Nootropic (*medhya*) plants from ayurvedic pharmacopoeia

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Introduction

In modern books of âyurvedic *Materia Medica* plants are often classified into different groups according to their *prabhâva* or "specific action". The *prabhâva* corresponds broadly to the western concept of pharmacological action (Mazars, 1995). Plants considered having a nootropic effect belong to the *medhya* (intellect promoting) group (from Sanskrit *"medhâ"*, intellect). They are used as stimulants for the central nervous system, to improve memory and attention, or against epilepsy or insanity. Some of them might have an interest in the treatment of Alzheimer's disease (and Parkinson's disease when associated with *Mucuna pruriens* (L.) DC).

In his book on Indian vegetable drugs P.V. Sharma (Sharma, 1987) deals with six "medhya" plants belonging to different families: *Bacopa monnieri* (L.) Pennell (Scrophulariaceae), *Centella asiatica* (L.) Urban (Apiaceae), *Celastrus paniculatus* Willd. (Celastraceae), *Convolvulus pluricaulis* Chois. (Convolvulaceae) and *Benincasa hispida* (Thunb.) Cogn. (Cucurbitaceae) have been used in Indian traditional medicine from very early times and are already mentioned in the *Caraka-samhitâ*, one of the two ancient Sanskrit medical treatises with *Sushruta-samhitâ* (1st century A.D.) (Sharma, 1983). As to *Lavandula stoechas* L. (Lamiaceae), it was borrowed from the Arabo-Persian pharmacopoeia. Except of *Benincasa hispida* and *Lavandula stoechas* these plants are used either alone or associated with other *medhya* plants in numerous Indian medicines (Giboin, 1949; Chopra *et al.*, 1956; Dash, 1979; Sivarajan and Balachandran, 1994).

Botany, galenic, chemistry, pharmacology

Bacopa monnieri is a creeping, glabrous, somewhat succulent herb growing in wet places. The plant is called *Aindrî* and *Brâhmî* in Sanskrit (Sharma, 1987).

The fresh pure juice can be drunk, but a water extract or a lipidic decoction can be made to be mixed with other ingredients including *medhya* plants. The fat-soluble fraction would be the most active as a promoter of memory.

B. monnieri is a saponin-rich plant. Most structures have already been isolated. The genins have been characterised as dammarane-type triterpenoids like protopanaxadiol and -triol glycosides from *Panax ginseng* (Araliaceae), and could be structurally related to jujubogenin, the major genin of *Zizyphus jujuba* Mill. (Rhamnaceae) (Garai *et al.*, 1996a, 1996b; Jain and Kulshrestha, 1993; Mahato *et al.*, 2000; Rastogi *et al.*, 1994). (Table 1 and 2)

Several studies have been done with an alcoholic extract. On rats, the extract increases both cognitive function and retention capacity, decreases retrograde amnesia and protects from phenytoin-induced cognitive deficit (Vohora *et al.*, 2000). The protein-kinase activity and the protein level were higher in the hippocampus. Other effects, like bronchodilatation and cardiovascular modifications were observed (Singh and Dahwan, 1997). *In vitro*, the extract showed a calcium antagonistic activity on vascular and intestinal smooth muscles of rabbit and guinea-pig (Dar and Channa, 1999), and a significant inhibition of the Sarcoma-180 cells growth (Elagovan *et al.*, 1995).

Centella asiatica is a slender, prostrate, glabrous herbaceous plant, rooting at the nodes. The leaves are simple, petiolate, palmately lobed (Kirtikar and Basu, 1935). The Sanskrit name of the plant is Mandûkaparnî. It is also called Brâhmî (Sharma, 1987).

The plant is used for memory improvement, wound healing and as a cardiotonic. The galenic form is an extract of the whole plant.

The major synthesized secondary metabolites are triterpenic acids and saponins. The essential oil (2-4%) of this Apiaceae contains until to 37 different components, with numerous terpenes.

