생 약 학 회 지
Kor. J. Pharmacogn.
25(1): 1~10 (1994)

Herbal Drug Interactions Due to Alteration of Metabolism

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Abstract—The screening of 150 Chinese drugs which are most frequently prescribed in Korean traditional medicine showed that at least 30% of the drugs affected barbiturate-induced hypnosis. This effect was mainly attributable to the alteration of drug metabolism. Phytochemical works resulted in the isolation of furanocoumarins, lignans, sesquiterpenes and saponins as drug metabolism modifiers. The structure-activity relationship is discussed.

Introduction

The traditional medicine has been in existence from ancient times and is widely practised almost every part of the world even in present times. For example, traditional Chinese medicine is practised in China and neighbouring countries such as Korea, Japan and Viet Nam and traditional Indian medicines such as Ayurvedic and Unani are practised in the Indian sub-continent.

The ancient Chinese medicine was first introduced into Korea some 1400 years ago, where it mingled with the existng native Korean empirical medicine which developed uniquely in the Korean ethnic and cultural context. Since that time traditional Chinese medicine has been constantly absorbed and a unique blend, a Korean traditional medicine called "Han Yak" was formed. This was the essential medical care in Korea until 1894 when modern western medicine was accepted.

At present, in South Korea, two medical systems: oriental medicine and western medicine, the basic principles of which are entirely different, are legally practised, co-existing rather than being integrated.

The drugs used by western therapy have been mainly synthetic compounds or pure isolates from natural products. They were discovered effective to some specific diseases. The contribution made by modern medicine to the prevention and treatment of such infectious disorders as the bacterial diseases can not be overstated.

However, diseases such as chronic hepatitis, rheumatoid arthritis, cholecystitis, bronchial asthma, eczema, hypertention and menopausal symptoms do not always respond well to modern methods of treatment. Moreover, some of synthetic drugs have recently been discovered to produce adverse reactions to humans.

On the contrary, drugs used in traditional medicine have been mostly natural herb preparations and people believe them to be less toxic and almost without side effects. Nevertheless most of them have hardly recognized therapeutic utility in western medicine for want of the equality, reproductivity of efficacy, safety and stability.

Even so some of them have been often to be effective in healing problems such as chronic

geriatric and systemic diseases that have proved recalcitrant to standard methods.

Therefore, herb therapy still retains an undiminished popularity among the Korean populace in spite of disadvantage that its mechanism of action is difficult to be explained scientifically and its clinical efficacy and safety have not been completely clarified by modern statistical methods.

Moreover, a number of herbal drugs and prescriptions have been covered by the National Health Insurance Scheme in Korea since 1987 and some preparations have been developed as the OTC drugs in these days. This obviously stimulates consumption of herbal preparations.

Herbal Drug Combination

In traditional medicine, a number of crude plant materials are prescribed alone or in combination in much the same manner according to the ancient diagnostic methods or sometimes in combination with modern synthetic drugs by today's medicinal practitioners without proper consideration of the possibility that one drug might interact with another.

Of course, a lot of literature on traditional Chinese medicine recorded on the effects caused by drug combination.

The drug combination effects described in traditional dispensatories[1] are:

1. Additive effect, Two or more drugs of the same physiological effect will produce the combined action of individual drugs when used together, such as *Anemarrhena* and *Phellodendron; Angelica* and *Cnidium;* Ginseng and Licorice.

2. Synergistic effect, Two or more drugs of different functions will potentiate the interaction of each other and promote their efficiency, such as Hoelen and *Astragalus; Anthriscus* and *Pinellia;* Rhubarb and *Scutellaria.*

3. Antagonistic effect, When two or more drugs are used together the reaction of one will depress the other, such as *Siler* and *Zingiber; Paeonia* and *Dendrobium; Machilus* and *Alisma.*

4. Inhibitory effect, One drug inhibits the other, such as *Astragalus* and *Siler; Bupleurum* and *Veratrum; Liriope* and *Sophora.*

5. Destructive effect, Two drugs may decrease the toxic interaction, when combined, such as *Siler* and *Aconitum; Zingiber* and *Pinellia; Angelica* and Arsenic which is mineral.

