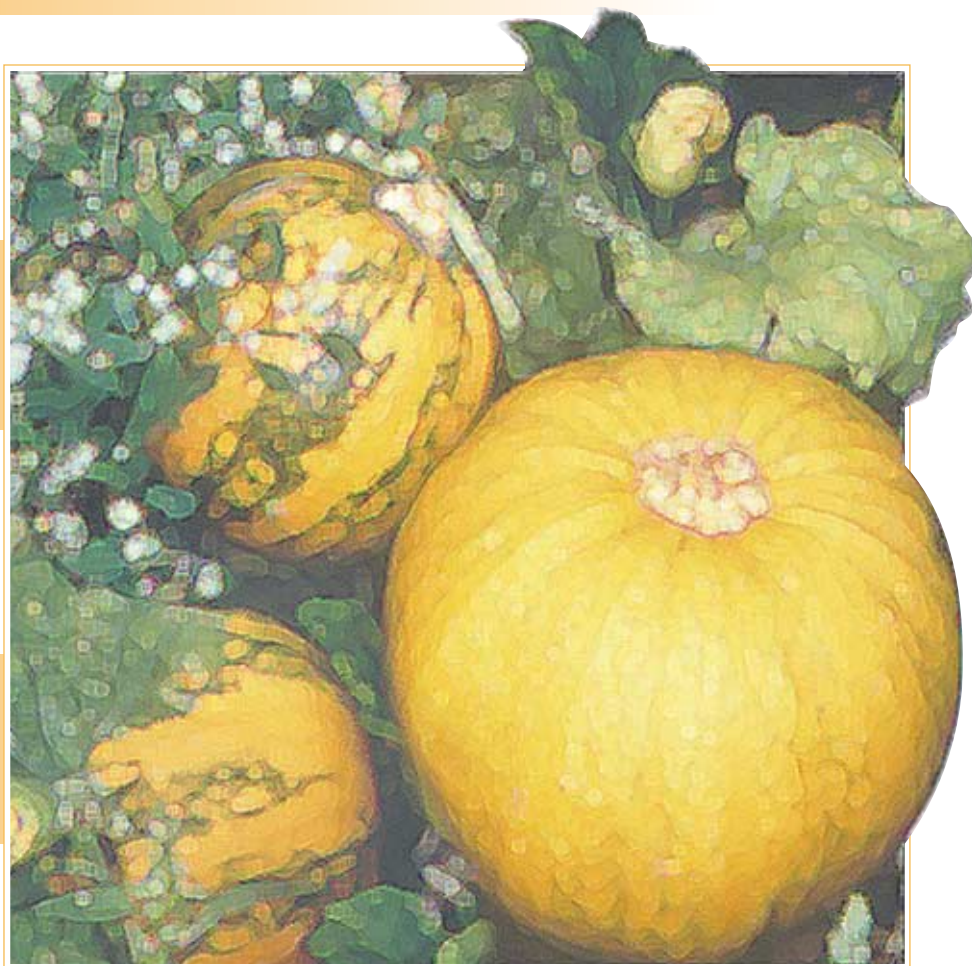


CUCURBITA PEPO L.

A NATURAL REMEDY
FOR BENIGN PROSTATIC HYPERPLASIA (BPH)





C. pepo seeds have been mentioned in many Pharmacopoeias including the British Herbal (4th Ed.) and the USP Pharmacopoeias (10th Ed.). In 1985 the Commission E for Phytotherapeutic Substances of the German Federal Health Office published a positive monograph on *Cucurbitae peponis semen* (seeds of *C. pepo* and related cultivars), with clinical indications for the micturition disorders associated with BPH.

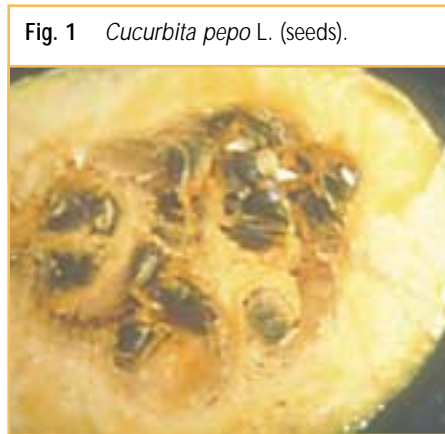


Fig. 1 *Cucurbita pepo* L. (seeds).