Numerous unsaturated fatty alcohols, flavonols, amino-acids, steroids and vitamins have been identified. The major genins and saponins are given on the tables 3 and 4 (Chapmann, 1982-2000 ; Dev *et al.*, 1989; Holeman *et al.*, 1994; Mahato *et al.*, 1987; Pinhas *et al.*, 1967; Pinhas and Bondiu, 1967; Sahu *et al.*, 1989; Singh and Rastogi, 1967). (Table 3 and 4)

The topical properties of *C. asiatica* extracts have been well documented. It is the only one of these *medhya* plants used in western medicine, as a cicatrising ointment (Bonte *et al.*, 1993; Inamdar *et al.*, 1996; Shukla *et al.*, 1999). Nevertheless, the nootropic potentialities of *C. asiatica* have been assessed in pharmacological and behavioral trials in rats. The administration of aqueous or ethanolic extract showed an antistress activity by reducing stress-induced ulcerization and by inducing a state of non-specifically increased resistance. These effects were comparable to those of diazepam (Sarma *et al.*, 1995; 1996; Valsala, 1998). A sedative and anticonvulsivant effect beside a low toxicity has been noticed, indicating a high therapeutic index (De Lucia *et al.*, 1997). *C. asiatica* causes an overall decrease in the turnover of central monoamines norepinephrine, dopamine and serotonine, known to be implicated in learning and memory process (Nalini *et al.*, 1992).

Celastrus paniculatus is a climber with stems up to 23 cm of diameter and 18 m high, with broadly elliptic ovate leaves. The seeds are enclosed in an orange-red aril, and taste bitter (Kirtikar and Basu, 1935; Sharma, 1987).

The oil is used in colleges by Indian teachers to increase the intelligence of their pupils.

This oil contains several terpenoids like paniculatadiol, b-sitosterol, celastrol, b-amyrin, pristimerin, but its most investigated components are its many sesquiterpenoids, dihydroagarofuran-type polyols or esters, presented in Table 5,6 and 7 (Brüning and Wagner, 1978; Hong *et al.*, 1991; Tu *et al.*, 1991; Tu and Yao, 1993). (Table 5, 6 and 7)

Pharmacological studies on mice and rats showed that the seed oil increases the pentobarbital-induced narcosis time (Ahumada *et al.*, 1991). A delay is required to get a reversal of scopolamine-induced deficit in memory performance. This effect suggests cognitive enhancing properties, but the mechanism of action is not related to an anticholinesterase-like action, as the current anti-Alzheimer's disease do (Gattu *et al.*, 1997). On the brain level, the seed oil of *C. paniculatus* increases the myelinisation and the protein content and decreases the dopamine turnover in rats, suggesting an increased mental activity linked to memory (Bidwai *et al.*, 1987; Nalini *et al.*, 1995). The same decrease on dopamine turnover is described for man (Nalini *et al.*, 1986).

Toxicological studies showed an antispermatogenic action and reversible fatty degeneration of liver and tubular damage in kidneys (Bidwai *et al.*, 1990a ; 1990b).

Convolvulus pluricaulis is a hairy perennial herb growing throughout the plains of India, with white to light pink flowers. One of its common Indian name is the Sanskrit name *Shamkhapushpi* (Kirtikar and Basu, 1935; Sharma, 1987).

The whole plant is used as a rejuvenating and as a nervine tonic in epilepsy and insanity.

It contains various products like scopoletin (a coumarin), b-sitosterol, fatty acids, fatty alcohols and sugars (Srivastava and Deshpande, 1975). The most notable constituents are tropane alkaloids. Only convolamine has been identified (Basu *et al.*, 1948), but other alkaloids (convoline, convolidine, convolvine, confoline, convosine, etc.) found in other species from this family are probably present beside to convolamine (Lounasmaa, 1988). Structures are presented in table 8.

Pharmacological studies on the alcoholic extract noticed an antagonist effect against amphetamines and tremorine, a potentiation of acetylcholine effect, of pentobarbitone-induced hypnosis and morphine analgesia, without having own sedative properties. A protective action on muscle against electroshocks has been showed (Barar and Sharma, 1966; Mudgal, 1975; Sharma *et al.*, 1965). The specific pharmacological action of convolvine has been investigated. It is a specific blocker of M_2 and M_4 cholinergic muscarinic receptors. Convolvine also potentiates the effects of arecoline, a muscarinic memory enhancer that ameliorates cognitive deficits in Alzheimer's disease (Asthana *et al.*, 1996; Mirzaev and Aripova, 1998).

Benincasa hispida is a climbing gourd cultivated in all Asia as vegetable. The fruit, broadly cylindrical, is covered with a waxy bloom, explaining the name of "wax gourd" (Kirtikar and Basu, 1935; Petelot, 1952; Sharma, 1987).

The fresh juice is used in insanity, epilepsy and other nervous diseases, and as an antidote for many kinds of poisoning.

