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KUDZU ROOT: AN ANCIENT CHINESE SOURCE OF MODERN ANTIDIPSOTROPIC AGENTS

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Key Word Index—*Pueraria lobata*; Fabacea; *Radix puerariae*; isoflavones; daidzin; daidzein; golden hamsters; alcohol abuse; antidipsotropic; mitochondrial aldehyde dehydrogenase.

Abstract—Kudzu (*Pueraria lobata*) is one of the earliest medicinal plants used in traditional Chinese medicine. It has many profound pharmacological actions including antidipsotropic (antialcohol abuse) activity. Although both the roots and flowers of kudzu, *Radix* and *Flos puerariae*, respectively, have been used to treat alcohol abuse safely and effectively in China for more than a millennium, their true efficacy, active constituents, sites and mechanisms of action have never been critically examined. Recently, we have demonstrated that a crude extract of *Radix puerariae* suppresses the free-choice ethanol intake of ethanol-preferring golden Syrian hamsters and have identified two of its isoflavones, daidzin and daidzein, that account for this effect. Since then, we and other investigators have confirmed these findings in rats that were either trained or genetically bred to prefer and consume large amounts of ethanol. This article summarizes recent progress on the pharmacological and biochemical studies of the antidipsotropic isoflavones isolated from *Radix puerariae*.

INTRODUCTION

Kudzu is a perennial leguminous vine of the genus *Pueraria* native to eastern Asia. It was imported to the U.S. from Japan in 1876 to be exhibited in the Japanese pavilion at the Philadelphia Centennial Exposition. Because of its decorative dense foliage and attractive, crushed-grape-like fragrant flowers, kudzu rapidly gained popularity as an ornamental shade plant in its new homeland [1]. Before long, kudzu's excellent nutritional value, remarkable hardiness and growing speed, and elaborate root systems were noted and the U.S. saw the plant come into prominence from 1910s to the 1950s in the fodder and fertilizer industry [2], and in soil conservation programmes throughout the South where agrarian economy was at its all time low [3]. Since the 1950s, the key roles of kudzu were gradually replaced through utilization of chemical fertilizers for soil enrichment, soy and grain as animal feed, and concrete embankments for soil conservation. At present, in the southern states of the U.S., kudzu is considered at best a nuisance, at worse a scourge, as it continues to overleap new growth throughout the South [4].

Kudzu is believed to have originated in China and has been part of its culture for over two millenia. Interestingly, the ecosystem in China, and for that matter in other eastern Asian countries as well, has apparently kept kudzu's rampant and vigorous vegetative reproduction in check. The Chinese value kudzu primarily for its healing power. The tea of the root of kudzu (*Radix puerariae*, RP) was first described in the Chinese materia medica Shen Nong Ben Cao Jing [The Pharmacopoeia of Shen Nong, Anonymous, ≈200 B.C.] as sweet and acrid in taste, cool in nature and was used as an antipyretic, antidiarrhetic, diaphoretic and anti-emetic agent. In Huang Di Nei Jing [The Internal Book of Huang Di, Anonymous] and Shang Han Lun [Thesis on Fevers, Zhang Zhongjing, ≈200 B.C.], the two classic texts of traditional Chinese medicine, RP was recommended for stiffness and pain of the neck, pain in the eye, febrile diseases, and for the induction of early

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measle eruption. Almost a thousand years later, the use of RP and FP (*Flos puerariae*, flower of kudzu) based medications for the treatment of alcohol related problems was documented: first as an amethystic (anti-alcohol intoxication) agent [Sun Simiao, ≈600 A.D.], and later as an antidipsotropic (anti-alcohol abuse) agent [Li Dongyuan, ≈1200 A.D.].

Although RP has been used in China for more than two millenia, only in the past three decades have serious attempts been made to evaluate its true efficacy, and identify and reveal the mechanism(s) of action of its active principle(s). In this regard, significant progress has been made in the studies of the effect of RP on smooth muscle, cerebrovascular and cardiovascular systems (for a review see [5]) which has led to the development of Yu Feng Ning Xin Pian, a tablet form of an RP product sold over-the-counter in China, Japan, Australia and other Asian countries for angina pectoris, migraine headache, hypertension, and acute sudden deafness. On the contrary, the antidipsotropic effect of RP has received no attention at all presumably because alcoholism and alcohol abuse have not been a health problem in twentieth century China.