Cucurbita pepo L. (syn.: *Cucurbita aurantia* Willd., *Cucurbita melopepo* L., *Pepo vulgaris* Moench.; English name: summer pumpkin), with all its evolved cultivar, is a herbaceous, monoecious, annual plant of the Cucurbitaceae family.¹

The pumpkin plant has been known, since the dawn of time, in China and other countries, and it is today widely cultivated as food and for decorative purpose, in all warm and temperate parts of the globe.

The seeds (Fig. 1) have been used in traditional medicine as an anthelmintic and taenicide, demulcent, diuretic and tonic. A tea made from the seeds has been used as a remedy for hypertrophy of the prostate gland.^{2,3}

Today the pumpkin seeds are utilized in the treatment of urological symptoms associated with Benign Prostatic Hyperplasia (BPH) (Fig. 2).

The production of pharmaceutical products from the pumpkin seeds obviously demands the use of a botanically defined specie, so as to obtain oils or extracts that are reproducible from a chemically point of view. We have chosen a Hungarian cultivar of *C. pepo*, characterized by husked naked seeds, for the production of a new drug for the therapy of BPH.³

The production of pharmaceutical products from the pumpkin seeds obviously demands the use of a botanically defined specie, so as to obtain oils or extracts that are reproducible from a chemically point of view. We have chosen a Hungarian cultivar of *C. pepo*, characterized by husked naked seeds, for the production of a new drug for the therapy of BPH.³

CHEMISTRY

Biologically active compounds

The seeds of this plant contain from 30% to 51% oil. Main fatty acids are linoleic acid (43-55%) and oleic acid (27-38%). Proteins represent another class of substances which are abundantly present in the seeds, with values that spread between 31% and 51%.

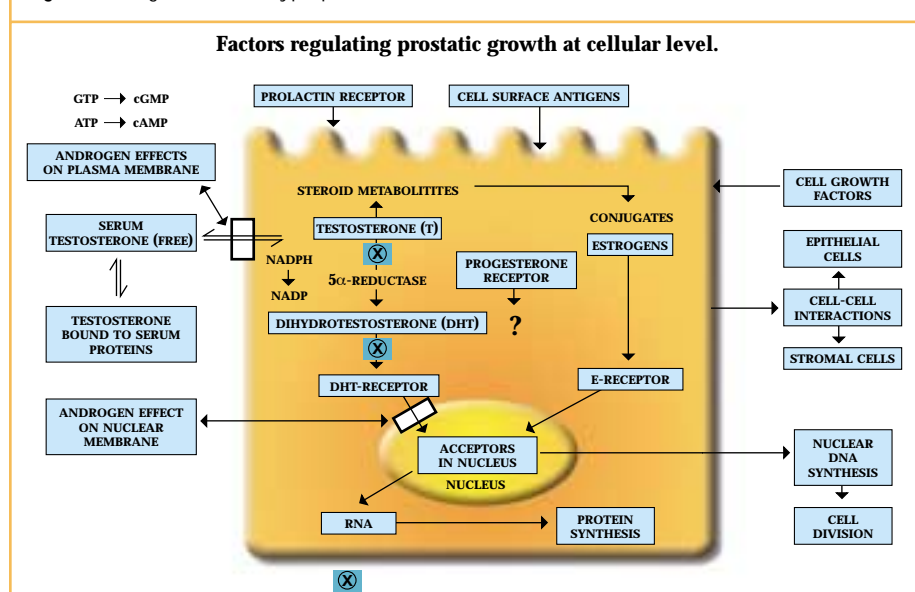
The carbohydrate content is between 6% and 10%, while that of minerals is between 4% and 5%.

In addition to phosphorous, calcium, potassium, iron, selenium and zinc were also found. The selenium is of particular importance as its content ranges between 0.08 and 0.40 µg/g, one of the highest values in plants.

Other substances described in the seeds of *C. pepo* include tocopherols and sterols in free and glucosidic forms. Beta and gamma tocopherols are present (0.03%). Minor amounts of Δ-5-sterols are found in the seeds, as opposed to their higher content in the rest of the plant. Delta-7-sterols are present in variable quantities (0.1%). The sterols constitute 55-60% of the oil non-saponifiable content.

