HEMP - BIOCHEMICAL DIVERSITY AND MULTIPLE USES

ELENA TRUŢĂ[1*], ŞTEFANIA SURDU[1], CRĂIŢA MARIA ROŞU[1], MARIA ASAFTEI[2]

Biochemical complexity. *Cannabis sativa* L. is one of the species with the most numerous and diverse uses in economy. It can be grown in most climates, is drought resistant, and requires little fertilizers, minimal pesticides or herbicides. Hemp is a very important plant by economical point of view for fibres, seeds, oils, as well as for the chemical constituents with large medical valences and uses in some diseases therapy or in amelioration of certain health troubles. This plant has an extremely complex and diverse chemical constitution. The hemp plants and the crude drug products thereof (marijuana, hashish, and hash oil) are characterized by a wide variety of chemical compounds. There are almost 500 (483 compounds, according to Grotenhermen and Russo, 2002; 525 compounds, according to Radwan et al., 2009) different identifiable chemical substances. The best-known and most specific class of hemp constituents is represented by the C_{21} terpenophenolic cannabinoids. Other phenol compounds include flavonoids, spiroindans, dihydrostilbenes, phenanthrenes, and dihydrophenanthrenes. The hemp specific flavour is due to volatile terpenes of essential oils, monoterpenes representing 47.9 to 92.1%, and sesquiterpenes 5.2-48.6% of total terpenes (Mediavilla and Steinemann, 1977). This specific flavour is used in training up of the dogs in view to track down the drug storehouses. The physiological role of volatile oils and resin is less known, probably they contribute to insect attraction or they act as protective mechanisms against animals. Also, the ether oils diminish the plant transpiration at high temperatures.

Hemp seeds contain 25-35% oils, 20-25% protein, 2—30% carbohydrates, and 10-15% insoluble fibres and minerals (Pate, 1999 – cf. Peiretti, 2009).

Compounds like friedelin, epifriedelinol, β-sitosterol, carvone and dihydrocarvone were isolated from roots (Sethi et al., 1978). Seeds contain oils (Petri, 1988), while among plant organs flowers are richer in oils than leaves (Lemberkovics et al., 1979). *The fatty acid composition* of fruits is of great interest, because of their use for nutritive and pharmaceutical purposes. If the complete fruit and seed are similar in this aspect, some differences are in the outer layer (Mölleken and Theimer, 1997) (Table 1).

Table 1. Variation of fatty acids in fruit compartments of Chinese hemp varieties

Fatty acid	Fruit (%)	Seed (%)	Shell (%)
Palmitic acid	6.23	7.60	6.83
Stearic acid	2.65	2.48	2.34
Oleic acid	10.22	10.38	37.74
Vaccenic acid	1.27	1.69	4.85
Linoleic acid	56.42	54.92	34.42
γ-Linolenic acid	2.45	2.72	0.97
α-Linolenic acid	18.60	17.45	11.30
Arachidic acid	0.60	1.07	0.78
Octadecatetraenoic acid	0.54	0.50	Not detected (<0.3%)
Eicosenoic acid	1.02	1.19	0.77

The seeds of *Cannabis sativa* L. represented an important source of nutrients in ancient cultures. Seed extracted oils contain more than 80% unsaturated fatty acids: linoleic acid (18:2 *omega*-6), α-linolenic acid (18:3 *omega*-3), γ-linolenic acid (18:3 *omega*-6), stearidonic acid (18:4 *omega*-3). In oil hemp, the *omega*-6:*omega*-3 ratio is 2:1 and 3:1, these values being considered optimal for human health (Callaway, 2004). The presence of unsaturated fatty acid and of tocopherols recommends the use of oil hemp in nutritional and pharmaceutical and medical purposes, because it decreases the risk of cardiovascular diseases, of some cancers and of senile macular degenerescence. Tocopherols act as antioxidatives and prevent against oxidation of unsaturated fatty acids. Fatty acid profile and amount in seed oils vary depending on developmental stage of hemp plants, genotype, age, harvest year, environmental conditions (Peiretti, 2009) Approximately 50% from unsaturated fatty acids is represented by α-linolenic acid. In studied provenances, the α-linolenic acid was detected only in seeds, this compound lacking in the other phenophases. Thus, the seeds are the unique source for γ-linolenic acid in hemp. In the 51 genotypes studied in 2000-2001 period, Kriese et al. (2004) evidenced a variation of oil content ranging from 26.25% to 37.50%. In the flower and the leaf of the same plant, the total amount of essential oil is 0.08-0.15%, the flower being richer than leaf with 0.01% (Lemberkovics et al., 1979).