The flesh (96% water) has a good nutritive value, and contains many fatty acids, sugars, aminoacids, vitamins and minerals (Duke, 1999). b-sitosterol, lupeol, alnusenol and *n*-triacontanol have been found in the juice, and isomultiflorenyl acetate in the wax (Faure and Gaydou, 1991; Lakshmi and Mitra, 1976) (Figure 1).

The *B. hispida* juice injected intra-peritonally showed a depressive action on the CNS, a potentiation of the pentobarbitone-induced narcosis and hypothalamus-related hypothermia. It acts as a cholinergic and a-adrenergic agonist (Ramesh *et al.*, 1989).

Lavandula stoechas forms a pretty little shrub, with narrow leaves and very small, dark violet flowers, terminated with a tuft of bright-

coloured leaflets. This was probably the lavender so extensively used in classical times by the Romans and the Libyans, as a perfume for the bath. The odour is more akin to rosemary than to ordinary lavender.

The Yûnânî (Greco-Arabian) medicine calls it *Ustûkhûdûs* and uses it by smoking or decoction as an expectorant, antispasmodic, against headache and nerve affections. In India, Yûnânî medicine practitioners use the powder of its dried flowers and leaves as a nerve tonic, intellect promoter (Cazin, 1997; Kirtikar and Basu, 1935).

The essential oil of *L. stoechas* contains more than 50 different terpenes: mainly fenchone (15-70%), camphor (2-56%), 1,8-cineole, eucalyptol, pinocarvyl acetate, myrthenol, etc. (Kokkalou, 1988; Ristorcelli *et al.*, 1998; Valentini *et al.*, 1993). Triterpenoids (oleanolic acid, ursolic acid, vergatic acid, b-sitosterol, a-amyrine, a-amyrine acetate, lupeol, erythrodiol) and flavonoids (luteoline, acacetine, vitexine) have also been isolated (Ulubelen and Olcay, 1988). (Table 9 and Figure 2).

The crude extract of *L. stoechas* and pure ursolic acid produced hypotension in rats, decreased the rate and contraction of isolated atrium and produced vasorelaxation in isolated aorta. The authors suggested that the hypotensive and bradycardic effects were due to the ursolic acid constituent (Aftab *et al.*, 1997). Scientific investigations have been led on lavender essential oil, showing a quantifiable sedative effect on man (Jellinek, 1998 ; Manley, 1996). However, no influence on cognitive performances has been pointed out (Ludvigson and Rottman, 1989). The aqueous-methanolic extract exhibited anticonvulsivant and antispasmodic activities, probably due to its calcium channel blocking property (Gilani *et al.*, 2000).

Current ayurvedic medicine

Many intellect-promoting medicines are currently available in India, mixing numerous plant extracts or powders with two or three *medhya* plants. This is why the formulations and preparations of compound medicines are very complex and involve a number of processes and apparatus. This complexity is explained by the care taken to combine ingredients in order to counterbalance, enhance or prolong the effects of some ingredients through the effects of others (Mazars, 1998; 1999). Some of them have been subjected to clinical trials. Some examples are given here. The botanical names are those indicated by the manufacturers:

REMEM (Zydus Industries, India): syrup, tablets. 10 species:
Centella asiatica* - *Celastrus paniculatus* - *Convolvulus pluricaulis *- Asparagus racemosus - Acorus calamus - Embelia ribes - Tinospora cordifolia - Achyrantes aspera - Terminalia chebula - Saussurea lappa.*

TIRUKATI: 13 species:
Bacopa monnieri* - *Convolvulus pluricaulis* - *Centella asiatica *- Asparagus racemosus - Valeriana wallichii - Rueraria tuberosa - Saussurea lappa - Embelia ribes - Tinospora cordifolia - Operculina turpethum - Pavonia odorata - Caryophyllus aromaticus - Foeniculum vulgare.*

AYUMEMO (Welexlabs, India): 5 species:
Centella asiatica* - *Convolvulus pluricaulis* - *Celastrus paniculatus *- Withania somnifera - Asparagus racemosus.*

ABANA (The Himalaya Drug and Co, India): syrup, tablets. 19 species:
Centella asiatica* - *Convolvulus pluricaulis* - *Celastrus paniculatus *- Balsamodedron mukul - Ocimum sanctum - Nardostachys jatamansi - Piper longum - Carum copticum - Zingiber officinalis - Cyperus rotundus - Acorus calamus - Embelia ribes - Syzygium aromaticum - Santalum album - Elettaria cardamomum - Foeniculum vulgare - Rosa damascena - Cinnamomum cassis - Crocus sativus.*