The structure of the major sterols of *C. pepo* are shown in Fig. 3 along with the structure of the other biologically interesting products described to occur in the seeds.³

Fig. 2 Benign Prostatic Hyperplasia.



INDENA'S EXTRACT

From the seeds of *C. pepo* an oily extract has been prepared by using CO₂ in supercritical conditions.

The oil was then fractionated in order to exclude unwanted and potentially irritant substances.

This oil, on the other hand, contains all the lipophilic compounds described above.⁴ Indena developed an analytical method using gas-chromatography

which, in addition to give a fingerprint for the standardization of the extractive procedure, also distinguishes the low molecular weight esters from the free acids and simple esters (Fig. 4).

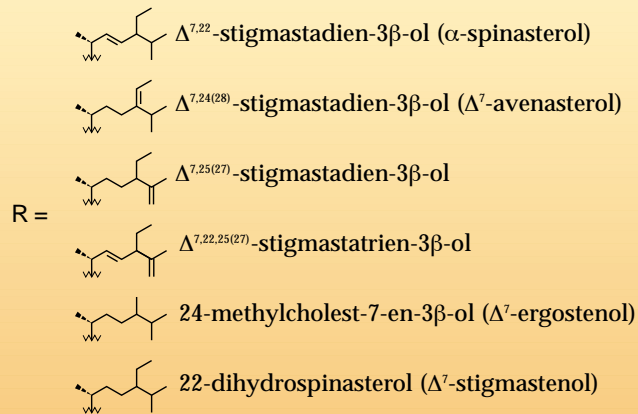
The separation of the different compounds has been achieved with a PS 255 fused silica column (20 m; 0.32 mm I.D.) in the case of total lipid analysis, and a DB17-bonded phase

fused silica column (30 m; 0.32 mm I.D.) in the case of unsaponifiable fraction analysis.

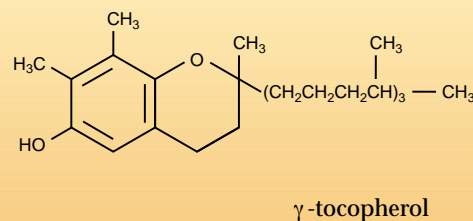
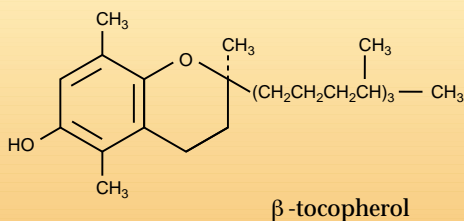
Helium was used as a transport gas with a gradient of temperature varying between 120 °C and 360 °C. The sterols identified in the lipophilic extract together with the high amount of squalene are characteristic and can be used as markers of this extract.

Fig. 3 Structures of the main compounds isolated from *C. pepo* seeds.

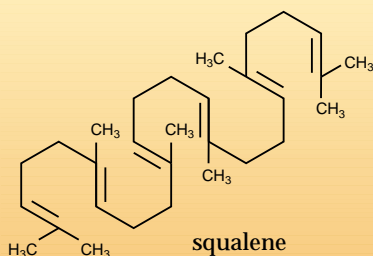
Δ⁷-STEROLS



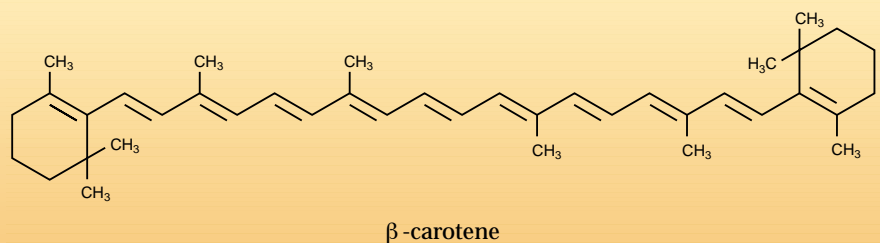
TOCOPHEROLS



TRANS-ISOPRENOIDS



CAROTENOIDS



PHARMACOLOGY

A series of *in vitro* and *in vivo* experiments have been carried out in our laboratories in order to investigate the mechanisms of action of the active principles present in the seeds.

