EXPERT REPORT

- VARUMIN 1 + 2

Inter-Evrogeneks, Novo Selo, R Macedonia
A. **Product profile**

a. **Type of application**

This application endorses the marketing authorization of Varumin 1 + 2.

b. **Chemical and pharmacological properties**

**Qualitative and quantitative composition:**

Varumin 1

100 ml solution contains:
- Water extract of herbal drugs * - 98.7 g
- Aloe - 0.3 g
- Propolis - 0.8 g
- Preservatives (MPB 0.18 g and PPB 0.02 g) - 0.2 g

* 100 ml water extract of herbal drugs contains:
- Visci albi herba (Viscum album) - 1.0 g
- Aqua purificata - ad 100.0 ml

Varumin 2

100 ml solution contains:
- Water extract of herbal drugs * - 99.0 g
- Aloe - 0.8 g
- Preservatives (MPB 0.18 g and PPB 0.02 g) - 0.2 g

* 100 ml water extract of herbal drugs contains:
- Inulae helenii radix (Inula helenium) - 1.6 g
- Visci albi herba (Viscum album) - 1.2 g
- Corni mas cortex (Cornus mas) - 0.6 g
- Calendulae flos (Calendula officinalis) - 1.0 g
- Milefolii herba (Achillea milefolium) - 0.4 g
- Cynodonii rhizoma (Cynodon daetilton) - 1.5 g
- Hyperici herba (Hypericum perforatum) - 1.4 g
- Aqua purificata - ad 100.0 ml

*MPB – methyl hydroxybenzoate
PPB – propyl hydroxybenzoate*

v. **Indications**

Varumin 1 + 2 is used for enhancing the general condition of the organism due to fatigue. It is used to strengthen the organism, as an additional help in the standard therapy for different acute and chronic diseases, malign diseases, anaemia and other conditions of the organism, which are characterized by lowered immunity.

**Posology and method of administration**

Varumin 1. The whole solution should be taken orally as a single dose (50 ml).
Varumin 2. After 6 h of taking Varumin 1, one soup-spoon of Varumin 2 should be taken four times a day (the duration of therapy being 5 days).

g. **Warnings and precautions**

**Contraindications**

This product may lead to oversensitivity to some of the constituents of the product, intestinal obstruction, inflammatory intestinal diseases (Crohn disease, ulcerative colitis), appendicitis and abdominal pain from any kind.

*Pregnancy and lactation* It is generally recommended that this product should be restricted during pregnancy and lactation, although it can be used after the recommendation of a doctor.

Not recommended for children under the age of 10.

**Side effects**

Abdominal pain and spasm, weakness and orthostatic hypotension may appear concerning elderly people. Some individuals can experience cardiac disorders and nephropathy.

**Interactions**

Long-term use of products containing Aloe with products containing cardiac glycosides or medicines for cardiac disorders can lead to excessive loss of potassium and can accentuate the effect of the cardiac glycosides and arrhythmia medicines.

Simultaneous use of products containing Aloe and thiazide diuretics and corticosteroids increases the possibility of potassium loss.

Products containing extracts of *Viscum album* can accentuate the effect of the cardiac glycosides, medicines for hypo/hypertension, antidepressants and anticoagulants.
B Expert Report

1. Introduction

Varumin 1 + 2 is a traditional herbal medical product intended for enhancing the general condition of the organism due to fatigue, for raising the strength and it is used as an additional help in the standard therapy for different acute and chronic diseases, malig

diseases, anaemia and other conditions of the organism, which are characterized by lowered immunity. The product contains two solutions intended for oral administration: Varumin 1 is intended for ‘cleaning’ the organism and for preparation of it for Varumin 2. Taking into consideration the composition and the active ingredients of both solutions, the usage of Varumin 1 eventually manifests a laxative effect and the usage of Varumin 2 results with laxative, anti-inflammatory, antineoelastic, antihyperglycemic, antibacterial, antiviral, immunostimulating and hypotensive effect and agglutinating activity. Several active ingredients show effects over CNS.

For each ingredient in the product Varumin 1+2, sufficient number of evidence can be found in literature; evidence that proves the usage of the above mentioned drugs in conditions previously described as appropriate for the use of Varumin 1+2. A short summary of selected data given below points out the essential information that is relevant for each of the above mentioned ingredients.