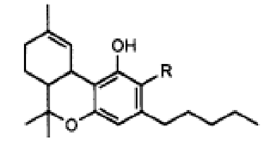
The most important *proteins* of hemp seeds are edestin, zeatin, and zeatinnucleoside, very digestible and with a significant content in all essential amino acids. Arginine, a semi-essential (conditional) amino acid is found in very high levels in hemp seeds. The only amino acids not reported in hemp are cystine, asparagine, glutamine, hydroxyproline, and hydroxylysine

Regarding the vitamins and pigments, in hemp have been reported vitamin K and two pigments (carotene and xantophylls).

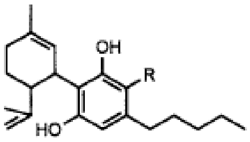
The data regarding the synthesis of *flavonoids* in *Cannabis* genus are sometimes contradictory, having a limited systematic value, because of the use of different analytic methods or of different plant organs, plant age, use of various provenances. Flavones Quantitative analysis of flavones, polyholosides and polyphenols in different sexual phenotypes evidenced different levels depending on plant sex and on analyzed organ (Truță et al., 2002).

Now, hemp is cultivated on large surfaces on globe, in agricultural and industrial purposes, for seeds, fibres, oils, but it is also cultivated as medicinal plant and in pharmacological purposes. These last utilizations are the consequence of the presence of psychoactive *terpenophenols*, generically named *cannabinoids*. The most important cannabinoids are Δ^9-tetrahydrocannabinol (Δ^9-THC), CBN (cannabinol), and CBD (cannabidiol), which chemically are a benzotetrahydropiran, a dibenzopyran, respectively a diphenol, followed by cannabichromene (CBC) and cannabigerol (CBG), as well as some derivatives (Page and Nagel, 2006) (Fig. 1). These compounds are criteria distinguishing between the hemp chemotypes (especially Δ^9-THC and CBD, and THC/CBD ratio). Genotype, climate conditions (temperature, light, humidity), developmental stage, plant age, drying modality of biological material are factors controlling and determining the cannabinoid phenotype of hemp plants.

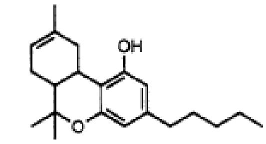
Geographic origin is also an essential factor – the most varieties synthetizing high THC amounts originated from latitudes situated at south of 30°N (Hillig and Mahlberg, 2004). Although in Europe only Indian hemp varieties were considered as producers of hallucinogens, in last years it was evidenced that psychoactive principles are synthetized also in European varieties, especially in drought conditions and at high temperature (Ciulei et al., 1993). To form THC, the hemp plants need daily average temperatures over 32^0C, on long periods, conditions rarely encountered in Romania.



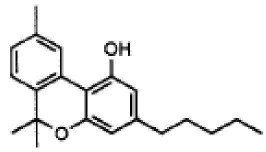
Δ^9-THC, R=H
Δ^9-tetrahidrocannabinolic acid (THCA), R=COOH



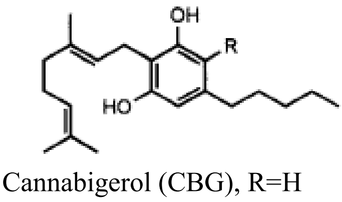
Cannabidiol (CBD), R=H
Cannabidiolic acid (CBDA), R=COOH



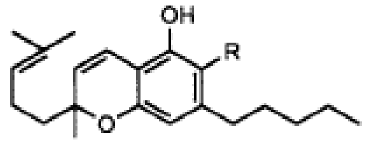
Δ^8-tetrahidrocannabinol (Δ^8-THC)



Cannabinol (CBN)



Cannabigerol (CBG), R=H
Cannabigerolic acid (CBGA), R=COOH



Cannabichromene (CBC), R=H
Cannabichromenic acid (CBCA), R=COOH

Figure 1. Structure of main cannabinoids (cf. PAGE and NAGEL, 2006)

The highest levels of THC are produced by Indian hemp (*C. indica*) and Chinese hemp (*C. sinensis*). The hemp varieties have similar cannabinoid patterns, but the percentage of each compound varies very much, because of ecological and ontogenetic factors (Turner et al., 1979). The most psychoactivelly cannabinoid is Δ^9-THC. CBD is inactive from this point of view, but it is used as marker in identification of hemp chemotypes. In stalks, the cannabinoids are present in smaller quantities than in leaves and inflorescences, and the inflorescences generally contain higher levels than leaves, although the cannabinoid spectrum is the same. Regarding the cannabinoid presence in hemp seeds, the opinions are different. Doorenbos et al. (1971) presented a classification of hemp parts, including the seeds, in the decreasing order of cannabinoid levels: *bract, flower, leaf, small stalk, big stem, root, seeds*, but Mölleken and Husmann (1997) not evidenced the presence of cannabinoids in hemp fruits.