The results obtained, according with the previous studies, indicate the following mechanisms as the credible base for the therapeutical effectiveness of the *C. pepo* oil:

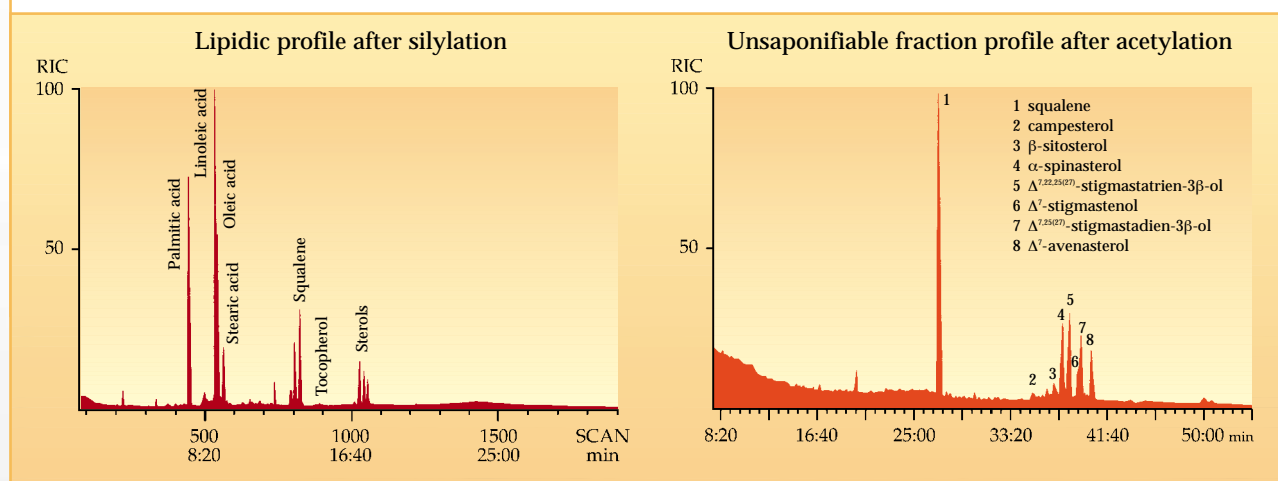
• Inhibition of 5- α reductase

The evaluation of the inhibitory action has been carried out measuring the conversion of testosterone into dihydrotestosterone, using a culture of humane prostate fibroblasts according to classical methods.^{5,6} Tested in these experimental conditions, the oily extract showed a good inhibitory action on the conversion of testosterone which constitutes a main target for the pharmacological control of BPH.

• Interference with prostaglandin biosynthesis

Recently, it has been demonstrated that the prostaglandin (PGE₂) content in prostatic fluid from patients with BPH and chronic prostatitis is abnormally increased and it represents an important contribute for hyperemia and vascular congestion. β -sitosterol, present in *C. pepo* oil, has shown to be a strong inhibitor of prostaglandin biosynthesis in prostatic tissue of patients with BPH and then to exert a marked anti-inflammatory action.^{7,9}

Fig. 4 GCMS analysis of *C. pepo* seed oil obtained by supercritical carbon dioxide extraction.



CLINICAL RESULTS

Clinical evaluations of the efficacy of *C. pepo* are rather scarce, and the literature reports empirical findings for the most part.¹⁰

Published clinical trials¹¹⁻¹³ refer to indications concerning the symptoms associated with BPH at first stages, as well as irritable bladder. Therefore, the pharmaceutical specialities available, above all in Germany, are mainly suitable for the treatment of dysuria associated with prostatic hyperplasia and urinary infections.

C. pepo seed extract, associated with *Serenoa repens* fruit extract, another

extract widely used for the same clinical indications, was tried in a double-blind, placebo controlled study.¹² The patients were randomly allocated to receive either active compound or placebo according to a centrally controlled code list.

The subjective variables used to evaluate the efficacy of the treatment were: difficulties with voiding, daytime and nocturnal urinary frequency.

The objective parameters were: urinary flow, voiding time, residual volume.

The results observed for the subjective variables and objective urological

parameters showed a statistical improvement in patients treated with the extract and no change in those receiving placebo (Table 1).

No unwanted effects were reported.

