract on the steroid receptors in uterus and mammary glands. Uteri of mice and rats contain relatively high amounts of estrogen and progesterone receptors.\textsuperscript{30} Similarly, the mammary gland is the target organ for hormone dependent and steroid receptors. They play a significant role in the modulation of the growth of breast cancer. Therefore, the effects of licorice root extract on the modulation of steroid receptors were evaluated in these two tissues.

Young Sprague Dawley female rats were maintained on modified AIN 76A diet. Diets were supplemented with 0.5, 5 and 10% licorice root extract (LRE). Animals consumed the licorice supplemented diet for 21 days. There was no effect of LRE on the body weight gain of the animals. Estrogen and progesterone receptors were measured by receptor titration assays. Typically, aliquots of cytosol prepared from the tissues were incubated with increasing concentration of [\textsuperscript{3}H]estradiol for estrogen receptors or [\textsuperscript{3}H]R5020 for progesterone receptors, either alone or in the presence of 100-fold excess unlabeled diethylstilbestrol or R5020 for 16 h at 0-4°C. Reactions were terminated by dextran coated charcoal treatment. Specific binding was calculated and Scatchard plots were generated. Results are shown in Table 27.3. As expected, the uterus contained high concentrations of estrogen and progesterone receptors. LRE increased estrogen receptors in a dose-related manner. There was a two-fold increase in the estrogen receptors with 10% LRE treatment. However, there was a dramatic down regulation of progesterone receptors by the licorice components. The binding was reduced from 413 femole per mg protein to 18 femole per mg as also observed for the protein. Such total “shut-down” of progesterone receptors was also observed for the mammary gland tissue. It is realized that both estrogen and progesterone receptor concentrations are very low in the mammary gland, nonetheless the trend consistent with that observed with uterus is quite evident.

To verify the effect of LRE on progesterone receptors a second experiment was carried out. Animals were either kept intact or ovariectomized. One week following the surgery, animals received a 30-day release 0.5 mg estrogen 17\beta pellets s.c., and either received a basal diet or a diet supplemented with 5% LRE for one month. Uteri were removed and steroid receptors were measured. Results are shown in Table 27.4. As expected, estrogen treatment enhanced both estrogen and progesterone receptors in ovariectomized animals. Ovariectomy almost totally inhibited available protein receptors, however, estrogen treatment increased it from 24 to 268 femole per mg protein. LRE, however, inhibited estrogen induction of progesterone receptors. Again these results clearly suggest that LRE down regulates progesterone receptors in rats.
In intact rats, the results were consistent to that described in the previous experiment. Although estrogen modestly increased estrogen and progesterone receptors, LRE up regulated estrogen receptors and down regulated progesterone receptors.

### Table 27.3

**Effect of licorice root extract on steroid receptors.**

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Treatment</th>
<th>ER (fmole/mg protein)</th>
<th>PR (fmole/mg protein)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uterus</td>
<td>Control</td>
<td>243 ± 174</td>
<td>413 ± 40</td>
</tr>
<tr>
<td></td>
<td>0.5% LRE</td>
<td>373 ± 142</td>
<td>10 ± 1</td>
</tr>
<tr>
<td></td>
<td>5.0% LRE</td>
<td>418 ± 101</td>
<td>25 ± 9</td>
</tr>
<tr>
<td></td>
<td>10.0% LRE</td>
<td>373 ± 142</td>
<td>18 ± 9</td>
</tr>
<tr>
<td>Mammary Gland</td>
<td>Control</td>
<td>4.0</td>
<td>25 ± 1</td>
</tr>
<tr>
<td></td>
<td>0.5% LRE</td>
<td>4.0</td>
<td>No Binding</td>
</tr>
<tr>
<td></td>
<td>5.0% LRE</td>
<td>2.0</td>
<td>No Binding</td>
</tr>
<tr>
<td></td>
<td>10.0% LRE</td>
<td>13.0</td>
<td>No Binding</td>
</tr>
</tbody>
</table>

Rats were fed either modified AIN 76A diet supplemented with LRE. LRE was obtained from the Arthur D. Little and Co. Steroid receptor assays represent mean of three experiments, each in duplicate. Scatchard plots were generated and the number of binding sites and binding affinity were calculated.

### Table 27.4

**Effect of ovariectomy and licorice root extract on steroid receptors in rat uterus.**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>ER (fmole/mg protein)</th>
<th>PR (fmole/mg protein)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intact</td>
<td>64</td>
<td>108</td>
</tr>
<tr>
<td>Intact + E\textsubscript{1}</td>
<td>70</td>
<td>173</td>
</tr>
<tr>
<td>Intact + E\textsubscript{1} + 5% LRE</td>
<td>162</td>
<td>No Binding</td>
</tr>
<tr>
<td>Ovariectomized</td>
<td>133</td>
<td>24</td>
</tr>
<tr>
<td>Ovariectomized + E\textsubscript{1}</td>
<td>198</td>
<td>268</td>
</tr>
<tr>
<td>Ovariectomized + E\textsubscript{1} + 5% LRE</td>
<td>139</td>
<td>158</td>
</tr>
</tbody>
</table>

Rats were either left intact or ovariectomized bilaterally. Animals were fed either modified AIN 76A diet or AIN 76A diet supplemented with LRE. Estrogen treatment was employed by transplanting an estradiol pellet dorsally in the animal as described in the text. LRE was obtained from the Arthur D. Little and Co. Steroid receptor assays represent mean of three experiments, each in duplicate. Scatchard plots were generated and the number of binding sites and binding affinity were calculated.
REFERENCES


15. Akao, T., Hayashi, T., Kobashi, K. and Kanaoka, M. Intestinal bacterial hydrolysis is indispensable to absorption of 18β-glycyrrhetic acid after oral


Licorice pharmacology present study, preventive effect aglycon glycyrrhizic acid. Licorice suppress tumor growth in animals used as medicinal anticarcinogen. Licoic used as medicinal anticarcinogen.

In Asia licorice is used as medicinal anticarcinogen. In the West licorice is used as a diuretic, antispasmodic, and as a flavoring agent. Licorice is used in the treatment of digestive disorders, such as ulcers and irritable bowel syndrome. It is also used in the treatment of respiratory disorders, such as asthma and bronchitis. Licorice is also used in the treatment of liver and kidney problems, as well as in the treatment of diabetes.

In addition, licorice is used as a flavoring agent in many products, such as chocolates, candies, and baked goods. Licorice is also used in the production of alcoholic beverages, such as beer and wine. Licorice is also used in the production of non-alcoholic beverages, such as sodas and soft drinks.

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