6. Opposed effect, Two drugs may cause a violent side reaction, when mixed together, such as *Scrophularia* and *Veratrum; Picrorrhiza* and *Scrophularia; Dichroa* and *Allium.*

Antagonistic, inhibitory and destructive effects are much alike in nature but of different degrees.

All the above mentioned effects were recorded in literature through empirical observation, and it is expected that some effects might be due to the sum of pharmacodynamic effects of the drugs and others might be due to the sum of pharmacokinetic drug interactions.

However, scientific research on this concept has not been carried out and even any attention has not been paid to this concept although a great number of compounds have been isolated from the medicinal plants and many pharmacological studies on them have been performed in these days.

Herbal Drugs Acting on Drug Metabolism

In our laboratory, a series of investigations have been carried out in recent years in an attempt to find out whether the vegetable drugs widely used in traditional medicine affect the activity of drug-metabolizing enzymes (DME), thereby, modifying the intensity of the therapeutical or toxicological responses of other drugs.

The test protocol employed in our initial screening for active drugs consisted of two methods. Hexobarbital-induced sleeping time prolongation test was used for DME inhibitory activity and sleeping time shortening test for DME inducing activity.

The reason why hexobarbital (HB) was used as a test drug is that first, the duration of HB action in the body is known to be regulated largely by the levels of liver microsomal DME, that oxidizes it and inactivates it and second, most of known DME inhibitors and inducers alter the duration of HB action.

In the screening tests male mice were used. In the first phase screening test animals were pretreated with a single intraperitoneal injection of 500 mg/kg of methanol extracts suspended in 0.5% CMC solution. When the extracts were toxic the dose was reduced. Thirty minutes after the sample pretreatment, 50 mg/kg of HB-Na was injected intraperitoneally and then the duration of sleep induced by HB was measured. At this dose, HB induced the control mice to sleep for 20 min on the average.

In the second phase screening test, mice were given the extracts once a day for three days and forty eight hours after the last dose of the materials, 100 mg/kg of HB-Na was injected and then the sleeping time was measured. In this test, the control mice slept for 73 minutes on the average.

In the assessment of this screening results the duration of hypnotic response of HB was considered an index of the rate of drug metabolism. However, prolonging effect on HB-induced sleeping time does not necessarily result from the inhibition of HB oxidation. Some of prolonging effects may be considered to result from the simple potentiation of the HB-induced hypnosis by a depressant component in plant without activity altering the rate of HB oxidation.

Therefore, the plant extracts which showed positive activity in the first phase screening test were subjected to the strychnine (ST) mortality test in order to make it clear whether sleeping time prolonging activity was caused by inhibition of DME or caused by simple potentiation of hypnosis.

The reason why ST was used as a test drug is that most DME inhibitors are known to cause not only an increase in the activity of HB which is a depressant but also an increase in the toxicity of ST which is a stimulant.

In the ST mortality test, 1.2 mg/kg of ST nitrate was injected 30 min after pretreatment with the extracts and the number of the animals dying within 30 min was recorded. At this dose, ST caused a tonic convulsion and about 50% mortality in the control group.

As the result of our biological screening of 150 herbal drugs belonging to 130 genera and 62 families which are most frequently prescribed in Korean traditional medicine, it was found that 30% of the plant extracts tested affected barbiturate-induced sleeping time[2].

According to the screening results, vegetable drugs could be classified into 4 groups.

Group 1. The drugs prolonging the duration of HB action by a single treatment.

Group 2. The drugs prolonging the duration of HB action by a single treatment, on the contrary, shortening the duration of action by repeated administration.

Group 3. The drugs impairing the HB metabolism.

Group 4. The drugs not affecting the duration of HB action.

Phenylpropanoids and Lignans

Twenty six drugs belonging to Group 1 caused a significant prolongation in barbiturate-induced sleeping time and an increase in ST toxicity

by a single administration. Whereas all drugs did not alter the sleeping time by repeated administration. Therefore, these drugs were suggested to contain DME inhibitors.