Another important application of pumpkin oil is in the dietetic field.¹⁴⁻¹⁶ This oil is reddish-brown on account of the presence of protochlorophyll and carotenoids, and thanks to its high content of polyunsaturated fatty acids, tocopherol and carotenoids, is used as an adjuvant in the treatment of diet-related hyperlipoproteinemia, as well as in the prophylaxis of atherosclerosis.

Table 1 Effect of treatment on objective and subjective evaluations (mean \pm s.d.).

Urological parameters	Treatment	Mean value before treatment	Mean value after 3 months	Difference between mean values	P value within groups	P value between groups
Urinary flow (mL/s)	Cuc.+Ser.	6.7 \pm 1.4	9.7 \pm 3.6	+3.0 \pm 4.0	<0.001	<0.001
	Placebo	6.6 \pm 1.3	6.9 \pm 1.8	+0.3 \pm 1.7	NS	
Micturition time (s)	Cuc.+Ser.	16.2 \pm 1.7	13.8 \pm 2.8	-2.4 \pm 3.6	<0.01	<0.05
	Placebo	15.6 \pm 2.4	14.9 \pm 1.9	-0.7 \pm 2.9	NS	
Residual volume (mL)	Cuc.+Ser.	135.0 \pm 43.9	92.5 \pm 48.0	-42.5 \pm 62.1	<0.01	<0.01
	Placebo	127.6 \pm 39.0	120.0 \pm 37.5	-7.6 \pm 22.9	NS	
Diurnal frequency	Cuc.+Ser.	7.3 \pm 1.3	6.3 \pm 1.0	-1.0 \pm 1.5	<0.05	<0.05
	Placebo	7.8 \pm 1.1	7.9 \pm 0.8	+0.1 \pm 0.8	NS	
Nocturnal frequency	Cuc.+Ser.	1.9 \pm 0.6	1.4 \pm 0.7	-0.6 \pm 0.7	<0.01	<0.01
	Placebo	2.1 \pm 0.7	2.0 \pm 0.9	-0.1 \pm 0.6	NS	
Evaluations	Treatment	Much better	Better	The same	Worse	P value between groups
Dysuria	Cuc.+Ser.	10	11	4	1	<0.001
	Placebo	1	4	14	8	
Patient's evaluation of therapy	Cuc.+Ser.	6	16	3	1	<0.001
	Placebo	0	3	19	5	



REFERENCES

1. Hegi G., "Illustrierte Flora von Mitteleuropa", Band 6, Teil 2, P. Parey Verlag, Berlin, 1979, pp A29-A36.
2. Madaus G., "Lehrbuch der biologischen Heilmittel", Band 2, 2nd Ed., G. Olms Verlag, Hildesheim, 1979, pp 1140-1145.
3. Bombardelli E., Morazzoni P., *Fitoterapia* 68, 291 (1997).
4. Bombardelli E., US 5,547,673, August 20, 1996.
5. Sultan C., Terraza A., Devillier C., Carilla E., Briley M., Loire C., Descomps B., *J. steroid Biochem.* 20, 515 (1984).
6. Carilla E., Briley M., Fauran F., Sultan Ch., Duveilliers C., *J. steroid Biochem.* 20, 521 (1984).
7. Zahradnik H.P., Schillfahrt R., Schoening R., Ebbinghaus K.D., Dunzendorfer U., *Fortschr. Med.* 98, 69 (1980).
8. Bach D., Walker H., Zahradnik H.P., *Therapiewoche* 35, 4292 (1985).
9. Bauer H.W., Bach D., *Urol. int.* 41, 139 (1986).
10. Schilcher H., Boesel R., Effenberger St., Segebrecht S., *Urologe [B]* 29, 267 (1989).
11. Nitsch-Fitz R., Egger H., Wutzi H., Maruna H., *Ehk.* 12, 1009 (1979).
12. Carbin B.E., Larsson B., Lindahl O., *British J. Urol.* 66, 639 (1990).
13. Schiebel-Schlosser G., Friederich M., *Z. Phytotherapie* 19, 71 (1998).
14. Mansour E.H., Dworschák E., Lugasi A., Barna É., Gergely A., *J. Sci. Food Agric.* 61, 73 (1993).
15. Wolfram G., *Ernährungs-Umschau* 23, 267 (1976).
16. Schilcher H., Nissler A., *Phys. Med. u. Reh.* 3, 141 (1980).