LEARNOL-PLUS (Dalmia Industries, India): syrup. 3 species:
Bacopa monnieri* - *Celastrus paniculatus *- Acorus calamus.*

TEJRAS (Sandu Brothers, India): syrup. 12 species:
Centella asiatica* - *Convolvulus pluricaulis* - *Celastrus paniculatus *- Eclipta alba - Cynodon dactylon - Asparagus racemosus - Withania somnifera - Nardostachys jatamansi - Acorus calamus - Zingiber officinalis - Vetiveria zizanoides.*

ALERT (Vasu Pharmaceutical PVT. LTD., Bajua (Vadodara), India): Capsules.
Celastrus paniculatus seed oil - Cow ghee.
Showed to reduce liver glycogen depletion after swimming in rats (Kakrani *et al.*, 1985).

BRAHMIGHRITHAM: tablets. 3 species:
Bacopa monnieri *- Cyperus rotundus - Saussurea lappa.*
Showed to have a protective action against chemical-induced seizures (Shanmugasundaram *et al.*, 1991).

BRAHMI RASAYAN: tablets. 4 species:
Bacopa monnieri *- Eugenia caryophyllus - Piper longum - Elettaria cardamomum.*
Showed to have an antinociceptive action, and to protect mice from electroshocks and chemoconvulsions, suggesting a GABA-agonist profile (Shukia *et al.*, 1987).

GERIFORTE (The Himalaya Drug and Co, India): tablets. 35 species:
Centella asiatica* - *Celastrus paniculatus *- Mucuna pruriens - Capparis spinosa - Cichorium intybus - Solanum nigrum - Cassia occidentalis - Terminalia arjuna - Terminalia chebula - Achillea millefolium - Tamarix gallica -* Saffron *(Crocus sativus) - Asparagus*

adscendens - Caesalpinia digyna - Asparagus racemosus - Withania somnifera - Glycyrrhiza glabra - Myristica fragans - Piper longum - Eugenia caryophyllata - Elettaria cardamomum - Carum copticum - Curcuma longa - Berberis aristata - Adhatoda vasica - Eclipta alba - Argyreia speciosa - Phyllanthus emblica - Allium cepa - Allium sativum - Phyllanthus niruri - Boerhaavia diffusa - Tinospora cordifolia - Raphanus sativus - Tribulus terrestris.
Showed to have tranquillising properties, and to improve cognitive performance in people suffering from neurosis (Gupta *et al.*, 1979).

SHANKHAPUSHPI (Unjha Pharmacy, India): syrup. 6 species:
Convolvulus pluricaulis - Centella asiatica *- Nardostachys jatamansi - Nepeta hindostana - Nepeta elliptica - Onosma brateatum.*
Shows an anti-epileptic activity (Dandekar *et al.*, 1992).

MENTAT or BR-16 (The Himalaya Drug and Co, India): syrup, tablets. 24 species:
Bacopa monnieri - Centella asiatica - Celastrus paniculatus *- Mucuna pruriens - Withania somnifera - Evolvulus alsinoides - Acorus calamus - Nardostachys jatamansi - Zingiber officinalis - Valeriana wallichi - Prunus amygdalus - Orchis mascula - Syzygium aromaticum - Embelia ribes - Terminalia chebula - Terminalia arjuna - Terminalia bellerica - Emblica officinalis - Tinospora cordifolia - Oroxylum indicum -Elettaria cardamomum - Foeniculum vulgare - Ipomoea digitata - Myristica fragrans.*
Mentat is the most clinically studied among the Indian nootropic medicines. It is prescribed for the treatment of memory disturbances (Kulkarni, 1996; Agrawal *et al.*, 1990), behavioural disorders (Patel and Pereira., 1991), mental retardation (Quadri, 1993; Dixit *et al.*, 1992; Dave *et al.*, 1993), psychiatric problems (Dixit *et al.*, 1993; Das and De Sousza, 1989). Many double blind clinical studies have been done to assess the different effects of the drug (Singh and Dhawan, 1997).

