

ODBORNÝ ČASOPIS DERMATOVENEROLÓGIE, ESTETICKEJ DERMATOLÓGIE A KOZMETIKY

DERMA

3. TISÍCROČIA

III. ročník 2/2003



Preparations containing Glycyrrhizic Acid in dermatological practice

First results of the international multicentre study

Zelenková, Hana.¹, Nejdková, Alena.², Škutilová, Eva.³, Urbáni, Milan⁴, Švecová, Danka.⁵, Cabalová, Jirina.⁶

Glycyrrhiza glabra – cortex from smooth fruit (Lékořice lysá – *Glycyrrhiza glabra*) – lasting medicinal herb, one of the oldest drugs in the world. The name comes from the Greek– Glykys – sweet, Rhiza – the root. Liquirita is a form of the Latin name, the oldest of this plant. Glabra – sticky, is the designation of the species and is related to the glands. The natural resin of the glands causes one leaf to stick to another. It belongs to the bean plant family (from the broad bean) and it contains honey.

Glycyrrhiza glabra was already referred to in Egyptian papyri many hundreds of years before Christ. It was used to cure catarrh in the respiratory tracts. Traditional Chinese medicine has used it for hundreds of years because of its anti-inflammatory effect. The effective tissues of the extract or of the drug from the root can be divided into two groups :

I – group – saponin type tissues – glycyrrhizin

II – group – flavonoids – likviricin and izolikviricin

Glycyrrhizin – acid type tissue (*Glycyrrhizic Acid* – *GL*) is contained in the plant in the form of potassium salt and calcium. It is widely sold and is the ammoniac salt in glycyrrhizin; it is used in the pastry industry.

GL is representative of tissues which have a cortico-mimetic effect. The best known is its expectorant effect. During the Second World War its positive anti-ulcer effect on the ulcerous mucous was confirmed. GL also has a laxative and diuretic effect. It is not recommended to use the drug over a long period of time – edemas are occurring (10).

¹ DOST Svidnik, Slovakia, ² Private Dermatology Outpatient Clinic, Žilina, Slovakia, ³ Private Dermatology Outpatient Clinic, Podunajské Biskupice, Slovakia, ⁴ Medical Hospital, Dermatology Department, Banská Bystrica, Slovakia, ⁵ Dermatology Clinic of the Medical Hospital, Bratislava, Slovakia, ⁶ Private Dermatology Outpatient Clinic, Prague, Czech Republic.

Objective studies have confirmed that GL contains a group of anti-virus tissues. The first study confirming this anti-viral effect came to light in the year 1979 (6). Afterwards, many studies of this type appeared (1, 2, 9, 15, 16, 17, 18, 19). The most complex and most numerous studies have been published by the Japanese; the publication of the authors Ohtsuki and Lahida in the year 1988: „The inhibitory effect of Glycyrrhizin on Polypeptide Phosphorylation by Polypeptide-dependent Protein Kinase (Kinase P) in vitro“ (14) is considered as the most important work.

The Spanish laboratory, Cheminova Internacional, has taken advantage in their production programme of the knowledge emanating from world-famous laboratories. To elaborate the product Epigen, which serves as a preparation for eliminating infectious symptoms provoked by virus, the results from the most recent scientific investigations in the world have been assessed. In the production of this preparation the biocatalytic process of molecular activation is used which guarantees the incomparable efficacy of the product (24). The basic objective of these investigations was to discover a treatment without using aggressive drugs which, on too many occasions, produce side effects and collateral effects. Before launching the Epigen preparation onto the market, laboratory trials from the clinical studies were carried out on a wide scale (3, 4, 5, 7, 8, 11, 12, 13, 20, 21).

The indicative group of Epigen is very wide: herpes simplex, - labialis, genitalis (herpetic vulvovaginitis, herpetic balanoposthitis), herpes simplex in relapse, herpes zoster, HPV infections – verrucae, condyloma accuminata.

