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**Главный редактор:**
С.М. Адекенов
(г. Караганда)

**Зам.главного редактора:**
К.У. Ушбаев
(г. Алматы)

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(г. Караганда)

**Адрес редакции:**
100009, г. Караганда,
ул. М.Газалиева, 4
тел.: 8 (7212) 43-31-44
e-mail: phyto_pio@mail.ru

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# ROPREN – THE FIRST POLYPRENOL PHARMACEUTICAL DRUG IN THE WORLD FOR THE TREATMENT OF DISEASES OF THE LIVER AND BRAIN

*V.S.Soultanov[1], P.D.Shabanov[2], V.I.Roschin[2]*
terri.punshon@aurabody.net
[1]Company "Solagran Ltd", Australia, Melbourne
[2]St Petersburg Academy of Forestry engineering RF, Russia, St-Petersburg

Data on the new drug "Ropren" – a plant hepatoprotector, which has appeared in the Russian pharmaceutical market, is presented in the review. Ropren represents the natural bioregulator, or transport lipid, which quickly metabolizes in the liver into dolichol, participating in glycosilation of membrane proteins and the formation of glycoproteins. The highest rate of dolichol metabolism is observed in the liver, kidneys and spleen. Excretion of dolichols with bile is considered the main pathway of their removal from the organism. Prospects and experience of application of "Ropren" in clinical practice are presented. The mechanisms of action of the drug are considered as well as the wide range of activity of polyprenols which is the basis for the drug. The probative clinical trials showed that in addition to Ropren's hepatoprotective effect, the drug also possesses neuroprotective and anti-depressive action. The antifibrotic, anti-atherogenous and anti-inflammatory activity of the drug is also shown. It is effective in various pathologies of the liver, including fat dystrophy of the liver and alcoholic cirrhosis associated with poly neuropathy.

## Introduction

The diversity of liver function disorders considerably complicate the medicinal improvement of such conditions and require the use of pharmacological substances with a wide spectrum of activity for best therapeutic effect. Moreover, it should be noted that immunological changes have an important role in the pathogenesis of various liver diseases.

Contemporary hepatology has a need for the research and development of new hepatoprotectors, especially of plant origin. The liver is involved in many pathological processes and when damaged can cause serious metabolic disorders: immune response, disorders of detoxication function and antimicrobial protection. Most often, liver disorders occur due to chemical (toxic, drugs, and alcohol damage) and immunological mechanisms. The variety of pharmaceuticals used in composite therapy of liver and bile-excreting duct disorders include more than 1000 names. However, among the variety of drugs available, those of plant origin are based on flavonoids of milk thistle (or a mixture of flavonoids), the main component of which is silymarin. Silymarin is a mixture of 3 main isomeric compounds, which is the basis for Legalon. Another group of hepatoprotectors contains essential phospholipids, which includes drugs such as Essentiale Forte, Phosphogliv, etc. At the same time, use of Essentiale for treatment of active hepatitis requires a certain caution as in some cases it can facilitate the activation of cholestasis and inflammatory activity. Currently, Heptral, which is based on ademetionine (an amino acid derivative), is considered as the most efficacious drug in clinical practice. It has a wide range of activity, but it is not a natural plant origin hepatoprotector. It should be noted, that the maximal hepatoprotective effect of this substance, can only be achieved with parenteral use of Heptral. Ademetionine has a predominant effect on toxaemia and to a much lesser degree on parameters of cytolysis and cholestasis. It is established that the hepatoprotectors' activity is related to the restoration of homeostasis in the liver, increase in stability of this organ to the effect of pathogenic factors, normalisation of functional activity, and stimulation of reparative-regenerating processes in the liver. Unfortunately, at present, none of the hepatoprotectors used in medical practice satisfy these requirements in full. However, in recent times, the arsenal of the latest hepatoprotecting substances has broadened due to the arrival of both new synthetic and natural drugs. Currently, natural plant therapeutic substances have a predominant use (up to 54%), whereas phospholipid drugs comprise 16%, and other substances, including synthetic, organic and amino acid based drugs encompass around 30% of the total number of "real" hepatoprotectors.

The pharmaceutical market has already got a principally new hepatoprotector, Ropren, based

on polyprenols from plants. Essentially, it is a natural bio-regulator or transport lipid that quickly metabolises in the liver into dolichol, which participates in glycosylation of membrane proteins and formation of glycoproteins. The highest rate of dolichol metabolism is registered in the liver, kidneys, and spleen. Excretion of dolichols with bile is considered as a main pathway for their excretion from the body.

**The biological role of plant polyprenols and their analogues - dolichols**

Further research of the activity and efficacy of plant polyprenols present the problem of extraction of a sufficient amount for the treatment of various diseases. The closest to human dolichols are prenols from coniferous trees. Nevertheless, the study of therapeutic properties of these compounds in the treatment of CNS, cardiovascular, oncological, and infectious diseases and their effect on modulation of the immune system are reflected in a large number of patents [1] and have never stopped. With the development of Ropren, it becomes possible to use polyisoprenoid alcohols for pharmaceutical purposes, and essentially launches a new era of non-toxic therapeutic substances.

In clinical practice disruptions of the metabolism of the isoprenoid pathway are registered relatively often during: various neurodegenerative disorders of the liver and CNS [2, 3]; gastrointestinal tract; immunodeficient conditions such as ulcerous colitis; alcohol liver cirrhosis; hepatocerebral degeneration; peptic ulcers and digestive system disorders as well as degenerative disorders of the neuromuscular system (osteoporosis, osteoarthritis, and spondylosis). Moreover, similar disorders have been registered in patients with vascular thrombosis and arterial occlusions [4, 5], as well as with immunodeficient conditions, including rheumatoid arthritis and other systemic disorders of the connective tissues [6]. It should be noted that the dolicholphosphate cycle is a necessary metabolic link in the processes of regeneration, differentiation, and proliferation of cells [4, 7].