Giving details about the active ingredients of Varumin 1, the following ones are worth mentioning: considering Aloe, German Commission E for evaluation of herbal medicinal products approves the use of Aloe (Aloe ferox Mill., Aloe vera Mill., Aloaceae former Liliaceae) in the treatment of constipation as ‘potent colon laxative’ for ‘patients for who an easy defecation with a soft stool is desirable’ (German Commission E Monographs, no. 154, 1985). According to the PDR for Herbal Medicines (2000), Aloe shows laxative, antibacterial/antiviral and antineoelastic effects.

Mistletoe herb (Visci albi herba, Viscum album L., Loranthaceae) is approved by the German Commission E (Monograph no. 228, 1984) for treating of ‘degenerative inflammation of the joints by eliciting cuti-visceral reflexes following local inflammation brought about by intradermal injections’ as well as for ‘palliative therapy for malignant tumors through non-specific stimulation’. According to the PDR for Herbal Medicines (2000), the drug shows hypotensive, cytotoxic and immunostimulative activity. Traditionally, it is used in the folk medicine of the Balkan region for ‘improving metabolism, regulation of high blood pressure, as haemostatic agent and for treatment of CNS disturbances (Dervendzi 1977, Petkov 1982, Tucakov 1984).

Propolis (bee glu) is a material gained by honeybees, well known and used in folk medicine in the world, on the Balkan Peninsula and on the territory of our country (Lukic 1988, Gorunovic 2001). Propolis is still very popular for medical use in traditional systems because it points out antibacterial, antiviral, antifungal, anti-inflammatory and local anaesthetic activity (Evans 2002, Capasso 2003). It has been used for a long time for treatment of laryngitis, gastric disturbances, dermatitis, duodenal and oral ulcers, etc. (Capasso 2003).
Giving details about the active ingredients of Varumin 2, the following ones are worth mentioning: the German Commission E (Monograph no. 85, 1988) approves elecampane root (Inulae heleniume radix, Inula helenium L., Asteraceae) for treating ‘complaints and problems affecting the respiratory and gastrointestinal tract’ as well as ‘for treating problems related to the kidneys and lower urinary tract’. According to the PDR for Herbal Medicines (2000), the drug shows antiphlogistic and antibiotic effects, antifungal, antimicrobial and anthelmintic activity as well as antitumor activity. Traditionally, in the folk medicine of the Balkan people elecampane is used ‘for enhancing the metabolism, treating the illnesses of the respiratory system, as a diuretic and for treating digestive disorders’ (Dervendzi 1977, Petkov 1982, Tucakov 1984).

The bark of the cornel tree (Corni mas cortex, Cornus mas L., Cornaceae) is a drug used in the folk medicine on the Balkan Peninsula for treating abdominal pain and regulating abdominal functions (Petkov 1982, Tucakov 1984).

Marigold flower (Calendulae flos, Calendula officinalis L., Asteraceae) is approved by the German Commission E (Monograph no. 50, 1986) for ‘topical use in treatment of inflammatory changes in the mucous membranes of the mouth and throat’ and ‘for external use in treatment of wounds, including those healing with difficulty as well as for ulcerus cruris (leg ulcers)’. According to the PDR for Herbal Medicines (2000), the drug shows antimicrobial and antiviral effects, topically granulation and epithelisation of damaged skin. Traditionally, in the folk medicine of the Balkan people marigold is used ‘for healing of wounds and ulcers on the skin, for treating inflammations in large intestine, for decreasing abdominal pain, etc.’ (Dervendzi 1977, Petkov 1982, Tucakov 1984).

Yarrow herb (Millefolii herba, Achillea millefolium L., Asteraceae) is approved by the German Commission E (Monograph no. 22a, 1990) for treating of ‘loss of appetite, dyspeptic disorders, such as mild crump-like complaints in the abdominal region, for hepatic and billiard disorders as well as in hip baths for painful, crump-like conditions of psychosomatic origin (in the lower part of the female pelvis)’. According to the PDR for Herbal Medicines (2000), the drug shows holagoge activity, spasmodic, antioedemic and anti-inflammatory effects. Traditionally, in the folk medicine of the Balkan people yarrow is used for ‘treatment of hepatic and billiard illnesses, as haemostatic agent for minor bleeding (from uterus or from hemorrhoids) and for improving the appetite’ (Dervendzi 1977, Petkov 1982).

Cynodonii rhizoma (Cynodon dactilon Pers., Poaceae) is a dried underground part of Cynodon spp. mentioned in the folk medicine of the Balkan people as diuretic agent and drug used for herbal treatment of obesity in a way of losing body mass (Petkov 1982, Tucakov 1984).

