CNS Drug Reviews
Vol. 6, No. 1, pp. 35–44

Overview of the Pharmacological Features of Honokiol

Yuji Maruyama and Hisashi Kuribara

Department of Neuropsychopharmacology (Tsumura),
Gunma University School of Medicine, Gunma, Japan

Key Words: Anxiolytic effect—Central actions—Herbal medicines—Honokiol—Magnoliaceae—Magnolol—Metabolism/Kinetics— Pharmacological effects.

ABSTRACT

This paper provides an overview of the pharmacological features of honokiol (3′,5-di-2-propenyl-1,1′-biphenyl-2,4′-diol), an isomer of neolignans isolated and identified from the stem bark of Magnoliaceous plants (*Magnolia obovata* Thunb, Wa-Koboku in Japanese). The magnolia bark has been utilized as a herbal remedy for the treatment of a wide variety of clinical disorders. Honokiol and magnolol (an isomer of honokiol) were recently identified as anxiolytic agents in the extracts of Saiboku-to, an oriental herbal medicine (Kampo). Behavioral evaluation through an elevated plus-maze test demonstrated that honokiol, 0.2–2 mg/kg, p.o., for 7 days, was at least 5000 times more potent than Saiboku-to. Honokiol has a comparatively lower risk of causing benzodiazepine-like side effects, such as central depression, muscle relaxation, amnesia, or physical dependence. In addition to these central actions, a wide variety of pharmacological effects and biochemical activities of honokiol have been reported during the past 10 years. The main effects, including the limited information regarding the metabolism and kinetics of the compound, are briefly introduced in this text. Information available on honokiol, including its specific and simple chemical structure, suggests the possibility of deriving more potent compounds in the drug design process.

INTRODUCTION

Honokiol (3′,5-di-2-propenyl-1,1′-biphenyl-2,4′-diol) was first isolated and identified from the stem bark of *Magnolia obovata* Thunb (Wa-Koboku in Japanese) by Fujita et al. in 1972 (4). The stem bark of this plant as well as that of *Magnolia officinalis* Rhed et Wils (a Chinese drug "Houp") have been used in traditional Chinese medicine for treatment of thrombotic stroke, typhoid fever, fever, and headache (16).

Address correspondence and reprint requests to Dr. Yuji Maruyama, Department of Neuropsychopharmacology (Tsumura), Gunma University School of Medicine, 3-39-22 Showa-machi, Maebashi, Gunma 371-8511, Japan. Tel./Fax: +81 (27) 232-4292. E-mail: yuji@akagi.sb.gunma-u.ac.jp

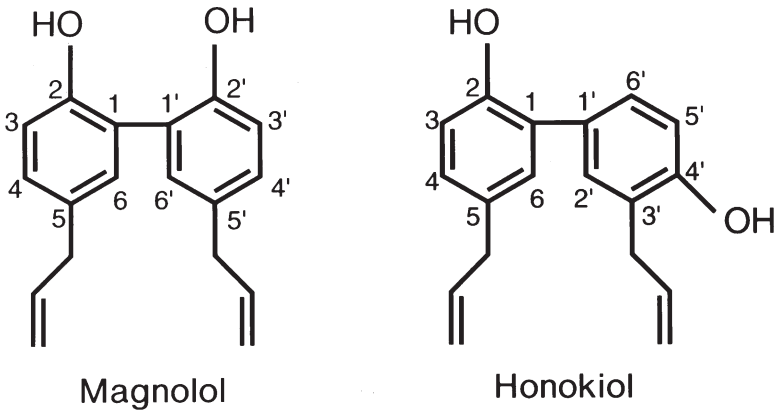

Fig. 1. Chemical structures of magnolol and honokiol.

The magnolia bark has also been utilized for several hundred years in herbal remedies composed of specified mixtures with other dried plant materials, such as in Kampo medicine in Japan, for the treatment of a wide variety of clinical disorders (14). Preparations, such as Hange-koboku-to, Yoku-kan-san, Saiboku-to, and Kami-kihi-to, for example, have been historically prescribed for clinical depression; anxiety-related disorders, such as anxiety neurosis, insomnia, and anxiety hysteria; thrombotic stroke; and gastrointestinal complaints. In 1998, Maruyama et al. (27) identified honokiol as well as magnolol (an isomer of honokiol) as anxiolytic agents in extracts of Saiboku-to (Fig. 1).