In the west, alcoholism and alcohol abuse are serious public health problems with staggering economic, social and medical consequences. Therefore, the identification of a suitable therapeutic agent that would selectively suppress the desire to drink alcohol has been a major goal of alcohol research. However, the lack of a well defined molecular basis for this disease has largely hampered a rational mechanistic approach to the discovery of such agents [6]. We have resorted to the vast clinical experience of earlier generations of Chinese herbalist physicians who have used folk medicines safely and effectively in the treatment of alcohol abuse and/or alcoholism. We began this project with a thorough literature search and found a list of 'stop drinking' formulae in the vast collections of ancient Chinese pharmacopoeias. Yet, most of the remedies listed in the ancient literatures were based on psychological aversion and have long been abandoned, presumably because of their ineffectiveness and/or undesirable side effects. The only medications that have survived historical trial-and-error scrutiny are those based on FP and RP. With this background information we began our search for safe and effective therapeutic agents with RP.

We considered that the search for new antidipsotropic agents requires a laboratory animal that voluntarily consumes alcohol, preferably in measurable quantities and can serve as a monitor. We chose the golden Syrian hamster (*Mesocricetus auratus*) because of its known natural preference to consume large quantities of ethanol in preference to water and the predictive validity of data obtained with this species [7–9]. Neither selective breeding, special training, nor the addition of dietary sweeteners are required to manipulate or induce it to prefer ethanol. Using this animal model we have confirmed the antidipsotropic effect of RP and identified two of its isoflavones, daidzin and daidzein, as the major antidipsotropic constituents of this crude preparation [9, 10]. The present article summarizes recent progress on the pharmacological and biochemical studies of these antidipsotropic agents isolated from RP.

RESULTS AND DISCUSSION

Golden Syrian hamsters prefer ethanol over water under free-choice condition

Unlike most outbred strains of laboratory rodents, golden Syrian hamsters exhibit a high preference for and consume large quantities of ethanol under a two-bottle free-choice regimen [7, 9]. A typical 130 g male hamster consumes only 3 to 8 ml of water each day, relatively low compared to that of other laboratory rodents. This has been attributed to the fact that hamsters are desert adapted animals with both renal and respiratory mechanisms for water conservation [11]. When these hamsters are given free choice between water and a 15% ethanol solution, they acquire most of their fluid intake from the ethanol solution with a concomitant decrease in water intake. In about 7 to 10 days, hamster ethanol intake reaches a relatively constant level which is more than 10 times higher than that consumed by humans considered to be heavy drinkers [12]. To consume such large amounts of ethanol, these hamsters must increase their total fluid intake 2- to 3-fold and, as a consequence, their urine output also increases significantly from about <2 ml day^{-1} to 5–10 ml day^{-1}. Although the amounts of ethanol consumed by different hamsters vary from 8 to 20 g kg^{-1} day^{-1}, the daily ethanol intake of each individual hamster is remarkably constant. This feature, together with the high volumes of ethanol intake, has been crucial to monitoring the search for new antidipsotropic agents from RP [9].

RP Extract, daidzin and daidzein suppress free-choice ethanol intake by golden Syrian hamsters

To verify the antidipsotropic activity of RP documented in traditional Chinese medicine, we prepared a crude methanol extract of RP and studied its effect on ethanol intake of golden hamsters. Six hamsters that consumed similar amounts of ethanol were selected for this study. During the saline control period, they consumed an average of ≈12 ml of 15% ethanol solution each day (Fig. 1). The crude extract of RP, administered interperitoneally (i.p.) at a dose of 1.5 g kg^{-1} day^{-1}, suppressed free-choice ethanol intake significantly ($\geq 50\%$). Ethanol consumption by these hamsters remained low during the daidzin-treatment period (day 1 to day 6) but increased gradually after the termination of RP administration (Day 7 to day 12). Administration of RP did not appear to affect water and total caloric intake significantly. This was the first time that the putative antidipsotropic effect