After many multicentre studies in different countries, Cheminova Internacional also addressed Czech and Slovak dermatologists inviting them to do a clinical study to verify the effectiveness of Epigen on patients who suffer from viroid infections: Herpes simplex, Herpes zoster, Herpes progenitalis, Condyloma accuminata; acute groups and groups with a relapse were studied. During the study it was discovered that Epigen is extremely positive in mucous diseases of the Pemphigus and Pemphigoid type. These results continue to be the object of in-depth studies.

The clinical study was carried out in six different centres of renown in the Czech and Slovak Republics: DOST Svidnik, Slovakia, Private Dermatology Outpatient Clinic, Žilina, Slovakia, Private Dermatology Outpatient Clinic, Podunajské Biskupice, Slovakia, Medical Hospital, Dermatology Department, Banská Bystrica, Slovakia, Dermatology Clinic of the Medical Hospital, Bratislava, Slovakia, Private Dermatology Outpatient Clinic, Prague,

Czech Republic. The study was done as an open study of the IV.Type, between 1.12.2002 and 30.5.2003. It was done after the product was registered (post-register study).

Material and Methodology

In the six different centres of work 46 patients were studied with the following diagnoses : Herpes simplex-labialis, genitalis (herpetic vulvovaginitis, herpetic balanoposthitis), Herpes simplex in relapse, Herpes zoster, Condyloma accuminata. (See Tab.1).

Of the 46 patients, 21 were men (with an average age of between 38 and 52 years) and 25 women (of an average age of between 40 and 48 years). The youngest patient was a child of 12 suffering from Herpes simplex, the oldest patient was a woman of 78 years suffering from Herpes zoster facialis 1.dx. The largest group had Herpes simplex and Herpes simplex in relapse. This group consisted of 21 patients.

Criteria for placing the patients in the corresponding group:

- the first attack of the disease
- relapse of the disease
- age between 12 and 80 years
- previous failure to cure with other preparations
- the resistance of the disease to other preparations

Criteria for expelling a patient from the group :

- gravity and lactation
- patients under 12 years
- poor collaboration between the patient and the doctor
- patients with a variety of different allergies
- patients taking steroids, immunomodulators, immunodepressives, local anti-viral preparations.

The following preparation was used for the patients selected: Spray or Cream with an effective tissue content of 0,1 g to 100 ml excipients.

Quantity of the applications : 3 – 5 times a day until the state improved. The period of application differed, depending on the diagnosis, and oscillated between 3 and 60 days.

Information about applying the product was obtained by the patients directly from the corresponding physician.

Documentation : each patient had the documentation of his/her case (a protocol).

Photodocumentation : 2 – 3x in the patients selected.

Screening in the basic laboratory : every patient.

PL serology : every patient.

The assessment of these two last parameters was not the object of the study.

Personal hygiene recommended: the use of non-irritant products, so as not to interfere with the curative process.

Other medication: only on the basis of recommendation from another doctor and, if necessary, to increase the patient's comfort.

The therapeutic effect was assessed on a 5 grade scale: :

1 – complete cicatrisation , 2 – notable improvement, 3 – improvement, 4 – no improvement, 5 – worsening.

Subjective assessment of the patient:

1 – excellent, 2 – very good, 3 – good, 4 – no change, 5 – irritation, worsening

Assessment of undesired effects and their relation to the application of the product.

Results

In all patients the tolerance of Epigen was very good. No patient interrupted the curative process (See Tab.2). After this study was over, the patients with a relapse continued to use Epigen with success. For the assessment of the effectiveness of the preparation and tolerance, see Tab.3.

Tab. 1 :

Basic data on the patients included in the International Multicentre Study:

(The effect of preparations containing Glycyrrhizic Acid (Epigen) in dermatological practice).