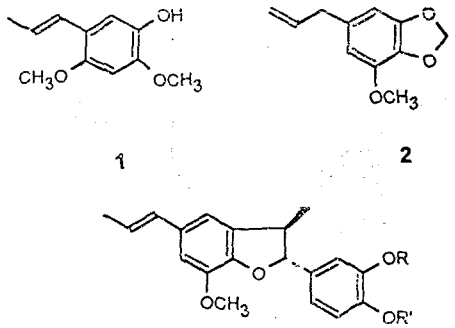
Among these drugs, bioassy-guided fractionation of the rhizomes of *Acorus gramineus*, which is said to have anodyne and sedative properties, was carried out and resulted in the isolation of asarone {1} as an active principle.

Asarone {1} was found in the essential oil from *Acorus* species as well as from *Asarum* species and reported to exhibit hypnosis-potentiating activity already in 1960[3]. But its mechanism of action has not been clarified yet. Our screening result suggests that **1** may inhibit the DME activity, thereby, reducing the rate of HB oxidation and consequently, showing hypnosis-potentiating activity.

The second drug investigated was *Myristica fragrans* which is used for a stomachic and condiment. Myristicin {2} and a series of neolignans {3-5} were isolated as active principles from the seeds[4] and macelignan [(2*R*, 3*S*)-1-(3, 4-methylenedioxyphenyl)-2, 3-dimethyl-4-(4-hydroxy-3-methoxyphenyl)-butane] {6} was isolated from the arils[5].

All the compounds a significant prolongation in the duration of hypnosis induced by HB and hepatic DME activity significantly decreased in compliance with hypnosis-prolonging activity[6-8].

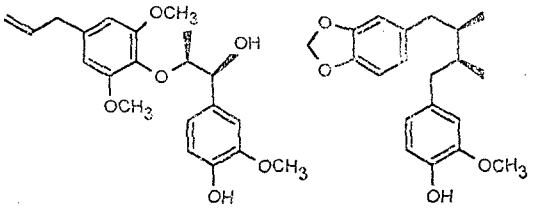
By the direct comparison of the half inhibition concentraton values of the isolates[6], it was found that the inhibitory activity of myristicin {2} and 8.O. 4′-lignan[1-(4-hydroxy-3-methoxyphenyl)-2-(4-allyl-2, 6-dimethoxyphenoxy)-propandiol] {5} which possess an allyl group was more potent than that of licarin B {3} and dehydrodiisoeugenol {4} which have no allyl moiety but a propenyl group. And the activity of **3** which has a methylenedioxy group was more potent than that of **4** which is devoid of it.



1 **2**

3 R=R'=CH_2

4 R=CH_3, R'=H



5 **6**

The investigation of the structure-activity relationship on inhibitory effect of several diaryldimethylbutane type lignans related to macelignan {6} also revealed that the lignans carrying a methylenedioxyphenyl nucleus were found to be more potent[8].

These combined results led to the following conclusion.

1. The presence of a double bond in propane chain of phenylpropanoids seems to be essential for the manifestation of the inhibitory effect on drug metabolism.

2. Allyl group is more potent than propenyl group.

3. Piperonyl group also plays a significant role in the elicitation of the activity.

Interestingly, it was found that compounds having a methylenedioxy group showed a distinct sedative activity[4]. At the dose of 40 mg of HB, the control mice got into a state of ataxia,

but they were not asleep. Administration of compounds **2** and **3** induced animals to sleep for 40 minutes at 200 mg dose, respectively. However, compounds **4** and **5** without a methylenedioxy group were almost completely inactive at the dosage used.

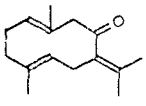
This observation strongly indicate that the piperonyl group may play a significant role not only in eliciting sedative property but also in intensifying inhibitory effect on drug metabolism.

Sesquiterpenes

Eight drugs belonging to Group 2 prolonged the HB-induced sleeping time by a single treatment but shortened the sleeping time by repeated treatments. Therefore these drugs may be expected to make complicated changes in intensity of the pharmacological and toxicological effects of other drugs.