It is assumed that the therapeutic effect, observed after treatment with polyprenols of higher concentration, is predominantly related to their transformation into dolichols, though their direct effect cannot be excluded. Dolichol is widely distributed in the tissues of mammals. The structural similarity of plant polyprenols and animal dolichols presents new possibilities for influencing deeper links of pathogenesis of many inflammatory-degenerative disorders, correction of which has remained unattended by medical practitioners until today.

According to the latest data, in the human body polyprenols are transformed into dolichols by means of reductase CRB5A3 [23] and restore the deficit of dolichols in organs and tissues. Dolichol is stored in each cell, including hepatocytes, in a phosphorylated and dephosphorylated free form. The role of dolicholphosphate has been studied in detail, because it participates in N-related glycosylation of proteins and has a key importance for the cell [8, 9]. Dolichols have been discovered in the body relatively recently: they have been isolated for the first time by Pennock J.F., et al. [10]. It is known that dolichol is a long and very hydrophobic molecule, which can penetrate a lipid bilayer more than 3 times. Therefore, the attached oligosaccharide is firmly anchored in the membrane.

It is also accepted that dolichol regulates fluidity of membranes, especially synaptic ones [11]. Intensive research has taken place in the area of the effect of dolichol and its derivatives on various structures of the brain, and a large amount of dolichol was found in the nigrostriatal system of the brain [12]. Currently, the exact mechanism of dolichol's degradation is not known. There is a proof that the level of dolichol increases with age, both in peripheral tissues and the brain. That is why dolichol was suggested as a biological marker of aging [13], as well as an antioxidant and inhibitor of cellular toxicity [14].

It is an interesting fact that in the brain of Alzheimer's patients the level of dolichol is decreased, whereas the levels of dolicholphosphate and ubiquinone are increased. In the brain of healthy individuals without Alzheimer's disease the situation is the opposite [15]. Current hypothesis suggests that the levels of dolicholphosphate and ubiquinone in the brain damaged by Alzheimer's disease may increase due to glycosylation, as well as due to the brain's need to protect itself from oxidative stress. The role of dolichol (and ubiquinone in this relationship) is unknown in the

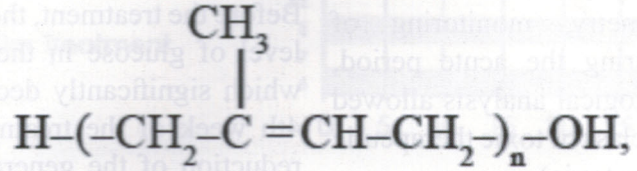
pathogenesis of Alzheimer's disease. In general, it is extremely important to perform more detailed study of the isoprenoid pathway of dolichol metabolism for the treatment of Alzheimer's disease.

Chemical and radioactive impact on hepatic cells also affects the levels of dolichol. The impact of carbon tetrachloride or irradiation of hepatic cells in rats leads to a reduction of the dolichol level, perhaps, due to the generation of free radicals [16]. Moreover, it is well known that ethanol increases the level of dolichol in the human blood and urine [17] and affects fluidity of membranes in the brain of mice [18]. The dolicholphosphate cycle is a key link in biosynthesis of glycoproteins in cellular membranes. This wide range of dolichol's activity and its presence in every cell, together with cholesterol, ubiquinone, and proteins, testifies to its important role in the body.

**Pharmacological characteristics of Ropren**

With the development of the pharmaceutical drug Ropren, it becomes possible to use polyprenol alcohols for pharmaceutical purposes, and essentially launches a new era of non-toxic therapeutic substances.

Ropren is obtained from pine and spruce needles. It is a mixture of polyprenols of high purity (95%) that contain 8-20 isoprene units and has the following structural formula (Fig.1.):



where n - the number of isoprene links form 8 to 20.

Fig.1. Structural formula of Ropren

Ropren is the first prenol prescription drug in the world developed by the Australian company «Solagran Ltd», and is manufactured at the St-Petersburg Pharmaceutical Factory in the form of drops for internal use.

**Pharmacological properties**

*Hepatoprotective and hypolipidemic activity*

Ropren normalises the processes of oxidative phosphorylation at the cellular metabolism level and facilitates restoration of hepatocyte membranes by competitive inhibition of oxidative processes. In the liver, it is metabolised into dolichol which participates in the glycosylation of membrane proteins and the formation of glycoproteins. Ropren also normalises the detoxification function of the liver.

As mentioned earlier, Ropren is a natural bio-regulator or transport lipid, which is quickly metabolised in the liver into dolichol. The highest rate of dolichol metabolism is registered in the liver, the kidneys, and the spleen. Excretion of dolichols with the bile is considered as a main pathway for their excretion from the body.

Ropren stimulates reparative-regenerating processes in the liver, restores the disrupted homeostasis, eliminates toxins, and facilitates activity of the antioxidant system. It has also been recorded, that Ropren has a stimulating effect on a non-specific resistance level (neutrophil and monocyte count). It has immunomodulating activity and increases the level of endogenic interferon and the duration of its circulation in the blood. It has a normalising effect on the altered status of the body, especially on the cellular link of the immune system that is indicated by increased content of active T-lymphocytes and Thelper/Tsuppresor index. Ropren reduces the level of allergic stress of the body that is confirmed by the reduction in circulating immune complexes and eosinophils in the blood Ropren is used for the following indications: fatty degeneration of the liver of various aetiology, hepatitis, liver cirrhosis (in composite treatment) and toxic liver damage (alcohol, drugs, and pharmaceuticals).

**Pharmacokinetics**

Ropren is absorbed relatively quickly into the system bloodstream and reaches its maximal concentration 3 hours after administration. The total average time of Ropren presence in the body (MRT) is around 10-11 hours. Half elimination time of Ropren (T1/2) is around 10 hours. After 48

hours, Ropren can be detected in the blood plasma in minimal amount (circa 0.1-0.2 mcg/ml). Total absolute bioavailability of the test-substance in the blood when orally administered was 75.2%. The value of apparent stationary distribution of Ropren - indicator Vss – is around 46 l/kg. The value of this parameter indicates that the test-substance does not only spread in the plasma and intracellular liquid, but also quite effectively enters into organs and tissues. The highest concentration of Ropren was registered after 4 hours in the adrenal gland, testicles, ovaries and pancreas (from 45.74 to 30.20 mcg/g). The longest retention time of the test-substance was registered in seminal glands, adrenals, bone marrow, pancreas, testicles, ovaries, kidneys and spleen.

