

Amino Acid Derivatives

Other Sulfur-Containing Compounds *

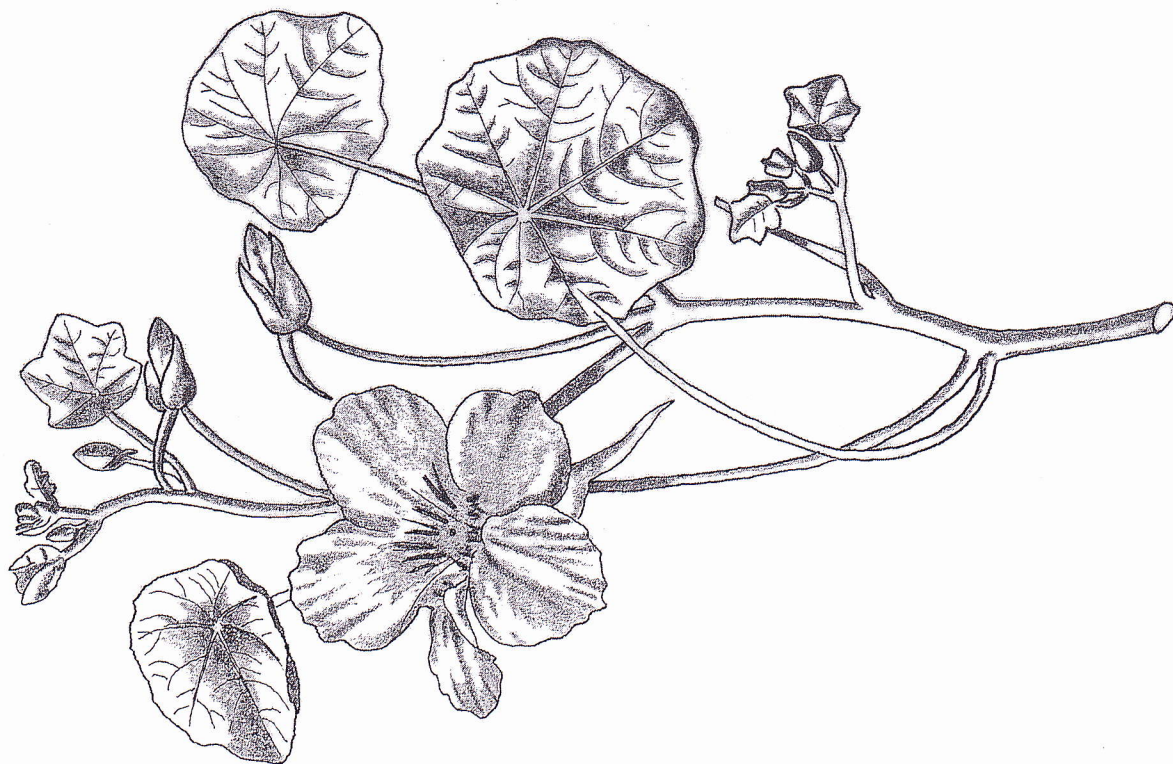
- **GARLIC**,
Allium sativum, Liliaceae

Garlic cloves have been used since antiquity for their antiseptic properties, and were the subject of a monograph in the French Pharmacopoeia until 1965. Largely used as a condiment, they are also used in phytotherapy.

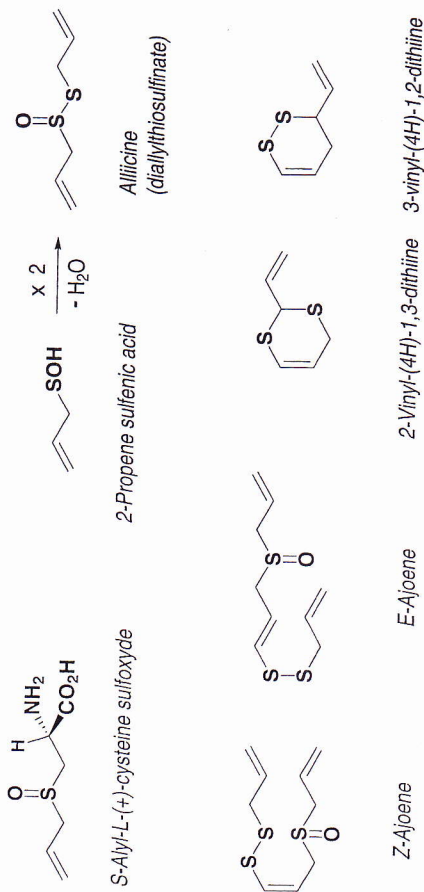
The Plant. A small herbaceous perennial plant, garlic has linear sheathing leaves, globose umbels of white or reddish flowers surrounded by a long caducous acuminate spathe, and a bulb (a "head of garlic") composed of bulbules (the "cloves") mounted on a flattened base, all wrapped in a shared whitish papery coat. The odor is weak, but grows strong and sulfury as soon as the tissues are damaged.