The male phenotypes were considered less active from pharmacological point of view, but at present it is known that the general tendency – the female plant produces a higher quantity of cannabinoids – refers only to the total cannabinoid level (THC + CBN), because in male plant the cannabichromene content is higher (Krejci, 1975; Taylor et al., 1985). The comparative analysis, performed by Ohlsson (1971) on THC levels in male and female plants grown in similar environmental conditions, not evidenced significant differences. More evident was the variation of cannabinoid ratio in relation with ontogenetic stage (Marshman et al., 1976). Numerous data plead for preponderance of genetic factor in determination of fibre and cannabinoid content, but without to cancel some environmental influences. It seems, indeed, that a higher stability of cannabinoid pattern characterizes the descendence of the same variety, even if the environmental conditions are different. It is, also, possible that the real THC content to be the resultant of action of environmental conditions, but the ratio of main cannabinoids to be under genetic control. However, the role of environment in the phenotypisation of this character must not be neglected.

Depending on THC and CBD content, some authors distinguished three cannabinoid phenotypes, the plants with <0.3% THC being considered as not having psychoactive potencies (Small and Beckstead, 1973) (Table 2).

Table 2. Cannabinoid phenptypes in hemp

Phenotype	THC%	CBD%
I (drug type)	>0.3 (both sexes)	<0.5 (both sexes)
II (intermediary type)	>0.3 (female)	>0.5 (both sexes)
III (fiber type)	<0.3 (female)	>0.5 (both sexes)

Fournier and Paris (1979) accepted 0.5% THC as maximum content tolerable for fiber hemp (Table 3).

Table3. Chemotypes in hemp

Phenotype	THC%	CBD%	THC/CBD
Fiber hemp	<0.5	>0.5	<1.0
Resin hemp	>0.5	<0.5	>1.0

Fournier et al. presented in 1987 another classification of hemp chemotypes (Table 4), in which the drug chemotype has THC >2%.

Table 4. Classification of cannabinoid phenotypes in hemp

Chemotype	Drug type	Intermediary type	Fiber type
THC (% d.w.)	>2	>0.5	<0.3
CBD (% d.w.)	-	>0.5	>0.5
THC/CBD	-	>0.5	<0.1

Bruneton (1995) considers the drug (narcotic or resin) type that CBD non-producing and having THC >1%, while the most variants with THC <0.3%, cultivated in temperate zones, constitute the fiber type. Grotenhermen and Russo (2002) accept the existence of three hemp types and take into consideration the psychoactivity of main chemical compounds of respective chemotypes (Table 5).

Table 5. Chemotypes of *Cannabis sativa* L.

Chemotype	Products	Main cannabinoids	THC content	Psychoactivity
Drug type	marijuana, hashish	Δ^9-THC	1-20%	Yes
Intermediate type		Δ^9-THC, CBD	0.3-1.0%	Possible
Fiber type	fiber, edible oil	CBD	<0.3%	no

It was tried to establish some morphological criteria serving to find the psychoactive forms. Small et al. (1976), Petri et al. (1988) consider the density of resin glands to be a morphological criterion to differentiate and select the drug producing hemp, although Turner et al. (1978) results infirmed this fact. Nor other morphological characters (fruit traits, internode length, stem diameter etc.) have not discriminatory value in relation with cannabinoid synthesis.

Pharmacological valences. Therapeutic potential. Risks of some cannabinoid use. Resin, secreted by hemp specific hairs is differently named, depending on its origin (*charas* - in Asia; *hashish* – in Mediterranean East; *chira* - in North Africa). Resin is harvested by special procedures and then is processed in view of consumption. Marijuana (marihuana) is a colloquial name for dried leaves and flowers of cannabis varieties rich in Δ^9-THC, while hashish is an Arabic name for cannabis resin or compressed resin glands, containing 5-20% Δ^9-THC. But there are several regional differences regarding the employment of the terms cannabis, marijuana, hemp, hashish. Leaves and flowered tips of female plants are collected, dried and cut in small pieces, this mixture being known as *bhang* and *ganja* – in India; *kif* – in Algeria and Morocco; *takrouri* – in Tunisia; *habak* – in Turkey; *haschich el keif* – in Syria and Lebanon; *djomba*, *liamba*, *riamba* – in Central Africa and Brasil; *dagga* – in Austral Africa; *marijuana* – in America; *grifa* – in Mexico. Often, the hemp material is mixed with various tobacco sorts.