Previously, Watanabe et al. (39,42) showed that honokiol exhibited a central depressant action, with successively higher doses eliciting muscle relaxation, sedation, sleeping, and anesthesia in mice. However, the dose that elicited the onset of anxiolytic activity was almost 100-fold lower than that reported by Watanabe et al. The level of anxiolytic activity was almost equivalent to that of diazepam but without diazepam-like side effects (21,22).

In addition to these central actions, a wide variety of pharmacological effects and biochemical activities of honokiol have been reported during the past 10 years. The main effects are briefly reviewed in this manuscript. Although the mechanism underlying the pharmacological actions has not been clearly elucidated, it should be noted that an unusual biphenyl compound, neolignan, revealed various *in vivo* and *in vitro* biophysiological activities, suggesting that there is a potential to develop potent derivatives from its simple and reactive chemical structure.

In line with the objectives of this journal, we will focus on a review of the central actions of honokiol, including metabolism and kinetics, and describe other bioactive features mentioned above.

CENTRAL EFFECTS OF HONOKIOL

The stem bark of *Magnolia officinalis* is one of the important components of the crude drug prescriptions in Kampo medicine, which have been used for the treatment of various

psychosomatic conditions. It is, therefore, believed that magnolia bark contains central nervous system (CNS)-acting compounds.

Central Depressant and Muscle Relaxant Effects

Behavioral Studies

Watanabe et al. (40) reported that ether extract, but not water extract, of magnolia bark showed a distinct central depressant effect as well as a centrally acting muscle relaxant effect. The ether extract of magnolia bark caused sedation at comparatively lower doses and loss of lighting reflex at higher doses. Furthermore, the ether extract antagonized oxotremorine-induced tremor and reduced convulsions caused by pentetrazole, strychnine, and picrotoxin.

Watanabe et al. (39,41,42) determined that honokiol and its isomer, magnolol, refined from alkaline soluble fraction of the ether extract, has central depressant and muscle relaxant effects in mice. Honokiol significantly inhibited clinging time on a wire mesh at 250 mg/kg i.p. (ED_{50} and 95% confidence limits for the muscle relaxant effect: 217 mg/kg, 161–291 mg/kg) and produced loss of righting reflex at 500 mg/kg. This sedative effect was produced by lower doses of honokiol. Similar effects were induced by magnolol (131 mg/kg, 94–183 mg/kg), ether extract (582 mg/kg, 388–873 mg/kg) and alkaline soluble fraction (530 mg/kg, 416–676 mg/kg). Thus, as muscle relaxants, honokiol and magnolol were approximately 2 and 4 times more potent, respectively, than the ether extract or its alkaline soluble fraction. These results suggest that honokiol and magnolol are the active components that elicit the central depressant and centrally-induced muscle relaxant effects of magnolia bark.

Electrophysiological Studies

The centrally-induced muscle relaxant effect of honokiol was confirmed by electrophysiological studies (41,42). Honokiol inhibited chicken spinal reflex for longer than 60 min (ED_{50} and 95% confidence limit for the inhibitory action: 11.1 mg/kg, 5.9–21.0 mg/kg), and this effect was antagonized by strychnine 200 μg/kg i.p. Magnolol also inhibited glutamate-induced potentials in frog ventral and dorsal roots (18). These results clearly indicate that the site of the actions of honokiol is in the CNS. Although there is no report on honokiol, magnolol suppressed penicillin-induced convulsion and spike discharge in the EEG in rats, indicating an anticonvulsant activity (39). Therefore, it is believed that magnolol, and probably honokiol, exhibits an inhibitory effect in higher brain centers (e.g., hypothalamic and reticular formation ascending activating systems, spinal cord) in rodents.