Conclusion

Western medicine has to face emerging demand of drugs able to treat diseases related to aging or poor coping with modern life. In this matter (and in others) the knowledge accumulated over 2000 years by some traditional medicines like the Indian Ayurveda could be very useful. This rational medicine selected some plants by virtue of their effects on man. The traditional therapeutical use deals with plants extracts or powder mixtures, which efficacy is often confirmed by scientific trials. Efforts remain to be done to explore the precise pharmacological actions of the different active molecules. Furthermore, confronted to traditional phytotherapies, western science should accept to question its Cartesian dogma that " the whole equals the sum of the parts ", and to explore the pharmacological or pharmacokinetic role played by the combination of different molecules belonging to the whole extract of the plant, phenomenon which has been called "totum-effect".

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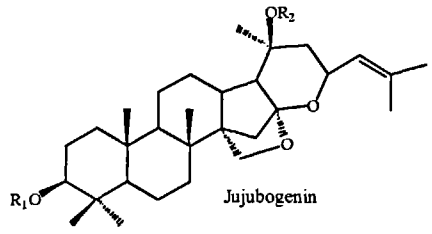
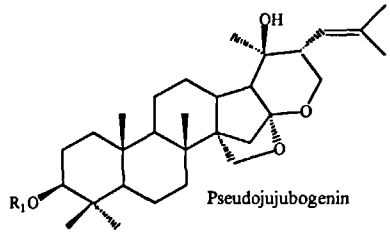
Table I. Jujubogenin-saponins from *Bacopa monnieri*



Jujubogenin

	R_1	R_2
Bacoside A_1	α-L-arabinofuranosyl(1→3)-α-L-arabinopyranose	H
Bacoside A_3	β-D-glucopyranosyl(1→3)-O-[α-L-arabinofuranosyl(1→2)]-O-β-D-glucopyranose	H
Bacopasaponine A	α-L-arabinopyranose	α-L-arabinopyranose
Bacopasaponine E	β-D-glucopyranosyl(1→3)[α-L-arabinofuranosyl(1→2)]-O-α-L-arabinopyranose	α-L-arabinopyranose
Bacopasaponine F	β-D-glucopyranosyl(1→3)[α-L-arabinofuranosyl(1→2)]-O-β-D-glucopyranose	-α-L-arabinopyranose

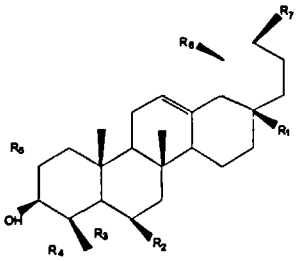
Table II. Pseudojujubogenin-saponins from *Bacopa monnieri*



Pseudojujubogenin

	R_1
Bacopasaponine B	α-L-arabinofuranosyl(1→2)-α-L-arabinopyranose
Bacopasaponine C	β-D-glucopyranosyl(1→3)[α-L-arabinofuranosyl(1→2)]-O-α-L-arabinofuranose
Bacopasaponine D	α-L-arabinofuranosyl(1→2)]-O-β-D-glucopyranose

Table III. Triterpenic acids from *Centella asiatica*

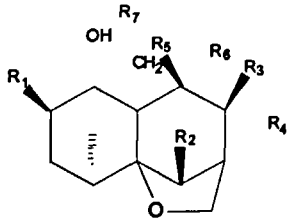


	R_1	R_2	R_3	R_4	R_5	R_6	R_7
Asiatic acid	COOH	H	H	CH_2OH	OH	CH_3	H
Madecassic acid	COOH	OH	H	CH_2OH	OH	CH_3	H
Madasiatic acid	COOH	OH	H	CH_3	OH	CH_3	H
Centoic acid	H	OH	OH	COOH	H	CH_3	H
Centic acid	H	OH	OH	CH_3	H	CH_3	H
Tankunic acid	COOH	OH	OH	CH_2OH	H	CH_3	H
Isotankunic acid (3a)	COOH	OH	OH	CH_3 (CH_2OH)	H	CH_3	H

Table IV. Saponins from *Centella asiatica*

	R_1	R_2	R_3	R_4	R_5	R_6	R_7
Asiaticoside A	[O- -L-rhamnopyranosyl(1→4) -O- -D-glucopyranosyl(1→6)]- O- -D-glucopyranose ester	H	H	CH_2OH	OH	CH_3	H
Asiaticoside B	idem	OH	H	CH_2OH	OH	H	CH_3
Madecassoside	idem	OH	H	CH_2OH	OH	CH_3	H