Results of toxicometry, monitoring of experimental animals during the acute period, and data of pathomorphological analysis allowed classifying Ropren as a V class of toxic therapeutic substances (practically non-toxic).

**Results and discussion**

Animal studies conducted at various St-Petersburg scientific centres (SPb MAPS, Institute of Influenza, Institute of Evolutionary Physiology and Biochemistry at the Russian Academy of Science, SPb Chemical Pharmaceutical Academy, etc.) reliably demonstrated that Ropren has a marked hepatoprotective effect. With toxic liver damage caused by such toxic agents as dichloroethane, acetaminophen, and carbon tetrachloride, it was established that the drug actively protects the liver from the toxic effects and restores its function, facilitates rapid healthy liver regeneration and restoration of homeostasis in comparison with such well-known drugs as Legalon, Essentiale Forte, and Gliatilin. Liver function was evaluated using biochemical parameters of the blood together with histological analysis and electron microscopy, which demonstrated that Ropren significantly improves functioning of the liver [19].

A randomised double-blind, placebo-controlled clinical trial of Ropren using the comparator-drug Essentiale Forte was conducted at the St. George Hospital (St-Petersburg), St-Petersburg Botkin S.P. Hospital No.30, 1st and 2nd Therapeutic Departments of St-Petersburg clinics - SPb MAPS and Centre for Prophylaxis and Treatment of AIDS and Infectious Diseases, in accordance with GCP regulations. The results showed that in the treatment of patients with chronic damage of the hepatobiliary system (120 patients in total; dose – 54 mg/day) Ropren demonstrated a wide spectrum of biological properties that provided a hepatoprotective effect. Therapy with Ropren led to earlier positive changes in parameters of "liver samples", such as reduction of ALT and AST, in comparison with Essentiale Forte. In the case of ALT, the positive effect was registered 10 weeks earlier and in case of AST, by 6 weeks earlier than that of Essentiale Forte. The treatment resulted in the normalisation of the lipid spectrum of the blood that was evident in the increase of anti-atherogenic lipoproteins, and a statistically significant reduction of atherogenicity coefficient by 1.6 times after 4 weeks of treatment. Before the treatment, the patients had an increased level of glucose in the blood, on average 11%, which significantly decreased as early as by the 4th week of the treatment. All patients had the reduction of the general level of activity of the antioxidant system in comparison to the normal value. Use of Ropren facilitated the sharp increase in activity of the antioxidant system, which after 6 weeks of the therapy increased by 94%, after 8 weeks – by 175%, and after 12 weeks – by 155%. This effect was not registered in patients who received Essentiale Forte. Ropren treatment did not cause any side effects, which can testify to its safety.

Another clinical trial, the purpose of which was the study of the polyprenol drug in the treatment of Alzheimer's type dementia with vascular brain damage was conducted at the St-Petersburg Scvorscov-Stepanov Psychiatric Hospital No.3 on 25 patients aged from 54 to 78. The average history of the disease was 1.5 years. The treatment course was 3-4 months; the test-substance was administered at the dose of 144 mg/day. The treatment was mainly accompanied by somatic therapy. Efficacy of the test-substance was based on the international scale of cognitive disorders (MMSE), unified scale for evaluation of Parkinsonism, electroencephalography data (EEG), biochemical blood and urine indices, and BuChE and MAO activity in the blood serum. Results of the trials demonstrated the positive effect of polyprenols on cognitive functions. There was expressed improvement of the cognitive functions, based on all analysed parameters, in 40% of the patients (Fig. 2)

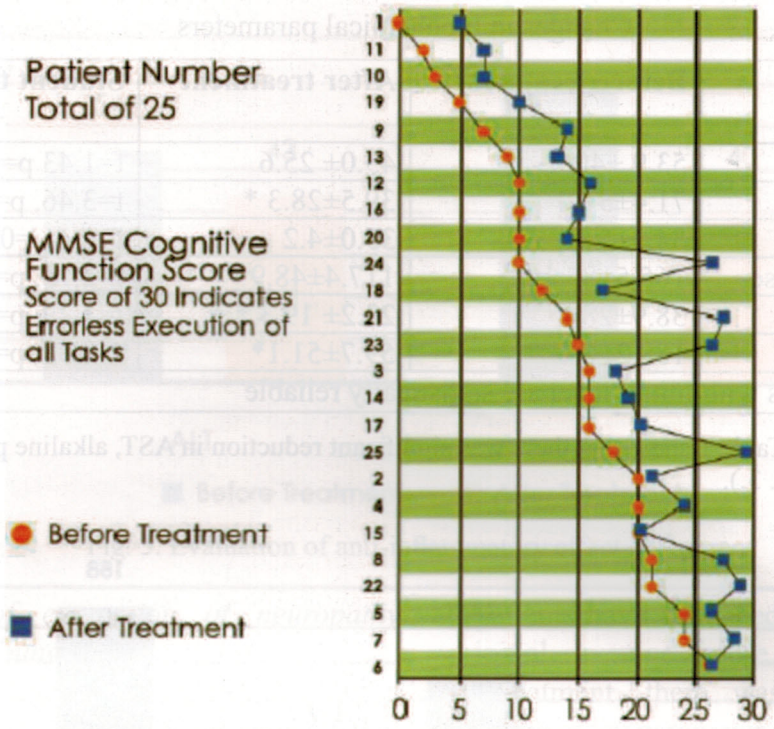



Fig. 2. Changes in cognitive function of patients after treatment with Ropren

Based on EEG data, it was registered that clinical conditions improved in 80% of the patients evidenced through the disappearance of delta-waves and paroxysms, the appearance of α-rhythm, and disappearance of local accent in the frontotemporal area. The test-substance has normalising effect on BuChE and MAO activity in the blood serum. Improvement of the neurological status was recorded in 25% of the patients, whereas the Parkinson's syndrome reduced as early as after 1 month, on average by 5 points as per the Parkinson's scale, which is a good prognostic factor for treatment of this disease. Based on the data obtained, it was concluded that Ropren has a good potential for the treatment of neurodegenerative disease of the Alzheimer's type.