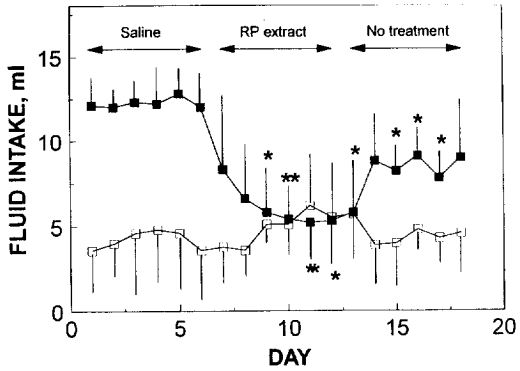


Fig. 1. RP extract suppresses free-choice ethanol intake of golden Syrian hamsters. Dose was 1.5 g kg^{-1} day^{-1}, i.p. Values are mean ± s.d. of the mean of 6 hamsters. (■) Intake of 15% ethanol solution. (□) Intake of water. *, $p < 0.05$; **, $p < 0.001$.

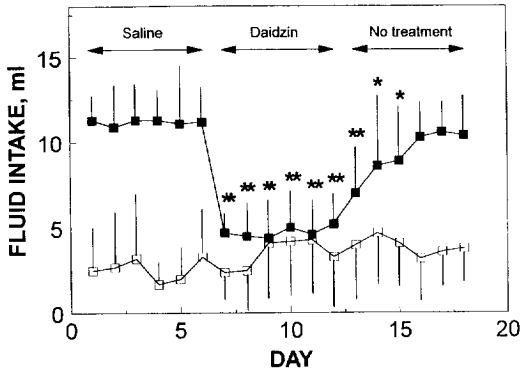
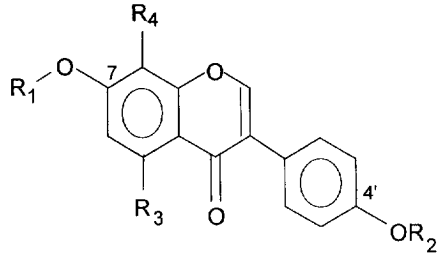


Fig. 3. Daidzin suppresses free-choice ethanol intake of golden Syrian hamsters. Dose was 150 mg kg^{-1} day^{-1}, i.p. Values are mean ± s.d. of the mean of 13 hamsters. (■) Intake of 15% ethanol solution. (□) Intake of water. *, $p < 0.05$; **, $p < 0.001$.



	R_1	R_2	R_3	R_4
Daidzein	H	H	H	H
Daidzin	Glc	H	H	H
Puerarin	H	H	H	C-Glc
Genistein	H	H	OH	H
Genistin	Glc	H	OH	H
Formononetin	H	Me	H	H
Daidzein-4',7-diglucoside	Glc	Glc	H	H

Fig. 2. Structure of RP isoflavones.

of RP was demonstrated in an ethanol drinking laboratory animal [9, 10].

Attempts to identify the active principle(s) in RP that suppressed hamster ethanol intake led to the discovery that two isoflavones, daidzin and daidzein (Fig. 2), are effective in this regard. The original experiment was done with thirteen hamsters that consumed similar amounts of ethanol, ≈11 ml of 15% ethanol per day. Daidzin, at a dose of 150 mg kg^{-1} day^{-1} (i.p.), suppressed hamster ethanol intake by > 50%. Ethanol intake gradually returned to that of the control level after the termination of treatment. Thus, the effect of daidzin was shown to be reversible (Fig. 3). We have now studied a total of 156 hamsters over a period of more than three years and in 148 of them ethanol intake was suppressed significantly (28 to 81% suppression) by daidzin. Suppression data obtained from this group of hamsters approximated a normal distribution with a mean ± s.d. = 53 ± 13%.

Daidzein, the aglycone of daidzin, also suppressed ethanol intake by the golden hamsters but appeared to be less potent. Thus a higher dose of daidzein (230 mg kg^{-1} day^{-1}) was necessary to produce ≈50% suppression. An equivalent dose of puerarin, the most abundant isoflavone found in RP, did not suppress hamster ethanol intake. Hamsters receiving RP extract, daidzin, daidzein or puerarin remained healthy and did not exhibit any significant changes in water, total caloric intake or body weight throughout these experiments.