Among these drugs, sesquiterpenes {7-9} were isolated as active principles from the rhizomes of *Curcuma zedoaria*[9], being used for a stomachic.

All the sesquiterpenes caused a marked prolongation in duration of hypnosis induced by HB as well as an inhibition of hepatic aminopyrine N-demethylase activity.



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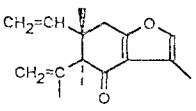

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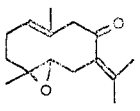

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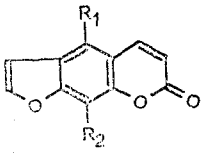
On the other hand, they induced a remarkable long duration of sleep even at a subhypnotic dose of HB, giving an evidence that they also possess a distinct sedative activity. Therefore, the hypnosis-prolonging activity of such sesquiterpenes seems to be a combination of inhibitory effect on DME activity and sedative property.

Furanocoumarins

From *Angelica* species, furanocoumarins were isolated as active principles: bergapten {**10**}, isoimperatorin {**11**}, oxypeucedanin {**12**}, isooxypeucedanin {**13**}, oxypeucedanin methanolate {**14**}, and imperatorin {**15**} from the roots of *A. koreana*[10], a remedy for common colds, and isoimperatorin {**11**}, isooxypeucedanin {**13**}, imperatorin {**15**}, phellopterin {**16**}, byakangelicin {**17**} and O-methyl-byakangelicin {**18**} from the roots of *A. dahurica*[11,12], a remedy for headache.

All the isolates prolonged HB-induced sleeping time and caused a remarkable increase in ST toxicity by a single treatment but shortened the sleeping time by repeated treatments[12,14]. The potency was as strong as that of SKF-525A



	R_1	R_2
10	$-OCH_3$	$-H$
11	$-OCH_2CH=C(CH_3)_2$	$-H$
12	$-OCH_2CH(O)C(CH_3)_2$	$-H$
13	$-OCH_2C(=O)CH(CH_3)_2$	$-H$
14	$-OCH_2C(OH)(OCH_3)C(CH_3)_2$	$-H$
15	$-H$	$-OCH_2CH=C(CH_3)_2$
16	$-OCH_3$	$-OCH_2CH=C(CH_3)_2$
17	$-OCH_3$	$-OCH_2C(OH)C(OH)(CH_3)_2$
18	$-OCH_3$	$-OCH_2C(OH)(OCH_3)C(CH_3)_2$

which is a well known most potent DME inhibitor.

Considering the fact that simple coumarins, dihydrofuranocoumarins and dihydropyranocoumarins did not produce any appreciable alterations in HB-induced sleeping time at the dosage used[14], the presence of a double bond in the furan ring and pyran ring attached to the coumarins seems to be essential for the manifestation of the DME inhibitory activity.

All the furanocoumarins tested caused a marked elevation of HB concentration in serum by a single treatment and a significant reduction in its level by repeated treatments[14]. The pattern of alteration in HB concentration in serum of the animals treated with the furanocoumarins was quite similar to that of animals treated with SKF 525 A, but not to that of animals treated with phenobarbital which is a well known DME inducer. This result obviously indicates that the furanocoumarins may belong to a DME inhibitor rather than an enzyme inducer.

As revealed by direct comparison of the DME inhibitory potency of coumarins by the half inhibition concentration values[14-16], psoralen, angelicin and xanthyletin, which are devoid of any side chain, showed weak activity. The inhibitory potency of pyranocoumarins seem to be much weaker in comparison with that of furanocoumarins. The presence of a side chain might potentiates the inhibitory activity and a large side chain (prenyloxy group) is more effective than a small one (methoxy group) and the potentiating intensity is not influenced by the location of the side chain. The inhibitory activity is depressed as the polarity of side chain increases.

Further evidence supporting the liver enzyme inhibitory activity of the furanocoumarins was obtained by ***in vivo*** experiment with imperatorin (**15**). An intraperitoneal injection of 30 mg/kg of **15** resulted in a significant decrease in DME activity and simultaneously, a significant diminution in cytochrome P-450 (P-450) concentration was observed[17]. The decreased activitiy of hepatic microsomal enzymes could be due to the reduced concentration of P-450 caused by exposure to **15**.