In Australia, during the randomised, placebo-controlled trials conducted at the Brain Sciences Institute, Swinburne University of Technology, Ropren was administered for 12 weeks to healthy volunteers aged from 65 to 80 at the dose of 100 mg/day [20]. The group of participants (80 people) showed significant improvement of active and long-term memory. In a subgroup subjected to EEG testing, an increase in alpha-frequencies and reduction of delta- and theta-frequencies were registered, meaning that Ropren can facilitate relaxation, concentration of attention, and improvement of cognitive functions. Moreover, the HDL/LDL coefficient significantly increased, whereas LDLP decreased. This data obtained in the experiment on humans is the basis for a large number of works conducted by researchers in Russia and demonstrates the capacity of Ropren to participate not only in the protection of the liver, but also of the brain [21, 22].

**Results of recent trials**

*1. Treatment of alcohol liver cirrhosis by Ropren*

The previously mentioned data is the basis for conducting trials of the hepato- and neuroprotective effects of Ropren in patients with alcohol liver cirrhosis, who satisfied the inclusion criteria and doesn't have any exclusion criteria [28]. The main objectives of the study were: Study of changes of biochemical and fibrosis indexes as well as subjective (by patient) and objective (by neurologist) evaluation of changes in symptoms of alcohol polyneuropathy.

*Evaluation of biochemical parameters*

In all patients biochemical blood indices were analysed before and after the treatment. Main results are presented in Table 1.

Table 1

Changes in biochemical parameters

| Parameter | Before treatment | After treatment | Student t-criterion (p) |
|---|---|---|---|
| ALT | 53.9 ±40.6 | 43.0± 25.6 | t=1.43 p=0.166 |
| AST | 71.4±51.0 | 39.5±28.3 * | t=3.46, p=0.002 |
| Albumin | 34.0±5.4 | 35.0±4.2 | t=1.1, .=0.26 |
| Alkaline phosphatase | 165.5±85.1 | 117.4±48.9 * | t=2.18, p=0.04 |
| Total bilirubin | 38.9±28.1 | 23.2± 19.3 * | t=3.29, p=0.003 |
| GGT | 188.2±263.9 | 59.7±51.1* | t=2.35, p=0.02 |
| * - differences with initial level are statistically reliable | | | |

Data presented in Table 1 show that there was significant reduction in AST, alkaline phosphatise, total bilirubin, and GGT (Fig. 3.).

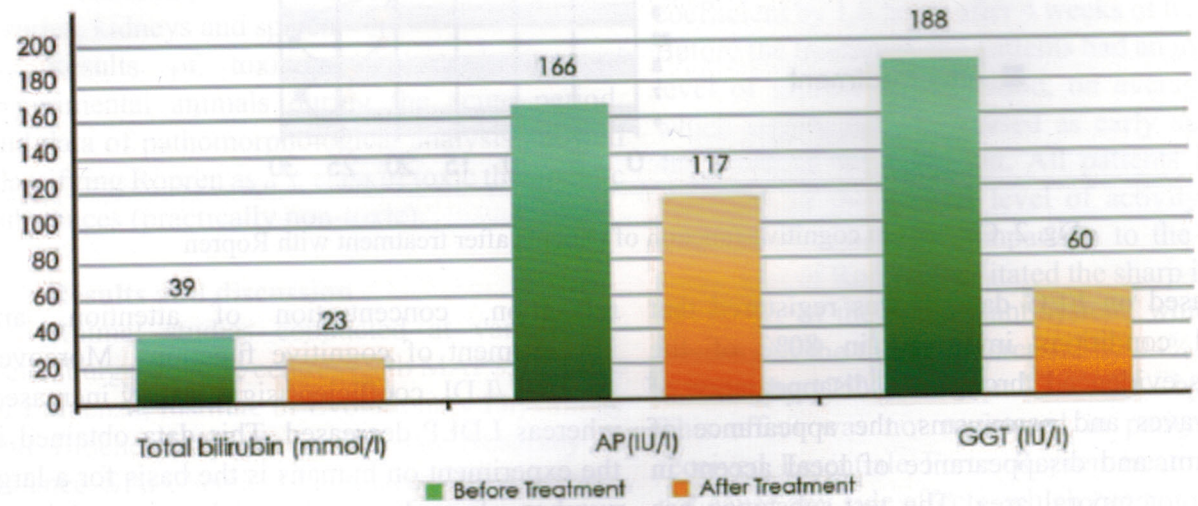



Fig. 3. Reduction of level of cholestasis markers after treatment with Ropren

Before treatment with Ropren, the time for completion of the digital test was on average 90.4±46.0 sec. After the treatment, there was a statistically reliable reduction of its duration up to 74.6±39.0 (t=3.7, p=0.001).

*Evaluation of fibrosis index*

Fibrosis index before the treatment was 6.0±2.1, whereas after the treatment, it was 5.3±2.4 (p=0.04). Fibrosis index is an integral parameter (Table 1). Its statistically reliable reduction is related to the increase of ALT/AST ratio and as a result to the reduction of the corresponding score. The anti-fibrotic effect of the test-substance was assessed by fibroelastomeric data [25].

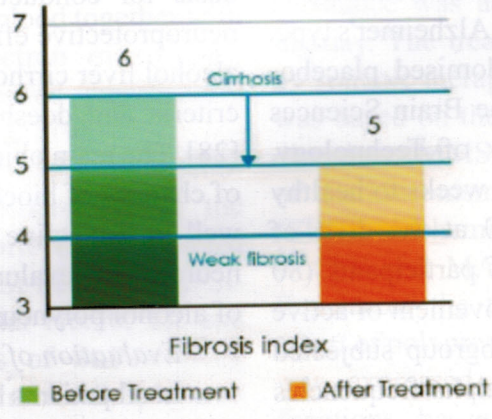



Fig. 4. Anti-fibrotic activity of Ropren (Bonacini M.)