Daidzin is the major antidipsotropic principle in the crude extract of RP

HPLC analysis showed that each g of RP extract contained 22 and 2.6 mg of daidzin and daidzein, respectively. This, together with the fact that daidzein is at least 3 times less potent than daidzin, suggests that it contributes little to the total antidipsotropic activity of the crude extract of RP. Comparison of the antidipsotropic activity of RP extract to that of pure daidzin, however, indicates that daidzin alone could not account for the total activity of the extract. The EC_{50} values estimated from the dose-response curves of pure daidzin, and daidzin administered as a component of crude extract are 23 and 2.3 mg per hamster per day, respectively. Thus, crude daidzin appears to be 10 times more potent than the pure compound. This discrepancy can be explained by one or both of the following propositions. First, in addition to daidzin, crude extract of RP contains other major active constituents that could either potentiate the effect of, or act additively or synergistically with daidzin. Second, the extract of RP contains one or more constituents that could increase the bioavailability of daidzin [13].

Daidzin analogues found in the crude extract of RP contribute little to its total antidipsotropic activity. Crude RP extract contains a number of isoflavones that are analogues of daidzin and hence could be

Table 1. Effect of RP isoflavones, alone or combined, on ethanol intake by golden hamsters

No.	Dose Isoflavones (mg/kg/day)	% Ethanol Intake Suppression‡
1 Daidzin	154	57 ± 12 (71)
2 Daidzein	231	56 ± 7 (12)
3 Daidzin + Daidzein*	77 + 115	61 ± 14 (3)
4 RP Extract	854	50 ± 8 (5)
5 Puerarin	137†	0
6 Daidzin	18.5†	0
7 Genistin	3.1†	0
8 Daidzein	2.3†	0
9 Daidzein-4′,7-diglucoside	1†	0
10 Genistein	0.15†	0
11 Formononetin	0.15†	0
12 Mixture of (1)–(11)*		0

* To make mixtures, isoflavones were first dissolved in methanol at a concentration of 1 mg ml^{-1} by sonication for 10 min. Appropriate aliquots were combined and methanol was then removed by flash evaporation in a 50° water bath. The dry materials were dissolved or suspended in sterile phosphate buffered saline for i.p. injection.

† Dose is equal to the amount of the specified isoflavone found in EC_{50} dose of RP extract.

‡ Data are mean ± s.d. of the mean of (n) hamsters.

antidipsotropic. HPLC analysis of this extract has identified 7 isoflavones with puerarin being most abundant (160 mg g^{-1} extract), followed by daidzin (22 mg g^{-1}), genistin (3.7 mg g^{-1}), daidzein (2.6 mg g^{-1}), daidzein-4′,7-diglucoside (1.2 mg g^{-1}), genistein (0.2 mg g^{-1}), and formononetin (0.16 mg g^{-1}). At suboptimal doses, daidzin and daidzein did not potentiate each other's activity, but rather they acted additively. Further, at a dose corresponding to the amounts present in an EC_{50} dose of RP extract, neither daidzin nor daidzein exhibited any measurable antidipsotropic effect. None of the other isoflavones identified in the crude extract of RP suppressed ethanol intake, either alone of in combination at the same amounts and proportions as found in an EC_{50} dose of the extract (Table 1). This lack of synergism among these compounds makes it unlikely that the small amounts of these isoflavones, including daidzein, could account for the enhanced antidipsotropic activity of the extract [13].

Crude extract of RP potentiates the bioavailability of daidzin. Herbalists who practice traditional Chinese medicine generally believe that crude drugs are superior to pure ones for a number of reasons. Among them, crude drugs are thought to be less toxic and their bioavailability is higher. To determine whether or not the crude extract of RP constitutes a more bioavailable form of daidzin than the pure compound, the two dosage forms were evaluated in hamsters in terms of the time course for the appearance of daidzin in blood. Results of these studies showed that the peak times (t_{max}) determined for pure daidzin, and daidzin given as the crude extract of RP are 63 and 33 min, respectively, and are independent of the dosages given (Fig. 4). The average maximal plasma daidzin concentration (C_{max}) in hamsters received the extract (containing 3.3 mg daidzin) is 10 times higher than that found in hamsters which received 6 mg of pure daidzin. The area under plasma daidzin concentration–time curves (AUC) estimated for both pure daidzin- and RP extract-treated hamsters was directly proportional to the amounts of daidzin administered. Within the dose range studied, daidzin administered as crude extract yields AUC values approximately ten times those obtained with the same dose of pure daidzin. Thus, daidzin given as the crude extract is more readily available to the hamsters than that given