Diagnóza	Muži		ženy		spolu	Počet aplikácií (denne)/ Ø	Doba aplikácie (dni)/ Ø
	počet	Ø vek	počet	Ø vek	Počet/ Ø vek		
Herpes zoster	6	51,7	2	67	8/59,62	3 – 5/ 4,1	7-14/ 9,7
Herpes simplex H.simplex recidivans	8	31,5	16	40,6	24/37,5	3-5/ 4,45	3 - 30/ 10,4
Herpes proenitalis	7	38,8	4	37,7	11/38,4	3 – 5/ 4,1	3 – 28/ 7,7
Codyloma acuminata	5	29,8	5	26,04	10/28,1	3-5/ 4,3	7 – 60/ 26,1
Verrucae vulgares			2	23,5	2/ 23,5	3-4/ 3,5	5 / 5
Spolu	26	40,6	29	36,7	55/38,5	Ø 4,29	Ø 12,4

Explanations :

Diagnóza = diagnosis

Muži = men

Ženy = women

Spolu = all the women and men

Počet aplikácií = number of applications, (denne) = daily

Doba aplikácie = duration of the application, (dní) = in days

Počet = quantity

Øvek = average age

Herpes Zoster : it is obvious that the application of Epigen has accelerated the cure of local manifestations. With the use of Epigen Spray or Cream the vesicles dried and there were no scabs, the abuse of analgesics was eliminated (one of the patients had already given these up on the third day). The cure left no cicatrization and this was also true of cases with strong, extensive manifestations. Moderate de-pigmentation was noted only in the case of one

man. The product was assessed both by the doctor and the patient as being exceptionally effective.

Tab. 2 :

The International Multicentre Study: The effect of preparations containing Glycyrrizinic Acid (Epigen) in dermatological practice – relapse cases, interruption of the application, NÚ.

Diagnóza	Muži		ženy		Spolu Počet/ Ø vek	Recidívy	Prerušenie	NÚ
	počet	recidívy	počet	recidívy				
Herpes zoster	6	0	2	0	8/59,6	0	0	0
Herpes simplex Herpes simplex recidivans	8	3	16	4	24/37,5	6	0	0
Herpes progenitalis	7	3	4	1	11/38,4	3	0	0
Codyloma acuminata	5	0	5	0	10/28,1	0	0	0
Verrucae vulgares			2	0	2/ 23,5	0	0	0
Spolu	26	6	29	5	55/38,5	11	0	0

Explanations :

Recidívy = relapses

Prerušenie = interruption

(The other data are the same as in Tab.1.)

Herpes simplex : In the majority of cases the application of Epigen has led to very good results. Almost all the patients, apart from certain exceptions, indicated very rapid relief – remission of the burning, the sensation that the area was no longer so sensitive. The vesiculation altered very quickly, manifesting only small haemorrhagic scabs; and a remission of the inflammatory infiltration was evident before 72 hours. On the fifth day, most of the patients declared that they were completely cured.

In the men the effect and tolerance was excellent in all of them; however, in the case of the women there were small differences. Ten women patients with the insemination of herpes simplex labii oris showed an exceptional effect and tolerance. Three women with permanent herpes on the lips used Epigen for one month with short interruptions, but in the end they were cured and in almost two months have suffered no relapse. In the case of two patients,

one with herpes simplex labii oris in relapse and the second with herpes simplex reg. glutealis in relapse, the cure was very slow, the effect and tolerance assessed as good, in comparison with other preparations which these patients had used previously. Only in the case of six women a relapse of herpes simplex labii oris occurred in a period of three months, but with a further application of Epigen, all traces of the herpes disappeared very rapidly, in less than 72 hours.

Tab. 3 :

The International Multicentre Study: The effect of preparations containing Glycyrrhizinic Acid (Epigen) in dermatological practice – effectiveness, tolerance.

Diagnóza	Účinnost'		Znášanlivost'	
	Muži		ženy	
	lekár	pacient	Lekár	pacient
Herpes zoster	6x1	6x1	2x1	2x1
Herpes simplex	8x1	7x1	11x1	11x1
Herpes simplex recidivans		1x2	2x2 3x3	3x2 2x3
Herpes progenitalis	7x1	6x1 1x2	4x1	4x1
Codyloma acuminata	4x1 1x2	3x1 2x2	4x1 1x2	3x1 1x2 1x3
Verrucae vulgares	2x1	2x1	2x1	2x1

Explanations:

Lekár = the doctor

Pacient = the patient

Účinnost = effectiveness

Znášanlivost = tolerance

(The other data are the same as for Tabs.1 and 2.)