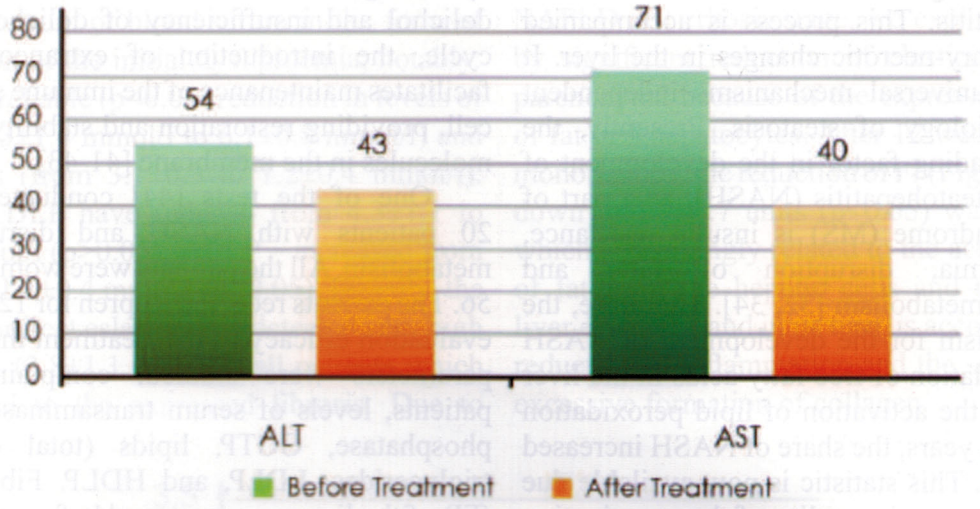



Fig. 5. Evaluation of anti-inflammatory effect of Ropren

*Evaluation of expression of neuropathy symptoms as per Young scale*

Objective evaluation of neuropathy by a neurologist using the Young scale showed that all patients have advanced or severe neuropathy – initial average score was 8.7±1.4. After the treatment, there was statistically reliable reduction of the parameter down to 7.5±1.9 (t=3.2, p=0.0005), Fig.6.

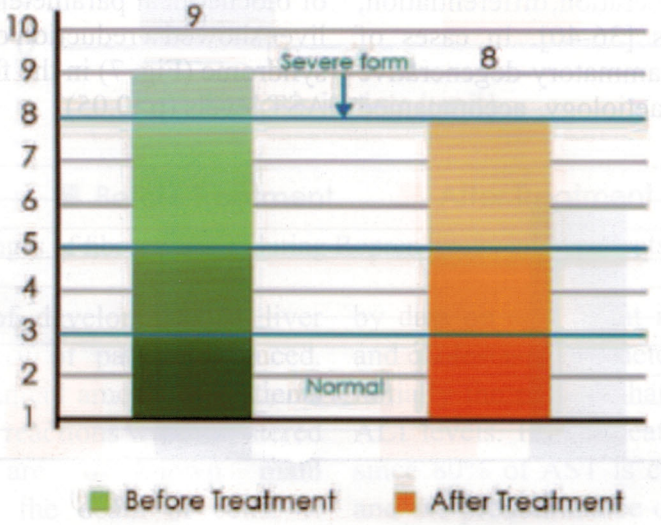



Fig. 6. Neuroprotective effect of Ropren (Young M.J.)

*2. Treatment of non-alcohol liver dystrophy by Ropren*

In recent years, the particular interest of herpetologists around the world is attracted to a non-alcohol fatty liver disease (NAFLD). The accepted risk factors for development of this pathology are obesity, diabetes mellitus II type, fasting, parenteral diet, presence of ileocecal anastomosis and excessive bacterial growth in the intestine, etc. [29, 30, and 31]. Currently, in terms of its topicality this aetiological group of disorders is comparable with viral and alcohol liver damage. Development of NAFLD includes stages of steatosis, steatohepatitis, fibrosis and liver cirrhosis. Liver steatosis is characterised by accumulation of fat in hepatocytes and stellar cells, that in its turn, is conditioned by an increased amount of free fatty acids in the liver due to their high concentration in food and their release during the lipolysis of fatty tissue and transformation into fatty acids because of an excessive amount of carbohydrates entering the liver. The reduction of a β-oxidation rate of free fatty acids in mitochondria and the simultaneous increase of their synthesis is accompanied by disruption in excretion of triglycerides from hepatocytes due to the reduction of synthesis and/or secretion of extremely low density lipoproteins (ELDLP) [32, 33].

The next stage of the disease is the formation of steatohepatitis. This process is accompanied by inflammatory-necrotic changes in the liver. It is based on universal mechanisms independent from the aetiology of steatosis. Presently, the established leading factor in the development of non-alcohol steatohepatitis (NASH), as a part of metabolic syndrome (MS) is insulin resistance, hyperinsulinemia, disruption of fatty and carbohydrate metabolism [32, 34]. Therefore, the main mechanism for the development of NASH is the accumulation of free fatty acids in the liver as a result of the activation of lipid peroxidation [35]. In recent years, the share of NASH increased up to 30-40%. This statistic is now available due to the improvement in quality of the examination of patients; the widespread use in medical practice of ultrasound method of analysis of the peritoneal area and morphological analysis of the hepatic tissue. Currently, non-alcohol steatohepatitis, which is one of the stages of NAFLD, is an individual nosological unit It is known that the dolicholphosphate cycle is a necessary metabolic link in the processes of regeneration, differentiation, and proliferation of cells [36-40]. In cases of acute and chronic inflammatory-degenerative liver diseases of various aetiology, accompanied by damage of cellular membranes and deficit of dolichol and insufficiency of dolicholphosphate cycle, the introduction of extraneous prenols facilitates maintenance of the immune status of the cell, providing restoration and stability of protein molecules in the membrane [41-43].