Furanocoumarins significantly not only inhibited carbon tetrachloride-dependent lipid peroxidation in liver microsomes but also inhibited carbon tetrachloride-induced hepatotoxicity as measured by s-GPT[18].

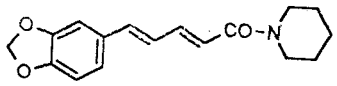
After the addition of **15** to the suspension of liver microsomes prepared from phenobarbital pretreated rats, the difference spectrum could be obtained, showing an absorption miximum at 390 nm and a minimum at 422 nm[17], indicating that it belongs to Type 1 binding spectrum according to the classification given by Schenkmans, *et al.*[19] This observation is indicative of binding of **15** to P-450. Incubation of hepatic microsomes from phenobarbial pretreated rats did not produce appreciable alterations in the concentration of P-450 by the addition of furanocoumarins or a NADPH-generating system separately[20]. Incubation of microsomes with coumarins in the presence of a NADPH-generating system, however, resulted in a loss of P-450. This finding is compatible with the interpretation that coumarins have to be metabolized in order to produce destruction of P-450.

Compounds which destroy P-450 are known secondarily to induce microsomal enzymes. As expected furanocoumarins actually induced P-450 when administered to animals daily for 7 days[17]. Therefore, it was concluded that furanocoumarins have biphasic effects on liver DME, i.e., inhibition followed by induction.

Amide Alkaloid

The extracts of fruits of two *Piper* species (*P. nigrum* and *P. retrofractum*) which are used for treatment of various fevers and digestive disorders were observed to exhibit not only a prolongation in hexobarbital-induced sleeping time by single treatment, but also a shortening in the sleeping time by repeated treatments, however, unlike other drug extracts, markedly reduced the strychnine mortality by a single pretreatment[21,22]. This result strongly suggested that there should be some constituents in these drugs, which possess a CNS depressant activity.

The bioassay guided fractionation gave an active crystalline compound identified as piperine {19}[23,24].



19

The mice pretreated with 19 slept considerably longer by HB administration as compared with untreated animals. However, there was no differences in the serum drug concentration 30 minutes after HB administration between control and test groups. Furthermore, the pretreatment with 19 completely protected the mice from the death due to ST. Moreover, 19 did not affect the activity of hepatic DME as well as P-450 concentration. Therefore, the mode of hypnosis-prolonging activity produced by 19 is obviously different from that produced by SKF-525 A and furanocoumarins.

The difference in the mode of action was shown in another way. When SKF-525A was given to mice just recovered from hypnosis induced by HB, the animals were visibly unaffected, but when 19 was given, the animals reverted almost immediately to a deep hypnosis. This indicates that 19 caused subhypnotic amounts of HB to become hypnotic. These combined results suggested that the hypnosis-prolonging effect 19 did not result from inhibition of HB metabolsim but from simple potentiating property.

As mentioned earlier, methanol extracts of *Piper* species decreased the HB-induced sleeping time when given repeatedly, suggesting the presence of DME inducers in these plants. Thus 19 was examined to determine whether it possesses inducing properties. Repeated oral administration of 19 to mice for 1 week, caused not only a shortening in HB-induced sleeping but also an incerase in DME activity and P-450 concentration in liver[25]. The activity was approximately 50% as potent as phenobarbital.

CO-binding difference spectrum of liver microsomes from rats treated with 19 showed an absorption maximum at 450 nm, indicating that 19 is a phenobarbital type inducer but not a 3-methylcholanthrene type inducer which induces a heme-protein known as P-448[25]. Piperine {19} interacted with hepatic microsomal suspension to give a Type 1 difference spectrum characterized by a peak at 385 nm and a trough at 420 nm. These findings, in the aggregate, suggested that 19 may be inhibit the drug metabolism in liver microsomes.