Table V. Polyalcohols from *Celastrus paniculatus*



	R_1	R_2	R_3	R_4	R_5	R_6	R_7
Polyalcool A	H	OH	OH	H	H	OH	H
Polyalcool B	H	H	H	OH	OH	H	H
Polyalcool C	H	H	OH	H	OH	H	OH
Polyalcool D	OH	OH	H	OH	OH	H	OH
Malkanguniol	H	OH	OH	H	OH	H	OH
Malkangunine	H	H	OAc	H	H	OBenz	OH

Table VI. Sesquiterpene alkaloïds from *Celastrus paniculatus*

	R_1	R_2
Celapanine	OFu	OAc
Celapanigine	OBenz	OAc
Celapagine	OBenz	OH

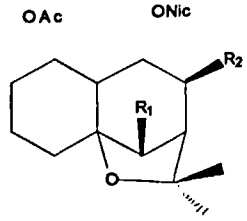
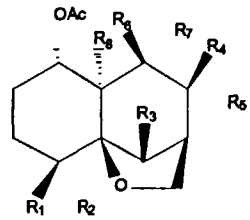


Table VII. Polyesters of *Celastrus paniculatus*



	R1	R2	R3	R4	R5	R6	R7	R8
1	H	CH_3	OAc	H	OAc	furancarbonyloxy	H	CH_3
2	H	H	OAc	H	cinnamoyloxy	H	benzoyloxy	CH_3
3	H	CH_3	OAc	OAc	H	H	benzoyloxy	CH_3OAc
4	H	H	H	OAc	H	furancarbonyloxy	H	CH_3OAc
5	H	CH_3	OAc	H	OH	H	benzoyloxy	CH_3
6	OH	CH_3	benzoyloxy	cinnamoyloxy	H	H	benzoyloxy	CH_3
7	H	CH_3	benzoyloxy	H	benzoyloxy	H	benzoyloxy	CH_3
8	OH	CH_3	furancarbonyloxy	H	cinnamoyloxy	H	benzoyloxy	CH_3

Table VIII. Tropane alkaloïds from *Convolvulus* sp

	R	R_1
convolidine	H	vanilloyl
phyllalbine	CH_3	vanilloyl
convolvine	H	veratroyl
convolamine N-oxyde	CH_3,O	veratroyl
convolamine	CH_3	veratroyl
convoline	OH	veratroyl
convolicine	OAc	veratroyl
confoline	CHO	veratroyl
convosine	O-iPr	veratroyl

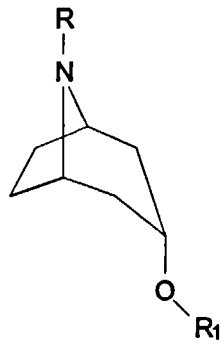
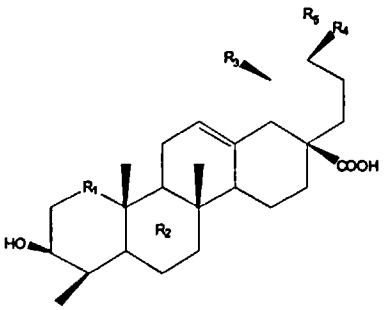
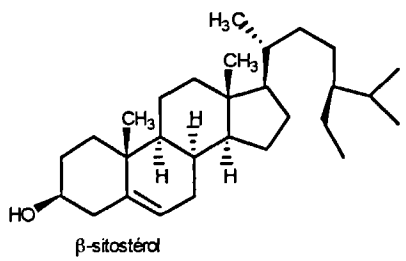


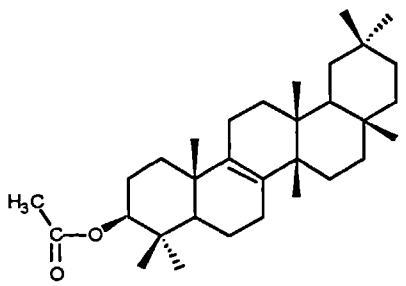
Table IX. Triterpenes of *Lavandula stoechas*

	R_1	R_2	R_3	R_4	R_5
Oleanolic acid	CO	H	H	CH_3	CH_3
Ursolic acid	CH_2	H	CH_3	H	CH_3
Vergatic acid	CH_2	H	H	CH_3	CH_3



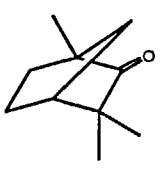


β-sitostérol

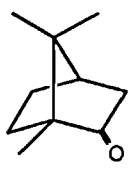


Isomultiflorenyl acetate

Figure 1. Some components of *Benincasa hispida*



Fenchone



Camphre

Figure 2. Major terpenes of *Lavandula stoechas*