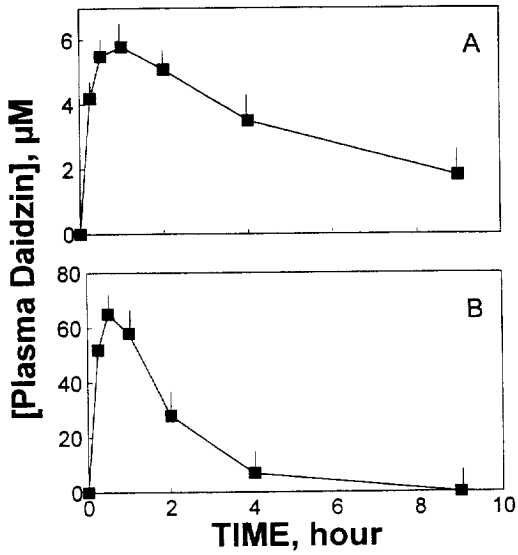


Fig. 4. Plasma daidzin concentration-time curves determined in hamsters given (A) 6 mg of pure daidzin, and (B) 150 mg of crude RP extract containing 3.3 mg of daidzin. Values are mean ± s.e. of the mean of 5 hamsters.

in pure form. It not only has a higher rate of availability (t_{max}) but also a much higher extent of availability (AUC). Replotting the dose response curves of pure and crude daidzin in terms of bioavailable daidzin rather than daidzin doses given yielded curves which are virtually superimposable. Pure, synthetic daidzin added to a crude extract of RP acquired the bioavailability of the endogenous daidzin that exists naturally in the extract [13]. These results strongly suggest that daidzin is probably the only major antidipsotropic principle in the crude extract of RP, and that additional constituents in the extract potentiate the bioavailability of daidzin in golden hamsters.

Daidzin suppresses ethanol intake in rats

To test the generality of the antidipsotropic effect of daidzin, we have extended our study to the rat. In this study, a two-lever choice procedure developed by Heyman [14] was adopted. Rats used in these experiments were trained to consume large and relatively constant amounts of ethanol in a short period of time. The amounts of ethanol consumed by a trained rat (after 35 to 40 weeks) range from 2.5 to 3 g kg^{-1} in a 30 min session. Training and experimental sessions were carried out in an operant chamber equipped with two levers. At one lever, responses earned 10% ethanol whereas at the other, responses earned an isocaloric starch solution. In this experimental setting, daidzin suppressed both ethanol and starch solution intake, but the suppression in ethanol intake was significantly larger (Fig. 5). This result not only shows that the antidipsotropic effect of daidzin also pertain to the rat but also indicates that daidzin remains efficacious in an experimental setting in which ethanol is a potent reinforcer. Furthermore, it demonstrates that the reduction in ethanol intake caused by daidzin is not simply a reduction in feeding behaviour. The latter point is of particular importance since calories probably play a very minor, if any, role in the regulation of human drinking [15].

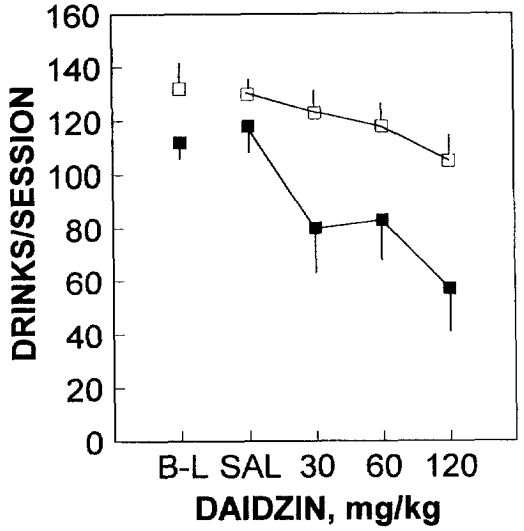


Fig. 5. Daidzin suppresses ethanol intake of rats. Daidzin was administered on three occasions and in ascending order. Saline (SAL) was administered five times through the course of the study. Baseline (B-L) was defined as the session just preceding the saline injection. Values are mean ± s.d. of the mean of seven rats. (■) Intake of 10% ethanol solution. (□) Intake of isocaloric polycose solution.