Chemical Composition. The drug contains carbohydrates (fructans), saponins (furostanol glycosides: sativin, proto-erubin B, and more), and is mostly known for its sulfur-containing compounds. The chief constituent of fresh undamaged garlic is alliin or S-allyl-L-(+)-cysteine sulfoxide. Upon cutting or bruising the tissues, alliin is degraded by an enzyme, alliinase (S-alkyl-L-cysteine lyase), to pyruvic acid and 2-propenesulfenic acid, with the latter being immediately transformed into allicin

* This will be purposely limited to thiosulfonates; sulfur, however, is not exceptional in plants



TROPAEOLUM MAJUS L.



(0.3% of the fresh weight). Air oxidation of alliin leads to 1,7-dithioocta-4,5-diene, known as diallyldisulfide: this is the chief constituent of garlic volatile oil. Thorough analysis of alcoholic garlic extracts also shows the presence of alliin condensation products, 6Z- and 6E-ajoenes (4,5,9-trithiadodeca-1,6,11-trien-9-S-oxide), and cycloadducts of propenethial (vinylthiines). It has been shown that multiple products identified by GC in various garlic volatile oils are no more than artefacts: HPLC analysis of products obtained by simple distillation under high vacuum at ambient temperature only shows thiosulfonates R-S(O)S-R', with alliin (R = R' = allyl) as the chief component (80-90%).

Pharmacological Activity. Tradition attributes to garlic several properties which have been verified experimentally, including the antibacterial and antifungal activities which have been shown *in vitro*. During the last ten years, animal experiments have demonstrated that garlic extracts are able to decrease blood cholesterol and triglycerides (in the rabbit and the rat), and have antihypertensive effects (in the rat). The nature and composition of the extracts is rarely specified, which limits the interpretation and comparison of the results that have been published on these and other activities. The activity against platelet aggregation, shown *in vitro*, is linked to ajoenes which inhibit lipoxigenase.

Activity in Humans. Although clinical trials are not rare, they are too often conducted with more or less well-defined preparations—which may explain the inconsistency of the results—and with questionable protocols. Several multicenter double blind trials tend to show the usefulness of garlic powder standardized for alliin as a blood cholesterol-lowering agent (600-800 mg/day x 4 months; about 9% decrease in cholesterolemia). Other trials (late 1990s) unambiguously show the lack of activity of the preparations that were tested (powder, essence) on serum levels of cholesterol and lipids. Other authors feel, on the basis of clinical observations, that standardized garlic preparations probably have a hypotensive activity in moderately hypertensive subjects and that they might have a beneficial effect on the

Garlic and Carcinogenesis. Several epidemiological studies show an inverse correlation between the regular consumption of garlic and the risk of stomach cancer. They confirm the observations made in the early 1980s in China where the frequency of stomach cancer was 13 times lower in a province where garlic consumption was 20 g/day than in another province where garlic was eaten only occasionally. Garlic consumption has no noted effect on the frequency of other tumors (lung, breast). These human data confirm what was shown by the majority of experiments conducted on different types of organs from several animal species, particularly the inhibition of the initiation of carcinogenesis by allyl disulfide and other sulfur-containing compounds formed in garlic bulbs. By acting on certain forms of cytochrome P450 and on the corresponding activities, allyl sulfides inhibit the metabolism of many carcinogenic chemicals (e.g., nitrosamines).