St. John’s wort herb (Hyperici herba, Hypericum perforatum L., Hypericaceae) is approved by the German Commission E (Monograph no. 228, 1984) for internal use in the treatment of ‘psychogenic disturbances, depressive states, anxiety, and/or nervous excitement’. For external use, oily hypericum preparations are recommended for treatment and after-treatment of incised and contused wounds, myalgia, and first degree burns’. According to the PDR for Herbal Medicines (2000) the drug shows antidepressive effect after oral administration, and in external use, anti-inflammatory and antimicrobial activity.
Traditionally, in the folk medicine of the Balkan people, St. John’s wort is used for regulating of gastric and intestinal functions, as an aperitif and stomachic, for treating hepatic and billiard disorders, nervous conditions and tensions, insomnia, and externally for healing of wounds, hemorrhoids, for massage in cold and flew conditions and for cleaning the skin’ (Dervendzi 1977, Petkov 1982, Tucakov 1984).

The following dosage is the recommended dosage by the German commission E and PDR for Herbal Medicines for the above mentioned drugs:

Varumin 1:
- *Aloe*: average daily dose 0.05-0.2 g, which suits 10-30 mg hydroxyantraquinone per day or 0.1 g single dose at evening (WHO 1999).
- *Visci albi herba*: recommended single dose for preparation of tea is 2-2.5 g; 2-3 times a day, approximately about 6-7.5 g daily dose.
- *Propolis*: recommended daily dose for oral administration is 3.0 g (Capasso 2003).

Varumin 2:
- *Inulae radix*: average daily dose is about 4 g.
- *Visci albi herba*: recommended single dose for preparation of tea is 2-2.5 g; 2-3 times a day, approximately about 6-7.5 g daily dose.
- *Corni mas cortex*: the drug is used in similar way as *Corni mas fructus* for which recommended single dose is one soup- spoon three times a day (approximately about 30 g per day) (Petkov 1982).
- *Calendulae flos*: single dose for oral administration is 1-2 g (average daily dose 3-6 g).
- *Milefollii herba*: single dose is 2-4 g; average daily dose 6-12 g.
- *Cynodonii rhizoma*: recommended daily dose is 20 g (Petkov 1982).
- *Hyperici herba*: average daily dose is 2-4 g.

Varumin 1+2 is recommended for use in doses which are in accordance with the recommended dosages for the above mentioned drugs which are the active ingredients of this traditional herbal medicinal product. Considering the dosage in which Aloe is taken during the oral administration, it is important to mention that posolgy of Varumin 1+2 has some specifics. The first day the therapy starts with administration of the whole Varumin 1 solution (50 ml that contain 0.15 g aloe). After 6 h of taking the first solution, the patient is supposed to take one soup- spoon of Varumin 2 solution (10-15 ml which contain 0.10-0.13 g aloe) four times a day.

In accordance with the monographs of the German Commission E and relevant data from PDR for Herbal Medicines (2000) as well as other relevant data from literature considering herbal drugs included as active ingredients in traditional herbal medicinal product Varumin 1+2, this expert report provides a critical review of the available pharmacological and toxicological studies, which may contribute to a better understanding of the
pharmacological actions and potential risks associated with the use of drugs within the product Varumin 1+2.

2. Pharmacodynamics

2.1. Active ingredients

Aloe

Aloe is consisted of the juice from the leaves of two species of Aloe plants (A. ferox and A. vera Syn. A. barbadensis), Liliaceae, which has been concentrated and allowed to solidify. Two types of aloe are produced, Aloe capensis or Kap-aloe from A. ferox and Aloe barbadensis or Barbados-aloe from A. vera (A. barbadensis), (Bruneton 1999, Evans 2002, WHO 1999).

Aloe is used as crude or purified drug known as Aloes extractum siccum. Quality standards for crude drug require total contents of hydroxyanthracene derivatives not less than 18% for Aloe capensis and 28% for Aloe Barbadensis, calculated as anhydrous aloin (barbaloin) (Ph. Eur., USP).

Besides hydroxyanthracene derivatives aloin A and B, Aloe contains other anthracene derivatives such as aloinosides A and B, free alo-emodin, 5-hydroxyaloins A and B (for A. capensis) and 7-hydroxyaloins A and B (for A. barbadensis), chromone derivatives of aloeresin group and sugar free aloesones, bitter-substance aloenin, traces of essential oil, mineral elements, etc. (Bruneton 1999, Evans 2002, WHO 1999).