Herpes progenitalis : the effect and tolerance were assessed by the physician and by the patient as exceptional. Also in the case of patients suffering from herpes simplex, in all the cases observed, an improvement in the vesiculation was obvious, as well as the disappearance of inflammatory manifestations before 72 hours. By the fourth or fifth day the complete cure was already evident in the case of almost all the patients. All patients assessed the disappearance of subjective annoyances, such as the burning and the pain, as exceptional.

Their psychic well-being improved considerably. Only three patients suffered a relapse, but with a further application of Epigen this disappeared rapidly. In the case of one patient no relapse occurred, although he had often suffered relapses on previous occasions.

Condyloma accuminata : with the application of Epigen to tiny condylomas (up to 1 mm in size) very good effect and tolerance have been achieved. The remission of the problem was obvious in the period of 7, or at most, 14 days. The most obvious effect was noted in a married couple. In the case of two women patients with very strong manifestations, it was necessary to apply Epigen 35 days in one, 60 days in the other.

In the case of patients with large condylomas it was necessary to apply a different cure, for example, cryotherapy. In these cases Epigen served extremely well for terminating the cure. Moreover, the patients using Epigen after cryotherapy, manifested an analgesic effect. There were no relapses.

There were no differences observed between the use of the Cream or the Spray. However, we would say that for the more affected areas and for the cure of intimate areas, we prefer the Spray.