One of the tests [44] conducted included 20 patients with NASH and disrupted lipid metabolism. All the patients were women aged 38-56. The patients received Ropren for 12 weeks. For evaluation efficacy of the treatment the following parameters were studied: complaints of the patients, levels of serum transaminases, alkaline phosphatase, GGTP, lipids (total cholesterol, triglycerides, LDLP, and HDLP. Fibrosis index (FI) of the liver was measured before and after the treatment using a method of indirect ultrasound elastometry by Fibro Scan.

After 12 weeks of Ropren monotherapy, a reduction of expression of dyspeptic (heaviness in right hypochondrium, flatulence, unstable stool) and asthenic (asthenia, fatigue, sleep disorders) symptoms was registered in all patients. Analysis of biochemical parameters of inflammation in the liver showed a reduction of expression of cytolytic syndrome (Fig. 7) in the form of reduced ALT and AST levels ($p>0.05$).

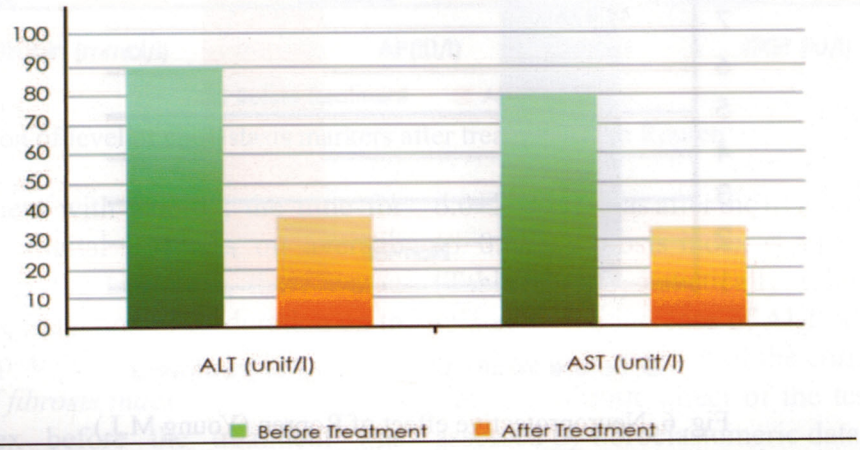



Fig. 7. Changes of transaminases during Ropren treatment in patients with NASH

There was a reduction ($p>0.05$) of activity of cholestasis enzymes - AP and GGTP (Fig. 8)

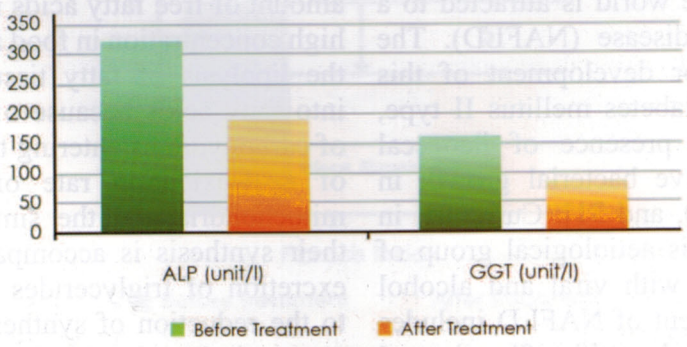



Fig. 8. Changes of cholestasis' enzymes during Ropren treatment in patients with NASH

A positive effect of Ropren was registered on the lipid spectrum of blood serum in the form of normalisation of the initial dyslipidemia, notably: statistically reliable ($p<0.05$) reduction in levels of CS (from 8.3±1.4 mmol/l to 6.1±0.8 mmol/l) and triglycerides (from 3.1±0.3 to 1.2±0.4 mmol/l). Levels of LDLP have reduced from 4.3±1.1 to 2.1±1.0 mmol/l ($p>0.05$), HDLP – increased from 0.75±0.2 to 1.1±0.4 mmol/l ($p>0.05$). Initially, the method of indirect eslastomeria detected very high values of FI (3.8±1.1 units) in all patients which corresponded to the expressed fibrosis. Due to the fact that the group contained no patients with NAFLD at cirrhosis stage, we explained this fact by significant reduction of elasticity of hepatic parenchyma because of the expressed infiltration of fat into hepatocytes. After 12 weeks of Ropren monotherapy, the reduction of FI (Fig.9, see below) down to 1.9±0.7 units ($p<0.05$) was registered , which is seemingly related to the active excretion of fat from the hepatic cells and restoration of liver elasticity, and in its turn, is accompanied by a reduction of inflammation and the suppression of excessive formation of collagen.

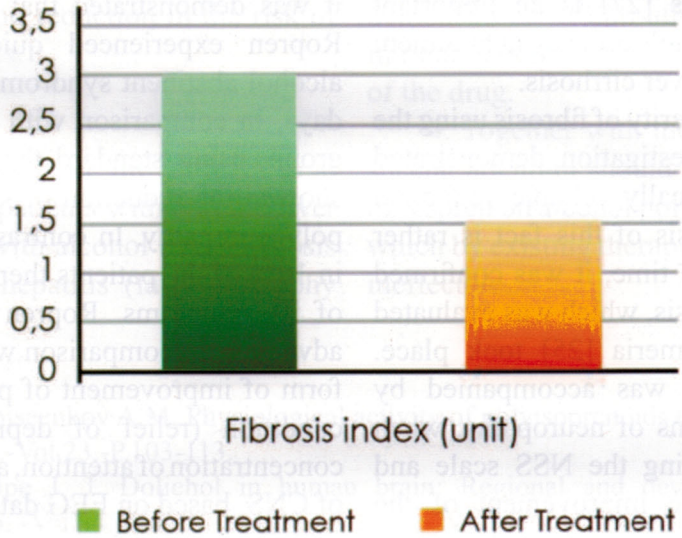



Fig. 9. Changes of fibrosis index during Ropren treatment in patients with NASH

Overall, the risk of development of liver cirrhosis in this category of patients reduced. Commitment to the treatment among the patients was high and no adverse reactions were registered

Presently, there are 6 known main mechanisms leading to the death of cells: 1. Damage of plasmatic membrane and cytoskeleton; 2. Dysfunction of mitochondria; 3. Loss of intracellular ion homeostasis; 4. Activation of enzymes of degradation of substances; 5. Oxidative stress as a result of inadequacy of pro-oxidant and antioxidant resources and 6. Immune mechanisms of hepatotoxicity of the cell. All these mechanisms of liver damage take place in patients with alcohol liver cirrhosis and partially in patients with non-alcohol fatty dystrophy of the liver.

