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# 甘草之生物藥學研究 -

## (壹) 甘草、甘草酸、甘草次酸於兔體中之動力學及蜂蜜對其腸內代謝及吸收之影響

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### 摘 要

中藥常用藥材水煎劑及濃縮散劑兩種劑型，而原藥材又有各種不同之炮製法，本研究以高效液相層析法進行甘草製劑及蜜炙後成分之含量分析，結果顯示，市售甘草藥材雖有甲、乙、丙、丁各種等級，但同等級藥材間含量相差甚多，而各等級藥材間之含量並無顯著差異。甘草經蜜炙後，甘草酸之含量並無明顯差異。

以家兔比較甘草及其成分甘草酸與甘草次酸之動力學，結果顯示，甘草酸能以原型及其水解產物甘草次酸被吸收，且比甘草次酸有較佳之吸收及較長之體內滯留時間。甘草水煎劑中甘草酸的吸收優於甘草酸純品，且水煎劑之吸收亦明顯高於濃縮散劑，可見水煎劑雖製備較不方便，但有其吸收較佳之優點。

以家兔探討蜂蜜對甘草及其成分甘草酸動力學之影響，顯示併服蜂蜜會增加甘草酸之代謝物甘草次酸在兔體內之吸收，使甘草次酸的  $AUC_{0-t}$  明顯增加了 53 %，而葡萄糖、果糖對甘草酸之體內過程並未造成影響，但

甲基糠醛使甘草次酸  $AUC_{0-t}$  增加了 29 %，因此蜂蜜造成甘草酸吸收的增加應與其中的 甲基糠醛有關。此外，家兔口服甘草水煎劑與炙甘草水煎劑後，血清中甘草次酸的  $AUC_{0-t}$  增加了 48 %，且延長了平均滯留時間。單服甘草水煎劑與併服葡萄糖及果糖後，併服葡萄糖者甘草酸濃度  $AUC_{0-t}$  減少了 75 %，而併服果糖者  $AUC_{0-t}$  減少了 52 %。

以家兔糞便細菌懸浮液研究蜜炙的基礎機制，結果顯示，在甘草酸方面，甘草酸水解為甘草次酸，甘草次酸再氧化為 3-去氫甘草次酸，且二者呈現明顯的一消一長現象。而在甘草水煎劑方面，甘草次酸的濃度較緩慢的增加，並無漸減的現象，而 3-去氫甘草次酸只有在最初產生極低的濃度。此外，甘草酸添加蜂蜜時，蜂蜜可促進甘草酸之水解，而甘草次酸添加蜂蜜時，甘草次酸濃度和 3-去氫甘草次酸的濃度，呈現一消一長的現象，故可印證甘草次酸和 3-去氫甘草次酸的轉換關係，且證實蜂蜜可抑制甘草次酸的氧化，從而增加甘草次酸之吸收。蜂蜜中糖類成分對甘草酸受糞便懸浮液中之腸道細菌作用的影響，顯示葡萄糖及果糖皆促進甘草酸之水解，同時亦抑制甘草次酸的氧化。

甘草水煎劑與添加蜂蜜溫孵時甘草次酸濃度漸漸增加，並無下降之現象，推測家兔口服甘草水煎劑時，蜂蜜增加甘草次酸吸收之作用機制應與甘草酸之水解有較大之相關，而與後續甘草次酸的氧化代謝無關。而蜂蜜之糖類成分促進甘草酸水解，使甘草酸吸收減少，所以家兔口服炙甘草水煎劑時，甘草次酸吸收的增加，主要原因應是蜂蜜中糖類成分促進了甘草酸的水解所致。

# Biopharmaceutical Studies of Licorice — Pharmacokinetics of Licorice, Glycyrrhizin and Glycyrrhetic acid in Rabbit and Effect of Honey on Their Enteric Metabolism and Absorption

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## ABSTRACT

Traditional decoction and commercial extract are two commonly used dosage forms of Chinese herbs. Moreover, various processed articles of Chinese herbs were described in ancient Chinese medical books. This study investigated the contents of constituents – glycyrrhizin (GZ) and glycyrrhetic acid (GA) in licorice and honey-treated licorice decoctions. The results indicated that the contents of GZ were in great variation within grades but not between grades, and the contents of GZ in decoctions of licorice and honey-treated licorice did not show difference.

Pharmacokinetics of licorice, GZ and GA in rabbits were investigated and compared. The result indicated that in addition to the absorption of GZ per se at small intestine, oral dosing GZ resulted in higher  $AUC_{0-t}$  and MRT of GA than those after oral dosing GA. The absorption of GZ from decoction is higher than GZ and commercial extracts. Our result suggested that traditional decoction had advantage for enteric absorption.

The studies of honey effect on the absorption and metabolism of licorice, GZ and GA were carried out in rabbits. The  $AUC_{0-t}$  of GA was significantly



enhanced by 53 % when honey was concomitantly given with GZ. The fate of GZ was not influenced by glucose and fructose but affected by 5-hydroxy-methyl-2-furaldehyde (HMF). It can be concluded that increasing GA absorption from GZ by honey was due to its component – HMF.

On the other hand, the  $AUC_{0-t}$  of GA after oral dosing of honey-treated licorice was significantly greater by 48 % than that after oral dosing of untreated licorice. The serum level of GZ after oral dosing of licorice coadministered with glucose and fructose resulted in lower  $AUC_{0-t}$  by 75 % and 52 %, respectively, than dosing licorice alone.

The mechanism of honey on GZ pharmacokinetics was investigated *in vitro* by using fresh rabbit fecal flora. The result showed that GZ was hydrolyzed to the aglycone GA, and then transformed to 3-dehydroglycyrrhetic acid (3-dehydroGA). Upon the incubation of licorice, the concentration of 3-dehydroGA was much smaller than incubation of GZ alone. On the other hand, the content of GA after incubation of GZ with honey was higher than that of GZ alone. The profile indicated that honey increased GA concentration by enhancing the bacterial hydrolysis of GZ to GA as well as inhibiting the oxidation of GA to 3-dehydroGA. The incubation of honey components – glucose, fructose and HMF with GZ showed accelerated hydrolysis of GZ and inhibited oxidation of GA.

As the incubation goes on, GA was found to generate from GZ and then gradually decline, whereas GA only increased gradually during the incubation of licorice decoction. Therefore the effect of honey on increasing GA absorption after oral dosing licorice decoction was attributable to the hydrolysis of GZ but nothing to do with the oxidation of GA. The incubation of sugars with licorice decoction showed accelerated hydrolysis of GZ. It can be concluded that the sugar increased the absorption of GA by enhancing the rate of GZ hydrolysis to GA in licorice decoction.