The first formal report on use as drugs of some hemp constituents dates by 5000 years, these compounds being administrated against malaria, constipation, muscle pain, birth pain; in mixture with wine, they were used as surgical anaesthetic (Robson, 2001). Hemp plants have been utilized to prepare remedy cures in Ayurveda and Chinese medical systems (as analgesic and anaesthetic) (Bruneton, 1995). Assyrian people used hemp products as „incense”, and Scythians „made dizzy” with vapours freed by the passage of hemp plant over hot stones. The doctors of British Army from India or Napoleon expedition in Egypt had the main responsibility in hemp introduction in Europe, in 19th century. Then, due to narcotic properties, hemp preparations became to be ingested in intellectual societies (as a consistent paste – „dawamesk”).

By time, the pharmacological valences of hemp were took into consideration and exploited in medical field, but the inconsistency of therapeutic activity, the bad storage of preparations, the difficulty to establish the optimal doses, as well as the risk showed by synthetic hypnotics and analgesics determined the gradual abandonment of hemp and its disappearance from the most occidental *pharmacopoeias* in the first moiety of 20th century. The hemp remained in British Pharmacopoeia until 1932, and in British Pharmaceutical Codex until 1949. THC was firstly isolated in 1964, and the first synthetic pharmaceutical cannabinoid product (*Marinol*®) was approved in USA in 1985 (Stott and Guy, 2004). Now, the clinical utilization of cannabinoids is restricted to oral administration of Dronabinol and Nabilone. Dronabinol is a synthetically manufactured (-)-trans-isomer of Δ^9-THC, and Marinol is a Dronabinol preparation in sesame oil, available in USA, Canada and some European countries. Nabilone, marketed in UK, Canada, and in some UE countries, is a synthetic derivative of Δ^9-THC with a slightly modified structure and was marketed starting from 1983. With regard to pharmacological activity, 1 mg nabilone corresponds to 10 mg Dronabinol.

The interest for cannabinoid utilization in medical purposes was relatively recent reactivated and is based on positive effects induced by synthetic cannabinoid administration subsequently to chemotherapy in different cancer forms, in order to diminish the secondary effects (nausea, vomiting), as well as on their utilization in attenuation of anorexia associated weight loss in AIDS. Also, the cannabinoids inhibited the tumour cell proliferation in animal cell cultures and in laboratory animals, accelerating cancer cell apoptosis in some forms of astrocytoma, glioma, neuroblastoma, phaeocytochroma etc. (Guzmán, 2003). They are usually well tolerated, and do not produce the generalized toxic effects of conventional chemotherapies. Other beneficial effects on some patients with cancers are pain diminution, muscle relaxation, and sleep amelioration (Walsh et al., 2003).

Δ^9-THC (Δ^9–tetrahydrocannabinol) is the most active *Cannabis sativa* compound; cannabinol, which is produced in large amounts is a weak cannabimimetic agent; and cannabidiol, which is abundant but has no cannabimimetic activity. Cannabidiol (CBD) is the nonpsychotropic hemp constituent, but it is important due to its numerous pharmacological activities. Ligresti et al. (2006), studying the anti tumour activities of five natural cannabinoids (CBD, CBG, CBC, CBDA, and THCA), confirmed that CBD is the strongest inhibitor of cancer cell growth and shows the lower cytotoxicity on non-cancer cells. The effect depends on CBD structure, because the addition of COOH group, like in CBDA, dramatically reduced the anti tumour effect. These characteristics plead for CBD utilization in cancer therapy.

The hemp cannabinoids are antiemetic, analgesic (the analgesic effect is comparable to aspirin effect); they reduce the intraocular pressure, diminish the anxiety, induce welfare in some neurological troubles, AIDS, and cancers. The drug therapy of muscle spasticity in multiple sclerosis generally has a low efficiency, but the patients recognized a cramp amelioration and pain relief after administration of some hemp preparations. Dronabinol reduced weight loss and stimulated appetite and weight gain in AIDS and several forms of cancers (Robson, 2001).

Cannabinoids exert protective effects on cardiovascular system, in myocardial ischemia (Grant and Cahn, 2005); also, they determine the improvement of some aspects of cognitive function (Ranganathan and D'Souza, 2006). Canniprene, another compound isolated from hemp, is a dihydrostilbene with inhibitive effect on lipoxygenase and cyclooxygenase, but also showing anti-inflammatory properties (Elsohly et al., 1990).