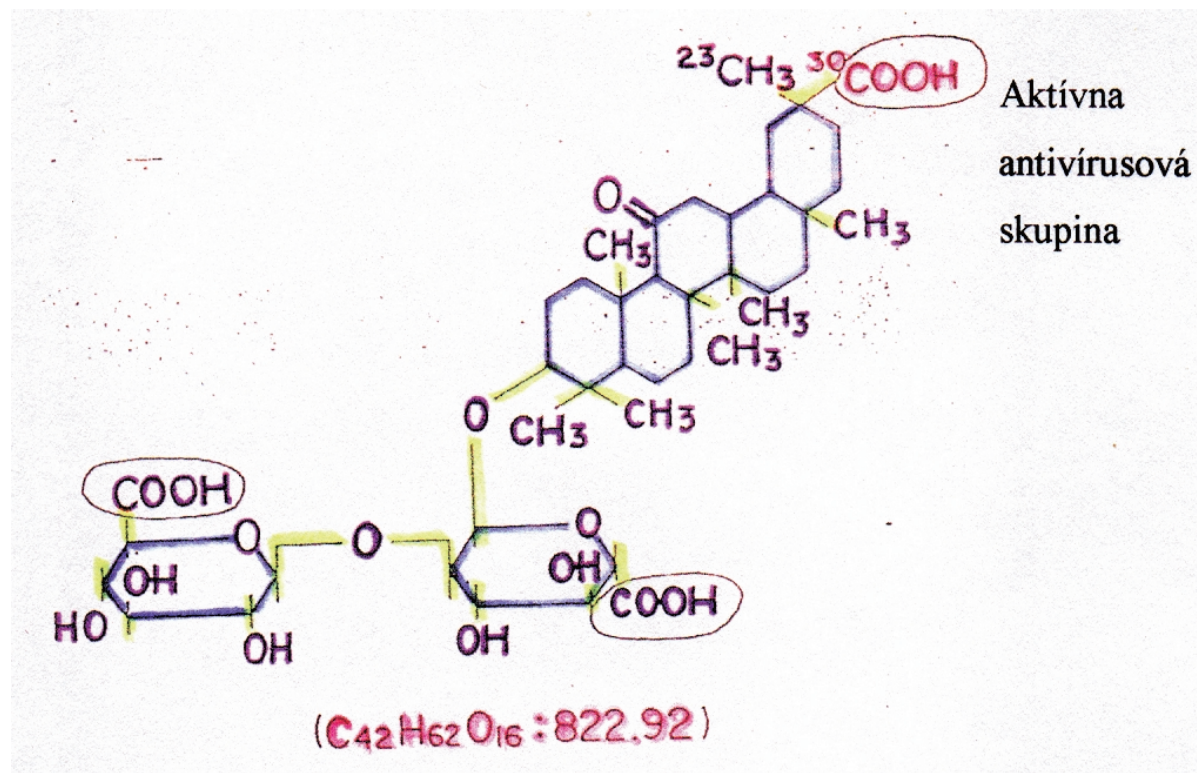
Discussion

Many articles and serious scientific studies have been written (9,10) declaring that *Glycyrrhiza glabra* does not only serve as raw material for the production of certain foods and sweets for children. *Glycyrrhiza glabra* is very widely used in the pharmaceutical industry, especially the drug from the root – *Radix liquiritiae* – *Radix glycyrrhizae glabrae* (10). Picking the roots and extremities of the cultivated plant is best during the third year of its vegetation. During the elaboration the root and extremity should be cleaned quickly, peeled (not obligatory) and dried at a temperature of 35°C. For its storage a dark place is recommended, protected against humidity and insects (10).

A species of the plant which grows in our conditions originates in the South of Europe and in the Near East. It is exported to Slovakia and to the Czech Republic from Spain, Russia and China; the plants differ because of the way they are packed together, because of the way they are peeled and because of other details. The Spanish species is the heaviest. The peeled Chinese species has the highest content of GL (5.5%), and the non-peeled species of the Spanish drug (8.9%). The cortex or the extract are very sweet, up to 50 times sweeter than

sugar beet. The black extract called succus has its origin principally in the Italian drug. It is of interest to note that false drugs in powder form exist!!! (10).

Chemical formula of GL (2, 4, 8).



Glycyrrhizic Acid (Glycyrrhizin – GL) is glycozhidic in character. Aglycon is represented by glycyrrhetic acid (glycyrrhetin). Pentacyclic Glucuronid of triterpene acid is steroidal. The sweet component (sugar) is characterised by two molecules of glucuronic acid. The successive separation of the sugar component results in the loss of sweetness.

Amongst the basic features of GL is that it makes water froth. Its haemolytic effectiveness is minimal. GL causes the inhibition of prostaglandine E2 in the affected tissue; it detains the spreading of the virus because it mitigates the action of the P Kinase viroid. The induction of interferons begins and this activates the macrophages and stimulates an increase in the phagocytaria and bacteroid capacities. The interferons have an anti-viral and anti-proliferic effect (3, 5, 8, 11, 12, 13, 19, 20, 21).

Finally, the GL effect can be characterised as: :

- antiulcer
- antiinflammatory
- antiviral (the capacity to inhibit ADN and NRA of the virus: varicella zoster, HIV, influenza A, B, herpes simplex, hepatitis).

A basic substance of Epigen from Cheminova Internacional Madrid is the aquatic extract of GL 0.1 g Excipients, c.s.p. 100 ml. During the laboratory trials in vitro its inhibitory effect was discovered. Experiments with animals have revealed a nil mortality index and minimal ocular and dermal irritation (3, 8, 13, 14, 15).

Many clinical studies carried out with Epigen over the last ten years in dermo-venerological and gynaecological clinics show how effective it is in the cure of infections (5, 7, 11, 12, 20, 22). Epigen has also been medicated in pregnant women, without any problem at all. The effectiveness of Epigen is 100%, especially in the first phases of the disease, and in relapse cases up to 90% (7, 12, 20, 21).