Neurochemical Studies

Honokiol, but not magnolol, elicited a concentration-dependent enhancement of 25 mM K^+-evoked acetylcholine (ACh) release from rat hippocampal slices. Addition of either tetrodotoxin, pilocarpine, or methoctramine had no effect on honokiol-enhanced ACh release (34). These results suggest that the central depressant effects of honokiol are

mediated by enhancement of K^+-evoked ACh release directly on hippocampal cholinergic terminals via receptors other than M_2 cholinergic subtypes.

Central Mediation of Gastrointestinal Functions

The effects of honokiol on gastrointestinal functions have not been reported. However, Watanabe (43) reported that magnolol (200 mg/kg i.p.) has a protective effect on stomach ulcer, stomach secretion, and bleeding. Magnolol had no effect on basal stomach secretion, although it strongly reversed the increased stomach secretion and bleeding caused by restraint and water-immersion stress. Stimulation of central GABA receptors by PCP-GABA (10 mg/kg s.c.) resulted in an increase in stomach secretion, which was almost completely inhibited by either vagotomization or magnolol (100 mg/kg i.p.). These results indicate that magnolol inhibits stress-induced increases in stomach secretion and bleeding, and produces antiulcer effects via an action on the CNS, probably by relieving stress-induced anxiety and nervous tension. Honokiol is expected to have magnolol-like effects on gastrointestinal function.

Honokiol and magnolol, at comparatively higher doses, exhibit protective effects on copper sulfate-induced vomiting in frogs (17). This effect is thought to develop through an action on CNS (44).

The central mediation of gastrointestinal function by honokiol and magnolol may be related to the clinical efficacy of magnolia bark on sensation of fullness in the chest and abdomen, indigestion, and diarrhea.

Anxiolytic Effects

Evidence obtained from nonplacebo-controlled studies, which have been empirically conducted for thousands of years for the treatment of a wide variety of clinical disorders, suggests that Saiboku-to, one of the most popular Kampo medicines containing magnolia bark, is able to relieve anxiety and/or nervous tension (14,15,28).

To confirm the anxiolytic effects of Saiboku-to, Kuribara and Maruyama (19) applied an improved elevated plus-maze test in mice. When Saiboku-to (0.5–2 g/kg p.o.) was administered daily for 7 days and plus-maze test was carried out 24 h after the last administration, mice exhibited significant and dose-dependent prolongation of time spent in the open arms without showing marked change in general activity. Furthermore, the anxiolytic effects of Saiboku-to were enhanced by diazepam and inhibited by flumazenil, an agonist and antagonist, respectively, of benzodiazepine receptors. These results suggest that benzodiazepine receptors may be involved in the development of the anxiolytic effect of Saiboku-to.

Nearly the same anxiolytic effects were observed when a chloroform-soluble fraction of Saiboku-to was administered daily for 7 days (20). Finally, we determined that honokiol derived from magnolia bark is the principal active anxiolytic compound in Saiboku-to (23). Other chemicals in magnolia bark, including magnolol, have no anxiolytic effect and barely influence the anxiolytic effects of honokiol (23).

Kuribara et al. (21) evaluated the characteristics of the anxiolytic effects of honokiol. A single oral dose of 20 mg/kg honokiol was required for a significant anxiolytic effect.

However, when honokiol was administered daily for 7 days and the plus-maze test was carried out 3 or 24 h after the last administration, significant anxiolytic effects were seen even at doses of 0.2 mg/kg and higher, and the anxiolytic potential of 0.2–1 mg/kg honokiol was almost equivalent to that of diazepam (Table 1). The combination of 7 daily administrations of honokiol (0.2 mg/kg p.o.) and a single administration of diazepam (1 mg/kg p.o.) enhanced the anxiolytic effects. The anxiolytic effects of honokiol were inhibited by flumazenil (0.3 mg/kg s.c.), (+)-bicuculline (0.1 mg/kg s.c.), CCK-4 (50 μg/kg i.p.), and caffeine (30 mg/kg i.p.). The anxiolytic effects of diazepam (1 mg/kg p.o.) were also inhibited by flumazenil and bicuculline, and diazepam completely reversed the anxiogenic effect of CCK-4. These results suggest that, like with diazepam, an agonistic action on benzodiazepine receptors is involved in the development of the anxiolytic effect of honokiol.