Results of trials involving patients with alcohol liver cirrhosis and NAFLD demonstrated the expressed cytoprotective effect of Ropren against all 6 damaging mechanisms. The reduction of the inflammatory reaction level was indicated by data on significant improvement of cytolysis and cholestasis parameters. It should be noted that initially the patients had AST levels higher than ALT levels. This indicates necrotic inflammation, since 80% of AST is contained in mitochondria and the predominance of AST over ALT activity occurs in the case of necrosis of hepatocytes. No additional treatment with other hepatoprotectors or corticosteroids was used, and therefore, the registered expressed hepatoprotective effect could only have been related to the use of Ropren. The improved functional condition of the liver led to an evident reduction of cholestasis (however, it could also take place due to other mechanisms of action of Ropren). The important mechanism of cytoprotective activity of the drug is its powerful antioxidant activity [25].

The observed anti-inflammatory and anti-fibrotic effects of Ropren can be related to its immunomodulating effect. This hypothesis was made in relation to the evident effect of the drug

that takes place with a short course of treatment. It is known that disruption of immune reactions after prolonged use of alcohol is one of the mechanisms of liver damage. Continuous effect of alcohol activates mediators of inflammation and sensitises T-lymphocytes, increasing by that the production of cytotoxic cells. Hyperproduction of cytokines activates transformation of fibroblasts with subsequent accumulation of excessive collagen and disruption of liver metabolism and leads to misbalance of reparation and regeneration processes in the damaged organ. Therefore, the immunomodulating activity demonstrated by authors in earlier studies [27] is an important additional factor of the drug's efficacy in treatment of patients with alcohol liver cirrhosis.

Evaluation of the severity of fibrosis using the Bonacini index in this investigation, demonstrated that there was a statistically reliable reduction of this parameter. Analysis of this fact is rather complex, but at the same time, it was confirmed that the reduction of fibrosis, which was evaluated by means of fibroelastomeria [25] took place. Treatment with Ropren was accompanied by the reduction of symptoms of neuropathy, when evaluated by patients using the NSS scale and by a statistically reliable improvement of the neurological status. Moreover, a statistically reliable improvement of quality of life in the form of increased vital activities and positive changes in the emotional state of the patients, was noted. This capacity of Ropren to correct somatoneurological consequences of prolonged abuse of alcohol can be explained by the central effect of the test-substance, which consists of moderate psychoactivation, according to literature data [26], mainly due to the capacity to regulate dopaminergic systems of the brain Clinically, this has also been confirmed in a study that included 90 patients with chronic alcoholism, in which it was demonstrated that patients who received Ropren experienced quicker relief from the alcohol abstinent syndrome (on average within 4 days, in comparison with 24 days in the control group, using standard therapy). The same study showed the reduction of symptoms of peripheral polyneuropathy. In contrast to the control group, in 10% of the patients there was total elimination of its symptoms. Ropren also demonstrated its advantage in comparison with basic therapy in the form of improvement of patients' psychosomatic condition (relief of depression), stability and concentration of attention, and functional condition of CNS, based on EEG data [24] (Fig. 10).

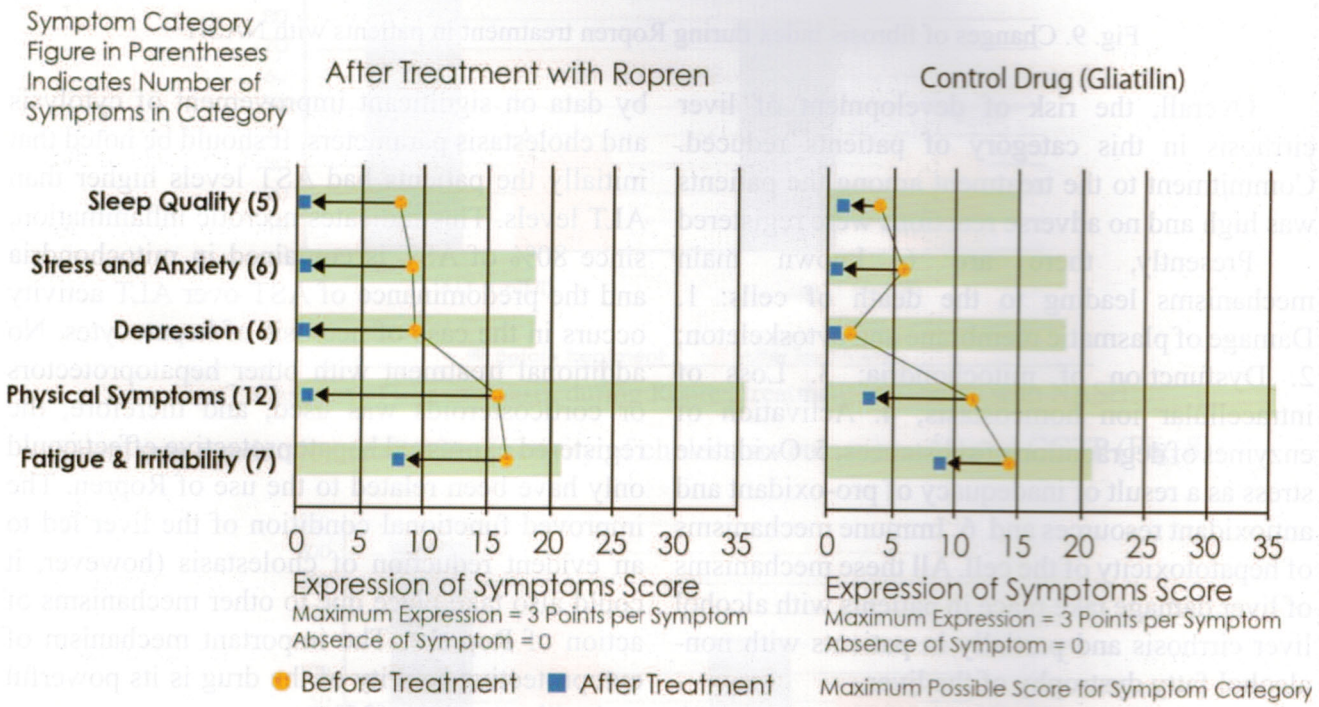



Fig. 10. Changes of severity of symptoms during clinical trials of Ropren

Results of the investigation showed the efficacy of Ropren treatment of patients with alcohol liver cirrhosis. Treatment for 4 weeks of patients with alcohol liver cirrhosis and alcohol polyneuropathy by Ropren leads to a statistically reliable improvement of biochemical parameters