Other metabolites with significant biological activity have been isolated especially from high-potency hemp (Δ^9-THC > 10%, w/w). For example, 4-acetoxy-2-geranyl-5-hydroxy-3-*n*-pentylphenol and 8-hydroxycannabinol displayed significant antibacterial and antifungal activities, respectively, while 5-acetyl-4-hydroxycannabigerol displayed strong anti leishmanial activity (Radwan et al., 2009). Other compounds manifested anti malarial or cytotoxic activities.

In time, numerous excesses have been produced in utilization of hemp chemical constituents, as result of lack of standardization procedures and of deficient dosage. Therefore, the treatments can induce grave effects – intoxication, sedation, dizziness, mouth dryness, decrease of blood pressure etc. If the small doses of THC firstly induce euphoria and relaxation, the increase of doses and extension of ingestion or inhalation time will determine grave manifestations: decrease of motor coordination, disturbance of long time memory and of verbal communication, anxiety, tinnitus, hallucinations, and in extreme situation the paranoid psychosis can install.

Verification of teratogenic potential of hemp etheric extracts on rat pregnant females determined the decrease of pregnancies as result of abortion increase, weight diminution of new born rats, decrease of descendence survival rate, fetal malformations (microcephaly, phocomelia). Other authors also reported the presence of fetal malformations in mice, rats, hamsters, and rabbits (Persaud and Ellington, 1968), but in other experiments their presence was not confirmed (Miras, 1965). It seems, however, that the pure THC (responsible for psychotropic effects) not induces teratogenesis (Singh et al., 1981).

The long time administration of hemp extracts determined gonadal lesions at the *Presbytis entellus entellus* males, but also induced liver disorders, with significant glycogen decrease and transaminase increase (Dixit, 1981). In rats was evidenced the blocking of luteinizing hormone and of ovulation (Nir et al., 1973).

In humans, Harmon and Aliapoulis (1972) described three males with gynecomastia associated to the excessive marijuana consumption. Marijuana can too determine the decrease of plasma testosterone level (Kolodny et al., 1974).

Even non-psychoactivelly compounds like CBD can have some cytotoxicity, dependent on dose and administration duration, reflected in reduction of rat hepatocytes viability in primary cultures, cytoplasmic changes, inhibition of DNA and protein synthesis, modifications of enzyme activities (Cohen and Stillman, 1976; Braut-Boucher et al., 1981).

Other hemp uses. Out of utilization of hemp extracts in pharmaceutical and medical domain, a number of varieties are producers of high quality stem fibres – basic material for textile industry, as well as of vegetal oils (20-40% in seeds). China is currently the prime producer of hemp textile. China had an uninterrupted hemp trade for approximately 6000 years.

Because of the terpene presence, the hemp essential oils are utilized to make soaps, creams, perfumes, or in aromatherapy. The hemp seeds extracted siccative oils serve to the preparation of dyes and soaps.

The seeds constitute food for exotic, domestic, and cage birds (parrots, canaries), while the residues remaining after oil extraction from seeds are administrated as „flat cakes" (30% proteins, 10% fats). These are used either in this form, singles, either they are added in concentrated fodders to feed those animals subjected to fattening (600 g „flat cakes" are equivalent, as nutritional value, to 1000 g cereals grains). In the case of pregnant cows, these cakes must be restrainedly utilized because they can produce abortions. After refination, the oils can be used in preserves industry.

The tow, which represents 40-50% from fibre production, is utilized in tapestry domain and as insulating material. Bags, cords, cables, water hoses, mattress cloth, tent canvas, and knapsacks are made by hemp fibres.

Hemp is a valuable, viable source of woody biomass. One acre (4074 m^2) of hemp is approximately 75% cellulose, whereas one acre of trees is only 60%; hemp can give two crops per year, whereas trees give one crop every 20-30 years. The wooden residues („puzderia") resulting after primary processing of hemp stalks and representing 45-50% by stalk weight constitute an important foundry fuel and is basic material for coal briquettes. Hemp stalk can be converted into 500 gallons (1 UK gallon=4.54 liters) of methanol/acre (*http://www.harbay.net/*).

The wooden residues or whole plant are utilized to obtain paper or special plates used to protect against noises in furniture industry and in constructions, while the P, K, Ca - rich ash remained after wooden residue combustion is applied as fertilizer. Also, husk resulted after seed harvesting represents a valuable fertilizer (10 t hemp husk is equivalent to 40 t stable refuse).

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http://www.harbay.net/

1 – Biological Research Institute, Iaşi
2 – Clinical Hospital „I.C. Parhon", Iaşi
* *trutaelena@yahoo.com*