Behavioral Side Effects

As mentioned above, honokiol has central depressant and muscle relaxant effects (39,42). However, it should be noted that, due to extremely high doses of honokiol and to Kampo remedies containing magnolia bark, it is difficult to assess accurately possible side effects. High doses are required because the concentration of honokiol in magnolia bark is 0.25–1.7%; 250–500 mg/kg honokiol is equivalent to 15–156 g/kg of magnolia bark, whereas honokiol and magnolia bark reveal an anxiolytic effect even at 0.2 mg/kg (21) and 11.6–80 mg/kg (23), respectively.

Kuribara et al. (22) assessed the behavioral effects of honokiol at doses required for anxiolytic effects, and the effects were compared to those of diazepam. Mice treated with 1–10 mg/kg diazepam, but not those treated with 0.1–2 mg/kg honokiol, once a day for

TABLE 1. Effects of seven daily p.o. treatments with honokiol and single p.o. administration of diazepam on the plus-maze, ambulatory activity, and traction performance in mice

Treatments		*n*	Plus-maze (sec)	Activity (counts)	Traction (sec)
3 h after last administration of honokiol					
Tween-80		10	10.2 ± 3.7	30.9 ± 2.3	60.0 ± 0.0
Honokiol	0.2 mg/kg	10	49.8 ± 110.8*	31.8 ± 3.9	60.0 ± 0.0
24 h after last administration of honokiol					
Tween-80		10	14.5 ± 5.2	30.3 ± 2.9	60.0 ± 0.0
Honokiol	0.1 mg/kg	10	26.8 ± 8.0	25.6 ± 3.8	60.0 ± 0.0
	0.2 mg/kg	10	43.0 ± 7.0*	27.1 ± 2.3	60.0 ± 0.0
	0.5 mg/kg	10	58.6 ± 13.2*	27.9 ± 3.8	60.0 ± 0.0
	1.0 mg/kg	10	41.2 ± 7.7*	29.9 ± 2.0	60.0 ± 0.0
	2.0 mg/kg	10	45.8 ± 6.8*	36.8 ± 2.6	60.0 ± 0.0
10 min after administration of diazepam					
Tween-80		10	12.3 ± 2.6	24.9 ± 1.7	60.0 ± 0.0
Diazepam	0.5 mg/kg	10	29.7 ± 4.8*	28.2 ± 3.0	55.2 ± 4.8
	1.0 mg/kg	10	43.5 ± 6.1*	38.9 ± 3.2*	42.6 ± 6.3*
	2.0 mg/kg	10	137.7 ± 17.8*	30.6 ± 4.2	14.6 ± 2.0*

*$p < 0.05$ vs. Tween-80-treated control group (21).

12 days showed withdrawal symptoms characterized by hyperreactivity and running-fit when they were challenge-administered with flumazenil (10 mg/kg i.p.) 24 h after the last treatment. Diazepam (0.5–2 mg/kg p.o.) dose-dependently prolonged hexobarbital (100 mg/kg i.p.)-induced sleeping, disrupted the learning and memory performance, and inhibited bicuculline (40 mg/kg i.p.)-induced convulsion. Honokiol (0.2–20 mg/kg p.o.), however, had no such effects. Furthermore, the prolongation of hexobarbital-induced sleeping by diazepam was not modified by honokiol. Diazepam (0.5–2 mg/kg p.o.) disrupted traction performance and caused disinhibition. Honokiol, on the other hand, following single and repeated administrations, did not change the spontaneous motor activity or traction performance (21). These results suggest that honokiol at doses required for anxiolytic effects is less likely than benzodiazepine anxiolytics to induce motor dysfunction, physical dependence, central depression, and amnesia. Thus, it is speculated that honokiol or its metabolite(s) selectively activate the benzodiazepine receptors related to the production of the anxiolytic effects.