The antidipsotropic effect of daidzin, daidzein, and a crude herbal extract containing both of them has also been confirmed by other investigators using Fawn Hooded and P rats under various conditions, including the two-bottle free-choice, limited access, and alcohol-deprived paradigms [16–18]. These results, together with the fact that daidzin is a constituent of a long standing Chinese herbal treatment for alcohol abuse, further reinforce our belief that RP and its isoflavones can be used safely and effectively in the treatment of alcohol abuse in humans.

Rats and golden hamsters respond differently to puerarin. While puerarin appears to suppress ethanol intake in rats [16–18] it has little if any effect on that in golden hamsters [9, 10]. This could reflect differences in pharmacokinetic and/or pharmacodynamic processes of this isoflavone in the two species, or could indicate differences in the molecular mechanisms that control their ethanol drinking behaviour. Comparative studies with these two animal species may prove helpful in elucidating the mechanism of action of these isoflavones.

Mechanism of action of daidzin

The molecular mechanism by which daidzin selectively suppresses ethanol intake in laboratory animals is unknown. In an early study we have shown that daidzin potently and selectively inhibits human liver mitochondrial aldehyde dehydrogenase (mALDH) [19]. This, together with the fact that alcohol abuse is extremely rare among individuals who have inherited an inactive variant form of mALDH [20, 21], would seem to suggest that daidzin might act by mimicking the consequence of this natural mutation of the mALDH gene.

7-O-*substituted daidzeins that inhibit mALDH also suppress hamster ethanol intake.* To ascertain the idea that daidzin might act by inhibiting mALDH, we have attempted to establish a link between mALDH inhibitory and hamster ethanol intake suppressive activity with a series of structural analogs of daidzin. In a previous study, we surveyed a group of commercially available isoflavonoid and flavonoid compounds and found that only isoflavones with a blocked 7-hydroxyl group were potent mALDH inhibitors [19]. For example, daidzin, the 7-*O*-glucosyl-derivative of daidzein is at least 200 times more potent than the aglycone daidzein. Therefore, the 7-*O*-substituted daidzein derivatives were the first group of compounds to be synthesized and examined. As predicted, all of the 7-*O*-substituted daidzein derivatives synthesized thus

Table 2. ALDH inhibitory and ethanol intake suppressive activities of 7-*O*-substituted daidzein

No.	R group (see Figure 2)	mALDH Inhibition* K_i	mALDH Inhibition* αK_i	EtOH Intake Suppression†, %
1	H- (daidzein)	9.2	180	32
2	Glc- (daidzin)	0.042	0.65	62
3	$HOOC(CH_2)_5$-	0.009	0.15	70
4	$HOOC(CH_2)_6$-	0.009	0.14	69
5	$HOOC(CH_2)_9$-	0.004	0.05	nd‡
6	$HOOC(CH_2)_{10}$-	0.003	0.04	nd
7	CH_3CH_2-	0.035	0.56	nd
8	$Br(CH_2)_6$-	0.003	0.07	nd
9	$(CH_3CH_2)_3N^+(CH_2)_6$-	0.005	0.08	nd
10	$NH_2(CH_2)_6$-	0.036	0.60	nd
11	$Br(CH_2)_6CO$-	0.02	0.26	nd
12	$(CH_3CH_2)_3N^+(CH_2)_2$-	0.08	1.6	nd
13	$ClCH_2CO$-	1.06	10.6	nd
14	$BrCH_2CO$-	1.8	20	nd
15	$(CH_3)_2N(CH_2)_3CO$-	1.75	24	nd
16	Puerarin	15	440	0
17	Chrysin	35	110	0
18	7,8-Dihydroxyflavone	35	270	0

* mALDH activity was assayed at pH 9.5 using acetaldehyde as the substrate.

† Ethanol intake suppressive activity of each compound was measured as described [8]. Dose = 70 meq hamster^{-1} day^{-1}, i.p.