Uses. In France, garlic-based phytotherapeutic products may claim only one indication [French Expl. Note, 1998]: traditionally used to treat minor vascular disorders. The German Commission E monograph states that garlic bulb is used as a complement in the diet of hyperlipemic patients and for the prophylaxis of the vascular changes induced by aging. The monograph contains a warning that garlic can (rarely) cause gastrointestinal distress and that it alters breath and skin odor.

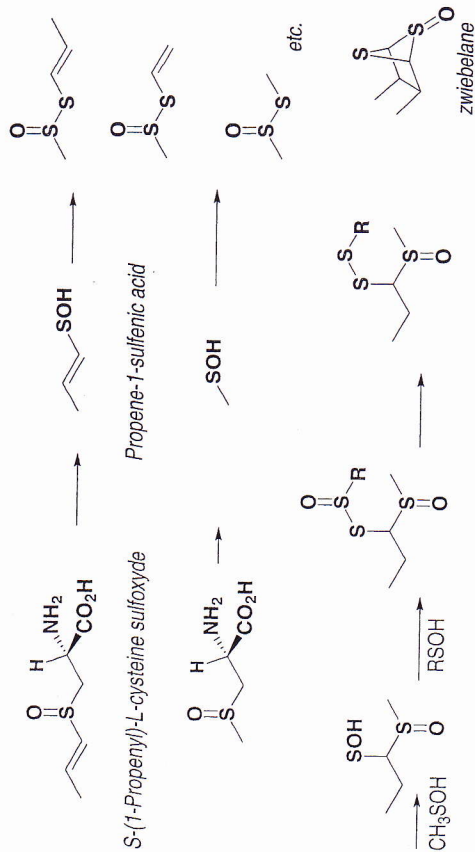
● ONION, *Allium cepa* L., Liliaceae

Numerous varieties are cultivated of this herbaceous plant with leaves that are generally cylindrical, with subglobose umbels of trimerous flowers initially covered by a membranous spathe. In the case of the common onion these varieties are grouped into two categories depending on whether the external part of the bulb is white or colored. The shape and size of the bulb differ with each variety (from 2 to 20 cm, flattened, spherical, or pear-shaped).

Chemical Composition. A fresh onion bulb contains fructans with a low degree of polymerization, heterogeneous polysaccharides, flavonoids (mainly quercetin glycosides, in colored onions: 2.5-6.5%), saponins (furostanol glycosides), sterols, and sulfur-containing compounds: *trans*-(+)-S-(1-propenyl)-L-cysteine sulfoxide and other cysteine derivatives (alkyl- and alkenylcysteines and the corresponding sulfoxide derivatives).

Upon bruising the bulb, the sulfoxides are degraded by alliinase and release pyruvic acid and alkylthiosulfonates, which are unstable and rapidly turn into disulfides (for example, dipropyl disulfide): *trans*-(+)-S-(1-propenyl)-L-cysteine sulfoxide, via 1-propenesulfenic acid, turns into the S-oxide of Z-propenethial (= thio-propanal S-oxide). Next, this leads, by addition on the alkyl- and alkenylsulfenic acids, to a series of 1-(methylsulfinyl)-propyl alkyl- (or alkenyl-) disulfides.

Other compounds have also been characterized in the extracts: cepaenes (α -sulfinyl/disulfides), zwiebelanes (bicyclic sulfur-containing derivatives), and sulfur-containing di- and tripeptides. In onion "oil", by far the major compounds are disulfides. The research previously cited shows that, as in the case of garlic, vacuum distillation only yields thiosulfonates [R = methyl or *n*-propyl, R' = 1-propenyl or methyl; the chief component is asymmetric: CH₃-S(O)S-1-propenyl(*E,Z*)].



Onion: formation of disulfides (for example: R = C₃H₇:3-ethyl-2,4,5-trithiaoctane 2-S-oxide)

Pharmacological Activity. Onion is a vegetable and a condiment, nevertheless it is considered by some to have "medicinal" properties. Onion juice, known for its diuretic properties (true diuretic or stimulant of water elimination?) is an antimicrobial agent *in vitro*, and experiments in animals demonstrate its hypoglycemic activity. Like garlic, it has an activity against platelet aggregation, and a fibrinolytic activity linked to some of the sulfur-containing compounds (most of them inhibit cyclooxygenase and lipoxygenase); the extracts also have an antiasthma activity (in the guinea pig) and an anti-allergic activity on the skin and the lungs (rubbing onion on a wasp sting to attenuate its effects is a well known remedy). Unfortunately, the extracts in use are unstable, therefore a valid comparison of the results is not possible. The pharmacology of the pure substances (or of standardized extracts) remains to be studied. Their clinical benefits also remain to be determined.