of cytolysis and cholestasis and a reduction of the fibrosis index as well as positive changes (as per Young scale and reduction of symptoms). There was improvement in vital activities of the patients and their emotional state. No side-effects were registered during Ropren therapy, and tolerance to the drug was good.

Results of another trial demonstrated that Ropren is effective in the treatment of patients with NASH. The test-substance reduced clinical biochemical activity of the disease and promoted normalisation of the lipid spectrum of the blood. The reduction in FI indicated the increase in elasticity of the liver and reduction in the risk of development of cirrhosis.

**Conclusions**

The conducted trials on the efficacy and tolerance of Ropren in patients with chronic liver disorders and patients with alcohol liver cirrhosis and non-alcohol steatohepatitis (fatty dystrophy of the liver) allows for making the following conclusions:

1. Ropren is an efficacious and safe hepatoprotector and can be recommended for the treatment of many liver disorders.

2. Special attention should be paid to the following properties of the drug, which can find a practical use: combination of hepato- and neuroprotective properties, anti-fibrotic effect, appearance of the effect after a relatively short course of treatment, antidepressant activity, and improvement of patients' quality of life.

3. Experimental and clinical trials also demonstrated anti-atherogenic, antioxidant, immunomodulating, and anti-inflammatory effects of the drug.

4. Together with the hepatoprotective effect, special attention should also be paid to the effect of Ropren on alcohol polyneuropathy, treatment of which by existing therapeutic methods is currently ineffective.

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## РОПРЕН – БАУЫР МЕН МИ АУРУЛАРЫН ЕМДЕУДЕ ҚОЛДАНЫЛАТЫН ӘЛЕМДЕГІ ЕҢ АЛҒАШҚЫ ПОЛИПРЕНОЛДЫҚ ФАРМАЦЕВТИКАЛЫҚ ПРЕПАРАТ

В.С. Сұлтанов[1], П.Д. Шабанов[2], В.И. Рощин[2]
[1] «Solagran Ltd» компаниясы, Австралия, Мельбурн
[2] РФ Санкт-Петербург ағаш техникалық академиясы, Ресей, Санкт-Петербург қ.

Шолу мақаласында ресейдің фармацевтикалық нарығында пайда болған өсімдіктекті гепатопротектор - жаңа Ропрен препараты туралы мәліметтер келтірілген. Ропрен бауырда долихолға тез ауысатын, мембрандық ақуыздарды гликоздеуге және гликопротеиндердің түзілуіне қатысатын табиғи биореттеуіш, немесе транспорттық липид. Долихолдардың зат алмасуының ең жоғары жылдамдығы бауырда, бүйректе және көк бауырда байқалады. Долихолдарды өтпен шығару оларды ағзадан шығарудың ең басты жолы болып есептеледі. Ропрен препаратын клиникалық тәжірибеде қолдану келешегі мен тәжірибесі келтірілген. Сондай-ақ, препараттың әсер ету механизмдері және полипренолдардың әсер етуінің кең спектрі қарастырылады, полипренолдардың негізінде осы препарат жасалған. Дәлелді клиникалық база жүргізілді, оның нәтижелері препараттың гепатопротекторлық әсерімен бірге нейропротекторлық және антидепрессивтік әсерге ие екендігін көрсетті, сондай-ақ, препараттың антифибротикалық, антиатерогендік және қабынуға қарсы белсенділіктері анықталды. Ол бауырдың түрлі патологияларында, сондай-ақ, бауырдың май жетіспеушілігінде, полинейропатияға жалғасатын алкогольдік бауыр циррозында тиімді.

## РОПРЕН – ПЕРВЫЙ В МИРЕ ПОЛИПРЕНОЛЬНЫЙ ФАРМАЦЕВТИЧЕСКИЙ ПРЕПАРАТ ДЛЯ ЛЕЧЕНИЯ ЗАБОЛЕВАНИЙ ПЕЧЕНИ И МОЗГА

В.С. Султанов[1], П.Д.Шабанов[2], В.И. Рощин[2]
[1] Компания «Solagran Ltd», Австралия, г. Мельбурн
[2] Санкт-Петербурская лесотехническая академия РФ, Россия, г. Санкт-Петербург

В обзорной статье представлены данные о новом лекарственном препарате Ропрен – гепатопротекторе растительного происхождения, который появился на российском фармацевтическом рынке. Ропрен представляет собой природный биорегулятор, или транспортный липид, который в печени быстро метаболизируется в долихол, участвующий в гликозилировании мембранных белков и образовании гликопротеинов. Наибольшая скорость метаболизма долихолов наблюдается в печени, почках, селезенке. Выведение долихолов с желчью считается главным путем выведения их из организма. Представлены перспективы и опыт применения препарата Ропрен в клинической практике. Рассматриваются также механизмы действия препарата и широкий спектр действия полипренолов, на базе которых был создан препарат. Приведена доказательная клиническая база, которая показала, что препарат наряду с гепатопротекторным действием обладает также нейропротекторным и антидепрессивным действием, показана антифибротическая, антиатерогенная и противовоспалительная активность препарата. Он эффективен при различных патологиях печени, в том числе при жировой дистрофии печени, алкогольном циррозе печени, сопровождающемся поли нейропатией.