In order to verify this suggestion, *in vitro* experiments were carried out, showing that 19 inhibited aminopyrine N-demethylation and HB hydroxylation. However, its potency was considerably less than that of SKF-525A and furanocoumarins. The reason why that a pharmacologically effective dose (30 mg/kg) of 19 did not inhibit the hepatic microsomal enzyme activities *in vivo* experiments may be explained by an assumption that it was too small to achieve an adequate concentration in the liver required to saturate the DME. When given in toxic dosage (100 mg/kg), the depression of

enzyme activities was observed.

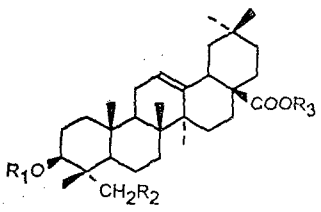
Triterpenoid Glycosides

Seven drugs belonging to Group 3 prolonged HB-induced sleeping time when treated with drugs repeatedly though they did not affect the activity by single treatment. This result suggested that the drug extracts caused the damage to liver, thereby, impairing drug metabolism in liver. Consequently hypnosis prolonging effect manifested itself even 48 hours after the repeated drug administration. As expected, consecutive parenteral pretreatments of the drug extracts increased serum GOT and GPT activities significantly which was accompanied by fatty degeneration and Kupffer cell activation in liver cells[26].

Bioassay guided fractionation of the drugs through solvent partition showed that activity was concentrated in butanol fractions. In contrast to the effect of parenteral administraion, however, no significant elevation in serum GOT and GTP levels could be observed even when administered orally the butanol fractions at a dose as high as 1 g/kg for 14 days. Hepatic P-450 level of butanol fraction-treated group, on the other hand, showed approximately two fold increase compared to that of the control[27], indicating a significant induction of hepatic DME.

Glycosides of hederagenin {20}, oleanolic acid {21~23} and melandrigenin {24} were isolated as toxic saponins from the roots of *Patrinia scabiosaefolia*[28] and the whole plants of *Melandrium firmum*[29].

Saponins are generally known to be hardly absorbed when orally administered and some saponins are easily degraded in the gastro-intestinal tract. From the discrepant findings with respect to the route of the administration, it can be postulated that one of major hepatotoxic principles might be saponins, which will undergo degradation in the gastro-intestinal tract into more easily absorbable smaller moiety such as prosapogenins or genins. The gradual absorption of these degradation products might provoke the induction of DME eventually leading to untoward effects.

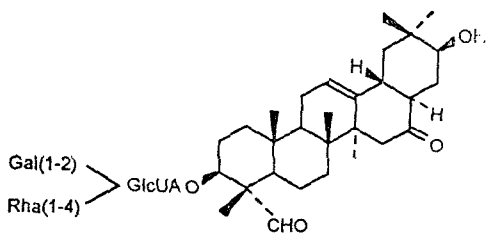


20 R_1= - Ara-2'-Ac, R_2=OH, R_3= -Glc(6-1)Glc

21 R_1= -Ara(2-1)Rha(3-1)Glc, R_2=R_3= -H

22 R_1= -Xyl(4-1)Rha(3-1)Glc(2-1)Xyl, R_2=R_3= -H

23 R_1= -Ara(2-1)Rha(3-1)Glc, R_2= -H, R_3=-Glc(6-1)Glc



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Conclusion

Several compounds isolated from Chinese medicinal plants were shown to modify the activity of hepatic drug-metabolizying enzymes. It goes without saying, however, that the caution is needed before extrapolating our data from experimental animals to human beings because there are a lot of reports on the species differences in drug metabolism[30]. Moreover it should be recognized that our research on the effect of herbal drugs on drug metabolism is just in an early stage and rather incomplete. Nevertheless, the possibility can be expected

that drug metabolism in man may be altered by some plant materials from our experimental data together with a few scattered reports by scientists in China[31], Japan[32] and India[33].

Harbal medicine already existed on the market long before the phase study was started. The safety and efficacy of herbal medicine may be partly explained by the fact that it has stood the test of time. However, more thorough scientific reseach aimed at drug interactions should not be neglected if we are to ensure their safety.

Such a study not only helps to increase understanding of the mode of action of herbal drugs but also should lead the way to new substantial improvements in the traditional herbal therapy.

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