Very promising effects have been achieved on patients suffering from mucous manifestations of the pemphigus and pemphigoid groups (23). After using Epigen, a patient who was suffering from the genital form of pemphigus vulgaris, noticed considerable relief from the pain, from the burning and drying of the areas affected. Still more effective was the case of a patient with pemphigus cronicus benignus familiaris – Hailey-Hailey on the skin of the perigenital area and of the axillae. The positive results achieved from the study of the nine patients are the object of a further study which will be presented in the EADV Congress in Barcelona 2003.

All those participating in the study confirmed that Epigen greatly reduces: edemas, hyperemias, burning, stinging and accelerates epithelisation of the eroded areas. In the 46 cases of the patients in this international multicentric study, we should add the assessment of Epigen's applicative qualities to its obvious qualities. It can be said that the application of this most effective preparation is extremely easy and rapid. It is only applied externally. In Slovakia and the Czech Republic it is registered in the form of Spray and Cream.

Aims and Discussion

Epigen (Laboratorios Cheminova Internacional) is a modern preparation, which has resulted from the experience of traditional empirical medicine. The antiviral effectiveness of the product has been repeatedly confirmed in several clinical studies. It offers a totally new alternative for the large group of diseases: Herpes simplex-labialis, genitalis (herpetic vulvovaginitis, herpetic balanoposthitis), herpes simplex in relapse, herpes zoster, condyloma acuminata, verrucae vulgares. It holds promise for the cure of bullous dermatoses. Epigen is perfectly tolerated in both forms; it does not provoke irritation and it is quite innocuous. The product is very easy to apply and does not cause any discomfort. Combining Epigen with other products, or with physical or mechanical assistance, does not present any problem.

Defending the grounds of products containing Glycyrrizinic Acid in dermatological practice has not been easy. The results of clinical trials carried out in many well-known clinics worldwide and also the results of this international multicentre study unanimously demonstrate, however, that Epigen from Cheminova Internacional Laboratories (Cream and Spray) enriches the range of dermatological products. The results of the study presented show the great effectiveness of the product and serve as a recommendation for its wide use in dermatological practice.

Written by : Prim.MUDr.Hana Zelenková, CSc
DOST Svidník, Slovakia

Bibliography:

1. Alarcon, B., Lacal, J.C., Fernandez-Sousa, J.M., Carrasco, L.: Screening for new compounds with antiherpes activity. *Antiviral. Res.*, 4, 1984, 5, s. 231-243.
2. Baba, M., Shigeta, S.: Antviral activity of glycyrrhizin againsts varicella zoster virus in vitro. *Antiviral.Res.* 7, 1987, 2, s. 99 – 107.
3. Badam, L.: In vitro studies of the effect of Glycyrrhizin from Indian Glycyrrhiza glabra Linn.on some RNA and DNA viruses. *Indian.J.Pharmacology*, 26, 1994, 3, s. 194 – 199.
4. Brochure de Investigadores (Cheminova International). Madrid España 1995.
5. Bogatyreva, I.I.: Experience in usage of Epigen at treatment of papillomavirus infection of the urogenital duct. Central Sci.-Research Institute of Dermatovenereal Diseases. Moscow, 1997.
6. Doll, R., Hill, I.D., Hutton, C., Underwood, D. L.: Antiviral activity of glycyrrhizic acid. *Lancet*, 11, 1979, s. 793-796.
7. Hildalgo, H.: Open controlled prospective multicenter study on the effectiveness, clinical safety and local tolerance of the repeated administration of activated glycyrrhizinic acid (Epigen) in local sprayings over a period of 5 days to patients suffering from genital herpes. Hospital General de México, April 1996.
8. Hirabayashi, K. et all.: Antiviral activities of glycyrrhizin and its modified compounds against human immunodeficiency virus type 1 (HIV- 1) and Herpes simplex virus type 1 (HSV – 1) in vitro. *Chem. Pharm. Bull.* 39, 1, 1991, s. 112 – 115.
9. Chandler, R., F.: Licorice more than just a flavour. *Can.Pharm.J*, 118, 1985, 9, s. 421-424.
10. Kresánek, J., Krejča, J.: Atlas léčivých rostlín a lesných plodov. Vydavateľstvo Osveta Martin 1982, s. 554 – 557.
11. Martín-Crevillente, O.: Study about antiherpetic activity of Epigen intimo against genital herpes. Ginecologic Center „Salud y mujer“, Madrid, 1995.
12. Martín-Crevillente, O.: Report on the results of the tests with the product Epigen (Laboratories Cheminova International, S.A., Madrid). Evaluate the effectiveness and the tolerance of the antiviral preparation Epigen in women with papilloma virus infection. Ginecologic Center „Salud y mujer“, Madrid, 1998.