‡ nd = not determined.

far are potent inhibitors of mALDH and nine of them (**3**–**11**) are even more potent than daidzin (Table 2). It appears that the long chain 7-*O*-(ω-carboxyalkyl) derivatives (**3**–**6**) are the best mALDH inhibitors obtained so far. Puerarin (**16**), the 8-*C*-glucosylderivative of daidzein, and the two flavonoid compounds, chrysin (5,7-dihydroxyflavone, **17**) and 7,8-dihydroxyflavone (**18**), are the poorest inhibitors of human mALDH.

The antidipsotropic effect of two of the best (**3**) and (**4**), and three of the poorest (**16**–**18**) mALDH inhibitors have been tested in ethanol drinking golden Syrian hamsters. Daidzin and daidzein were also assayed at equivalent doses for comparison. As previously observed, both daidzin and daidzein were antidipsotropic. At an i.p. dose of 70 meq hamster^{-1} day^{-1}, daidzin or daidzein suppressed hamster ethanol intake by 62 or 32%, respectively. At equivalent doses, the most potent mALDH inhibitors (**3**) and (**4**) suppressed hamster ethanol intake by 70%, somewhat better than daidzin whereas the poorest mALDH inhibitors (**16**–**18**) exhibited no detectable antidipsotropic activity. These results are consistent with our hypothesis that daidzin, and presumably other antidipsotropic isoflavones as well, suppress hamster ethanol intake by inhibiting mALDH.

Daidzin does not act by an ethanol sensitizing mechanism. In principle, mALDH inhibitors could affect ethanol intake by at least two routes. On the one hand, it might serve as an ethanol-sensitizing agent by inhibiting the acetaldehyde metabolizing enzyme, mALDH, subsequent to drinking and thereby allow acetaldehyde to reach toxic levels. On the other hand, it could disrupt an as-yet-undefined physiological pathway involving mALDH and alter the concentration of some intrinsic metabolites that control ethanol drinking behaviour.

To determine whether or not daidzin suppresses hamster ethanol intake by inhibiting acetaldehyde metabolism, we have studied acetaldehyde clearance in daidzin-treated hamsters after ethanol administration. Acetaldehyde clearance in disulphiram (a known broad acting ALDH inactivator)-treated hamsters were also studied for comparison. Figure 6 shows that daidzin-treatment that suppressed hamster ethanol intake by $>50\%$, had no effect on either acetaldehyde (A) or ethanol (B) metabolism as compared to that of the control hamsters. On the other hand, disulphiram treatment greatly impaired hamsters' ability to metabolize acetaldehyde. In these hamsters, plasma acetaldehyde concentration rose rapidly after ethanol administration, reached 0.6 mM within 50 min and its level continued to rise. Four hours after ethanol administration, plasma acetaldehyde concentration approached 0.9 mM which is 225 times higher than that registered in the control hamsters [Fig. 7(A)]. Ethanol metabolism was also inhibited in disulphiram-treated hamsters [Fig. 7(B)]. These results clearly eliminate an ethanol-sensitizing mechanism and indicate that the action of daidzin differs from that proposed for the classic, broad-acting ALDH inactivator, disulphiram [22, 23].

The physiological function of ALDH-2, and for that matter other ALDH isozymes as well, is unknown