Interaction with Centrally Acting Drugs

An evaluation of the interaction of Saiboku-to and its fractions with centrally acting drugs, methamphetamine and haloperidol, was carried out using discrete avoidance response in mice (1). Saiboku-to, at 2 g/kg p.o., slightly decreased the response rate and the percent avoidance caused by suppressing the avoidance response. Methamphetamine (0.5 mg/kg s.c.) and haloperidol (0.1 mg/kg s.c.) stimulated and suppressed, respectively, the avoidance response. Saiboku-to (2 g/kg p.o.), and ethanol and chloroform extracts of Saiboku-to slightly enhanced haloperidol-induced suppression of the avoidance response. Diazepam (0.25 and 0.5 mg/kg s.c.) showed a similar effect. Methamphetamine (0.5 mg/kg)-induced avoidance was not modified by any treatments.

A preliminary evaluation of the interaction of honokiol with centrally acting drugs was carried out. Honokiol (0.1–10 mg/kg p.o.) did not change the avoidance response following a single administration and insignificantly modified methamphetamine-induced avoidance stimulation or haloperidol-induced avoidance suppression (authors' unpublished data). These results indicate that the interaction of honokiol with centrally acting drugs is almost negligible and that the central depressant effect of Saiboku-to is caused by unknown chemical(s) rather than by honokiol.

METABOLISM AND KINETICS OF HONOKIOL

Finding and Isolation of Honokiol in Magnolia Bark

As briefly mentioned in the Introduction, Fujita et al. (4,5) first isolated a new biphenyl compound in the methanol extract of the bark of *Magnolia obovata* Thunb (Wa-Koboku). This compound was an isomer of magnolol and was named honokiol after Honoki, a Japanese name of *M. obovata* Thunb. Honokiol was also found in *Magnolia officinalis* Rhed et Wils (Houp) and another allied plant, *M. tripetala* L. (6,46). The contents of honokiol in the methanol extract from the dried bark of *M. obovata*, *M. officinalis*, and *M. tripetala* were estimated to be 0.09–0.39, 0.34–1.17, and 1.83–4.03%, respectively (6). Hot water

extracts of *M. obovata* and *M. officinalis*, contained 0.23–1.53 and 0.25–2.34% of honokiol, respectively (23, authors' unpublished data).

Distribution, Metabolism, and Pharmacokinetics of Honokiol

The pharmacokinetic study revealed that the half-lives of disposition in the rat plasma samples were 49.22 ± 6.68 and 56.24 ± 7.30 min after i.v. administration of honokiol 5 and 10 mg/kg, respectively (35), and 54.15 ± 5.14, 49.05 ± 5.96, and 49.58 ± 6.81 min after i.v. administration of magnolol 2, 5, and 10 mg/kg, respectively (36). These results indicate that honokiol and magnolol show similar pharmacokinetic characteristics, and their half-lives of disposition are almost independent of the doses. There are species differences in the half-lives of magnolol. Thus, the half-lives in rabbits (14.56 ± 1.77 min for 5 mg/kg i.v., and 15.71 ± 3.00 min for 76 μg/kg/min i.v. infusion) were approximately one third of those in rats (37). However, the administration schedules scarcely changed the half-life. These results indicate that the kinetics of disposition of both honokiol and magnolol are linear (first order).

After i.v. administration magnolol is almost uniformly distributed in the brain tissues (38). Magnolol is metabolized to isomagnolol (the side chains being transformed from propenyl group to allyl group), hydrogenated and forms hydroxy derivatives, glucuronites, and sulfates (10,11,37,38). It is suggested that tissue enzymes and intestinal bacterial enzymes are involved in the metabolism of p.o. administered magnolol (10,11). Unfortunately, the metabolic pathways of honokiol have not been investigated. However, it is expected that the distribution in the brain and metabolism of honokiol are similar to those of magnolol.

MISCELLANEOUS BIOCHEMICAL AND PHARMACOLOGICAL EFFECTS OF HONOKIOL

Numerous biochemical and pharmacological effects of honokiol have been reported. The central effects were reviewed in this article as representative actions of honokiol, while other major effects will be briefly introduced below. Some, but not all of these effects may involve CNS.

Biochemical Activity

1. Cholesterol acyltransferase (ACAT) inhibitors were isolated from the extract of Magnolia obovata leaves and identified as abovatol, honokiol, and magnolol (24).