13. Numazaki, K., Nagata N., Sato, T., Chiba, S.: Effect of glycyrrhizin, cyclosporin A and tumor necrosis factor alpha on infection of U-937 and MRC-5 cells by human cytomegalovirus. *J. Leukocyte Biol.* 55, 1994, 1, s. 24-28.
14. Ohtsuki, K., Iahida,H.: Inhibitory effect of glycyrrhizin on polypeptide phosphorylation by polypeptide-dependent protein kinase (Kinase P) in vitro. *Biochemical and Biological research communications.* 1988; Vol. 157, No 2, s. 597 – 604.
15. Pompei, R.: Impaired recovery of infectious Herpes simplex virus from glycyrrhizic acid treated cells. *Riv. Farmacol.Ter.*12, 1981, 1, s.43-46.
16. Pompei, R., Marcialis, M.A.: Effect of glycyrrhizinic acid on Herpes simplex virus type 1 glykoprotein synthesis. *Universita di Cagliari, Italy, IG-MOD.* 83, 1985, 2, s.385-391.
17. Pompei, R., Pani, A., Flore, O. et all.: Antiviral activity of glycyrrhizic acid. *Experimentia,* 36, 1980, 3, s. 304
18. Pompei, R., Pani, A., Flore, O., Marcialis, M.A., Loddo, B.: Glycyrrhizic acid inhibits virus growth and inactivates virus particles. *Naturo,* 281,1979, s. 689 – 690.
19. Shigota, S., Yokota,T., Iwabuchi,T., Baba, M., Konno, K., Ogata, M., De Clerc E.: Comparative efficacy of antiherpes drug against various strains of varicella-zoster virus. *J. Infect. Dis.* 147,1983,s 576 – 584.
20. Skripkin,J.K.: Investigation of clinical effectiveness and tolerance of „Epigen“ firm „Cheminova International“ Spain. *Moscow* 1997.
21. Takahara, T., Watanabe, A., Shiraki, K.: Effect of Glycyrrhizin on hepatitis B surface antigen:A biochemical and morphological study. *J.Hepitol.* 21, 1994, 4, s. 601 – 609.
22. Zelenková, H.: The use of preparations containing glycyrrhizinic acid in dermatology practice. *Kongres juhoslovanskej dermatovenerologickej spolocnosti, Belehrad,* 10.11.2002.
23. Zelenková, H., Stracenská, J.: Použitie prípravkov s kyselinou glycyrrhizinovou (glycyrrhizinic acid) v dermatologickej praxi. *Lipovský den,* 11.1.2003
24. Gonzáles,A. : Prevention and treatment of tumorous, viral and other degenerative illnesses. *Scientific Departement of Cheminova and Catalysis, Madrid, Spain,* January 2001.

Pictures :



Herpes simplex – before applying Epigen Cream

Herpes simplex – after 4 days of applying Epigen Cream

Herpes zoster – before applying Epigen Cream

Herpes zoster – after applying Epigen Cream



Herpes simplex permagnum – a girl of three years old, before applying Epigen Cream.

Herpes simplex permagnum – a girl of three years old, after applying Epigen Cream for 5 days.



Herpes genitalis before applying Epigen Cream.

Herpes genitalis after applying Epigen Cream for 4 days.

Herpes genitalis, the third day of applying Epigen Cream.

Herpes genitalis after the fifth day of applying Epigen Cream

Translated by :

14 de October de 2003