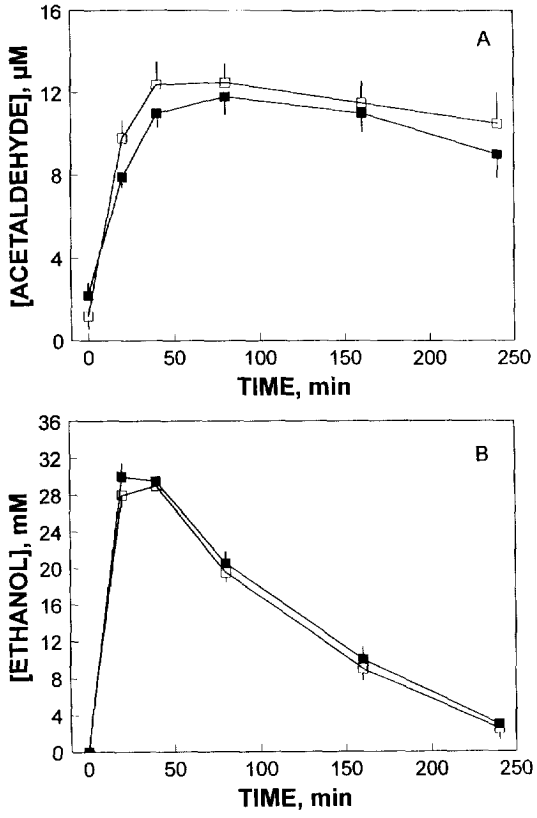


Fig. 6. Time course of plasma (A) acetaldehyde, and (B) ethanol concentrations in the control (□, received 1 ml saline per day for 6 consecutive days) and daidzin-treated (■, received 154 mg kg^{-1} daidzin per day for 6 consecutive days) hamsters after receiving an acute dose of ethanol (1.3 g kg^{-1}, i.p.) time = 0. Values are mean ± s.e. of the mean of 9 hamsters.

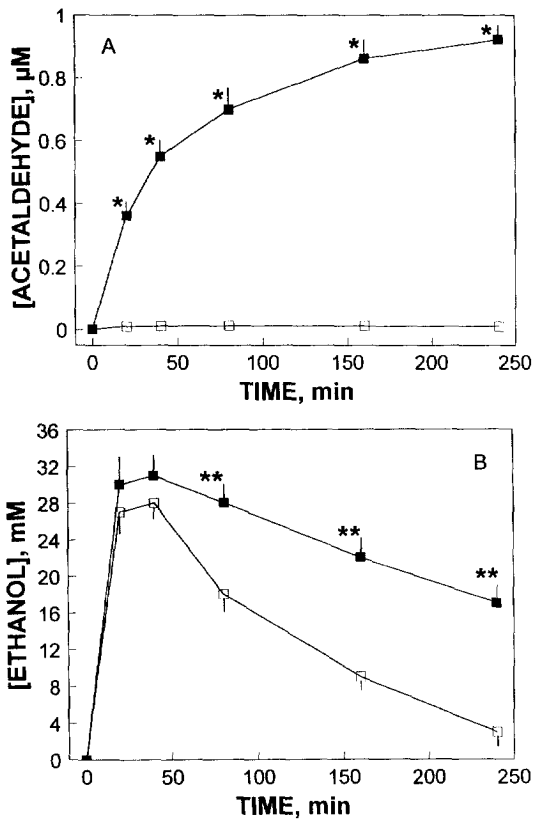


Fig. 7. Time course of plasma (A) acetaldehyde, and (B) ethanol concentrations in the control (□, received 1 ml saline per day for 6 consecutive days) and disulphiram-treated (■, received 154 mg kg^{-1} disulphiram per day for 6 consecutive days) hamsters after receiving an acute dose of ethanol (1.3 g kg^{-1}, i.p.) at time = 0. Values are mean ± s.e. of the mean of 6–9 hamsters. *, $p < 0.001$, **, $p < 0.01$.

at this time. Since mitochondria have been shown to catalyze monoamine catabolism [24] and that mALDH has very low K_m values toward the aldehyde metabolites of these neurotransmitters [25], it is likely that mALDH plays an important role in the catabolism of monoamine neurotransmitters, such as serotonin or dopamine. Hence, based on the data obtained thus far, we propose that the antidipsotropic isoflavones suppress ethanol intake by modulating activity of the central reward pathways through inhibiting the catabolism of monoamine neurotransmitters.

CONCLUSION

The confirmation of the antidipsotropic activity of RP extract in strictly controlled animal experiments and the identification of daidzin as its major active principle are the most exciting developments in our alcohol research program directed at the identification of potent new antidipsotropic drugs. The fact that daidzin is derived from RP, an herbal medicine that has already been used safely and effectively by thousands of alcohol abusers in China for over a millennium strengthens our belief that daidzin and/or its active analogues could be developed into effective and safe therapeutic agents for the treatment of human drinking problem. Unlike most antidipsotropic agents described in the literature, daidzin was discovered based solely on empirical clinical information rather than any preconceived theories or hypotheses. This unique quality of daidzin may hold the key to the delineation of the specific biochemical pathway(s) that monitor ethanol drinking.

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