New Constituents

Polar constituents of Celery seed.

Kitajima J, Ishikawa T, Satoh M. *Phytochemistry* 2003; **64**(5): 1003-1011

From the water-soluble portion of the methanol extract of celery seed (fruit of *Apium graveolens*) five sesquiterpenoid glucosides (celerioside A–E) and three phthalide glycosides (celephtalide A–C) were isolated, together with six aromatic compound glucosides, two norcarotenoid glucosides and a lignan glucoside. Their structures have been determined by normal chemical spectral investigations.

Key Finding: The antiarthritic activity of celery seed has been attributed to the phthalides which are a component of the essential oil. This finding identifies water-soluble components (glycosides of the phthalides) which would not be found in the essential oil.

Practical Implications: These components are extracted well with aqueous alcohol and as such would be found in ethanolic liquid extracts, but not in the essential oil.

Metabolism

Identification of novel electrophilic metabolites of *Piper methysticum* Forst (Kava).

Johnson BM, Qiu SX, Zhang S et al. *Chem Res Toxicol* 2003; **16**(6): 733-740

To investigate a possible mechanism(s) of the reported kava-induced hepatotoxicity, an extract of kava was incubated *in vitro* with hepatic microsomes, NADPH, and glutathione (GSH). Electrophilic intermediates that were generated via metabolic activation were trapped as GSH conjugates and removed from the protein mixture using ultrafiltration. Positive ion electrospray LC-MS/MS with precursor ion scanning was used for the selective detection of GSH conjugates, and LC-MS(n) product ion scanning was used to elucidate their structures.

Using this *in vitro* MS-based screening assay, two novel electrophilic metabolites of kava, 11,12-dihydroxy-7,8-dihydrokavain-o-quinone and 11,12-dihydroxykavain-o-quinone, were identified. Mercapturic acids of these quinoid species were not detected in the urine of a human volunteer following ingestion of a dietary supplement that contained kava; instead, the corresponding catechols were metabolized extensively to glucuronic acid and sulfate conjugates. These observations indicate that the potentially toxic quinoid metabolites, under most circumstances, are probably not formed in substantial quantities following the ingestion of moderate doses of kava. However, the formation of electrophilic quinoid metabolites by hepatic microsomes *in vitro* suggests that such metabolites might contribute to hepatotoxicity in humans when metabolic pathways are altered (eg because of a drug interaction, genetic difference in enzyme expression, etc) or if conjugation pathways become saturated.

Practical Implications: The identification of these electrophilic metabolites in rat microsomes and the correlation of these to the human hepatotoxicity typifies a flaw which is often repeated in the literature. Rat microsomes are much more robust than human microsomes and metabolise materials which are not able to be processed by the human liver. The use of animal testing models must be treated with caution when extrapolating to human case studies.

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Since 1996 Reg has worked with MediHerb in Quality Assurance, Production, Technical, and Research areas. His background includes experience in the brewing industry and he has been working in the herbal area since 1994. His present position is Research Manager where he is responsible for the group's research activities such as clinical trial management, phytochemical research, and agronomic research. Reg is regarded as a leading phytochemist around the world and has been invited to present at numerous international scientific conferences.