The regular consumption of onions, like that of garlic, lowers the risk of stomach cancer considerably. The results of a large-scale cohort study carried out in the Netherlands in the late 1990s confirm the conclusions of many previously published case-controlled studies (follow-up for 3.3 years; daily consumption $\geq 1/2$ onion [raw or cooked?]; rate ratio = 0.5 [noncardia only]).

Uses. Onion is currently marketed as a soft extract promoted as a "pelvic decongestant" but unlike garlic, its bulb is not listed in the French Explanatory Note of 1998. Folk medicine has long used onion for boils, anthrax, or whitlows, among other applications. *Allium cepa* is frequently used in homeopathy (coryza).

BIBLIOGRAPHY

Garlic

- Berthold, H.K., Sudhop, T. and von Bergman, K. (1998). Effect of a Garlic Oil Preparation on Serum Lipoproteins and Cholesterol Metabolism. A Randomized Controlled Trial, *JAMA*, **279**, 1900-1902.
- Block, E., Naganathan, S., Putman, D. and Zhao, S.-H. (1992). *Allium* Chemistry : HPLC Analysis of Thiosulfonates from Onion, Garlic, Wild Garlic (Ramsoms), Leek, Scallion, Shallot, Elephant (Great-headed) Garlic, Chive and Chinese Chive. Uniquely High Allyl to Methyl Ratios in some Garlic Samples, *J. Agric. Food Chem.*, **40**, 2418-2430.
- Dorant, E., van den Brandt, P.A., Goldbohm, R.A., Hermus, R.J.J. and Sturmans, F. (1993). Garlic and its Significance for the Prevention of Cancer in Humans: a Critical Review, *Br. J. Cancer*, **67**, 424-429.
- Ernst, E. (1997). Can Allium Vegetables Prevent Cancer? *Phytomedicine*, **4**, 79-83.
- German, K., Kumar, U. and Blackford, H.N. (1995). Garlic and the Risk of TURP Bleeding, *Br. J. Urol.*, **76**, 518.
- Isaacsohn, J.L., Moser, M., Stein, E.A., Dudley, K., Davey, J.A., Liskov, E. and Black, H.R. (1998). Garlic Powder and Plasma Lipids and Lipoproteins. A Multicenter, Randomized, Placebo-controlled Trial, *Arch. Intern. Med.*, **158**, 1189-1194.
- Jain, A., Vargas, R., Gotzkowski, S. and McMahon, F.G. (1993). Can Garlic Reduce Levels of Serum Lipids? A Controlled Clinical Study, *Am. J. Med.*, **94**, 632-635.
- Silagy, C.A. and Neil, H.A.W. (1994). A Meta-analysis of the Effect of Garlic on Blood Pressure, *J. Hypertens.*, **12**, 463-468.
- Steinmetz, K.A., Kushi, L.H., Bostick, R.M., Folsom, A.R. and Potter, J.D. (1994). Vegetables, Fruit, and Cancer Colon in the Iowa Women's Health Study, *Am. J. Epidemiol.*, **139**, 1-15.
- Warshafsky, S., Kamer, R.S. and Sivak, S.L. (1993). Effect of Garlic on Total Serum Cholesterol. A Meta-analysis, *Ann. Intern. Med.*, **119**, 599-605.

Onion

- Breu, W. (1996). *Allium cepa* L. (Onion). Part 1: Chemistry and Analysis, *Phytomedicine*, **3**, 293-306.
- Dorant, E., van den Brandt, P.A., Goldbohm, R.A. and Sturmans, F. (1996). Consumption of Onions and a Reduced Risk of Stomach Carcinoma, *Gastroenterology*, **110**, 12-20.
- Dorsch, W. (1996). *Allium cepa* L. (Onion). Part 2: Chemistry, Analysis and Pharmacology, *Phytomedicine*, **3**, 391-397.