2. Magnolol and honokiol inhibit the acyltransferase activity in rat spleen microsomes and membrane fractions of human polymorphonuclear leukocytes (46).

3. a. Honokiol showed a strong antioxidant effect that may explain clinical indication for protection of hepatocytes from ischemia-reperfusion injury (2).

b. Magnolol and honokiol protect mitochondrial respiratory chain enzyme activity against NADPH-induced peroxidative stress and protect red cells against oxidative haemolysis (9).

4. a. Rate constants for the reactions between hydroxyl radicals and biphenyl compounds, such as honokiol, were estimated by competitive reactions for hydroxy radical between honokiol and 5,5-dimethyl-1-pyrroline-*N*-oxide (30).

b. Biphenyl compounds including honokiol inhibit UV-induced mutations by scavenging hydroxy radicals that were generated by UV irradiation in *Salmonella typhimurium* TA 102 (7).

Pharmacological Activity

1. Exposure of human lymphoid leukemia Molt 4B cells to honokiol showed both growth inhibition and the induction of apoptosis (12).

2. Ligustici Chuanxiong Rhizoma (Senkyu) ether extract enhanced skin permeability of lipophilic natural compounds, such as honokiol (29).

3. Honokiol protected myocardium from damage induced by ischemic injury and suppressed ventricular arrhythmia during ischemia and reperfusion (33).

4. Antioxidant effects of magnolol and honokiol were 1000 times higher than those of α-tocopherol, determined by quantitating lipid peroxidation (26).

5. a. Antiplatelet effects of magnolol and honokiol were due to an inhibitory effect on thromboxane formation and inhibition of intracellular calcium mobilization (32).

b. Honokiol inhibited platelet aggregation induced by a few aggregating agents (31).

6. Some of the naturally occurring flavonoids and lignans, inhibited cell growth by a nontoxic mechanism, possibly via cessation of DNA, and/or protein synthesis in leukemic cells (13).

7. Honokiol interfered with the interaction between the acetylcholine receptor and its agonists, suggesting that honokiol may also affect the steps in exocytosis caused by an increase in intracellular calcium, possibly at the site of action of calmodulin (25).

8. Honokiol blocked leukotriene synthesis by inhibiting 5-lipoxygenase activity and inhibited also immunoglobulin E-mediated production of these leukotriens in RBL-2H3 cells, suggesting that honokiol may exhibit antiallergic action (8).

9. Three phenolic compounds, including honokiol, exhibited significant activity against Gram-positive and acid-fast bacteria and fungi (3).

CONCLUSION

Honokiol and magnolol, isomers of neolignans, have been isolated from the bark of *Magnolia officinalis*. The compounds are naturally occurring phenylpropanoids and distributed only in limited Magnoliaceous plants. The stem bark of magnolia has been prescribed for the therapy of anxiety, neuronal disturbance, or gastrointestinal disorder in traditional Chinese medicine and Kampo medicine in Japan.

Recently, the principal active anxiolytic components in Saiboku-to, of Kampo medicine, have been isolated and identified as honokiol and magnolol. A behavioral assessment through an elevated plus-maze test showed that honokiol was at least 5000 times more potent than Saiboku-to when mice were treated orally for 7 days. Also, honokiol is associated with a comparatively lower risk of producing benzodiazepine-like side effects, such as central depression, muscle relaxation, amnesia, or physical dependence. These re-

sults suggest that honokiol is an anxiolytic with characteristics different from those of benzodiazepines. It is also expected that a new type of nonbenzodiazepine anxiolytics may be developed by evaluating the mechanisms of central action of honokiol and its derivatives. An outline of this investigation has been summarized here.

There has been very little information about the pharmacokinetics of honokiol, particularly in regard to its central effects. Therefore, similar information on magnolol is included in the relevant section. Other miscellaneous effects reported in various articles are introduced in the last part of this review, suggesting a wide variety of pharmacological bioactivities of honokiol.

By reviewing the available information on honokiol and examining its simple yet specific chemical structure (shown in Fig. 1) we can facilitate the development of more potent compounds, targeting concrete pharmacological effects in the drug design process. Based on this consideration, several compounds revealing potent central effects have been synthesized and investigated..

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