Visci albi herba

Mistletoe herb (Visci albi herba, Viscum album L., Loranthaceae) is dried herbaceous part of the plant mistletoe, which grows as semi-parasite plant on different trees from Rosaceae (such as apple-tree, plum tree, pear-tree, etc).

Mistletoe contains different chemical constituents: triterpenoids and steroids, amines phenols such as flavonoids (e.g. quercetin derivatives), etc. For the biological and pharmacological activity the most important components of the plant belong to several different groups of specific proteins such as viscotoxins A₂, A₃ and B, and lectines (glycoproteins) (ML I, ML II and ML III, (Bruneton 1999, Evans 2002, WHO 1999, Kulevanova 2004).
Propolis

Propolis is a resinous material, dark-coloured collected by honeybees from the buds of living plants mixed with bee wax and salivary secretions (Sljahov 1990, Gorunovic 2001, Evans 2002). Large amount of propolis composition are resins (40-60 %) chemically still unknown, wax (about 30 %) and different impurities (up to 20%).

The active constituents of propolis are phenols and phenilpropanoides, mainly free and ester-bound alcohols (vanilil alcohol), acids (caffeic, ferulic, coumaric), aldehydes and other components such as flavonoids (up to 6.0 %) (Evans 2002), terpenes, lignans, lipids, mineral elements (Mn, Cu, Zn) (Evans 2002), sugars, etc. (Capasso 2003). Depending on the floral characteristics of the geographical origin of propolis, the chemical composition of some constituents varies a lot, qualitatively and quantitatively. Besides other constituents of propolis, this variation mainly refers to flavonoids. Propolis, originated in Europe, is mainly a product obtained by preparation of cuticle waxes from Populus spp., Fagaceae, which consequently gives the reason of a specific flavonoid composition consisting of hrizin, galangin, tektohrizin, acacetin, quercetin, etc. (Gorunovic 2001).

*Inulae radix* (Helenii rhizome)

Elecampane root (*Inulae radix, Inula helenium* L., Asteraceae) is dried root of the elecampane plant, which is native for the southern part of Europe. It is naturalised in central Europe, Near East and North America.

The drug possesses chemical composition characterized by the presence of sesquiterpene lactones (eudesmanolides such as alanaltolactone, isoalantolactone, dihydroalantolactone and others and germacrene D-lactone). The mixture of alantolactone derivatives is known as helenin. Besides them, the drug contains small amounts of essential oil, polyacetylenes, triterpens (friedelin, dammarandienol, dammarandienol acetate), sterols (β-sitosterol and stigmasterol), large quantity of inulin (40%), etc (Wichtl 1994).

*Corni mas cortex*

The drug is represented by dried bark of cornel-tree *Cornus mas* L., Cornaceae. It possesses similar chemical composition to that of the plant fruits (*Corni mas fructus*), containing organic acids, tannins, etc. (Tucakov 1994, Petkov 1982).

*Calendulae floss*

Marigold flowers (*Calendulae flos, Calendula officinalis* L., Asteraceae) are the ray florets of the completely unfolded, collected and dried capitula of the plant. Marigold is native for Europe. Today it is cultivated in the Mediterranean region, Balkan Peninsula, Germany.
The drug is characterized by different classes of chemical constituents: essential oil (0.12-0.40 %) with menthone, isomenthone, γ-terpinene, α-murulene, γ- and δ-cadinene, caryophyllene, α- and β-iunone, geranilacetone, carvone, caryophyllene ketone etc.; sesquiterpenes; flavonol glycosides (3-O-glycosides of isorhamnetin and quercetin, 1.5%); triterpene saponins based on oleanolic acid (2-10 %) (i.e. calendulosides); triterpene alcohols (α- and β-amyrs, taraxasterol, calenduladiol, arnidiol, faradiol, pentacyclic triterpene triols, etc.); carotenes, xanthophylls, polyacetylenes, phenol-carboxylic acids, bitter substances, sesquiterpene lactones, tannins, immunostimulant polysaccharides (rhamnoarabinogalactan and two arabinogalactans) (Wichtl 1994).

**Milefolli herba**

*Milefolli herba* is dried herbaceous part of yarrow (*Achillea milefolium* L., Asteraceae) collected in flowering stage.

The drug contains essential oil (0.2-1.0 %) which depending on the origin, may contain up to 50% chamazulene (azulene chemotype) or no chamazulene (azulene-free chemotype). In azulene type of essential oil large amount of α- and β-pinene are also present, followed by caryophyllene, while in azulene-free type camphor, sabinene, 1.8-cineole, α-pinene and isoartemisiaketone are the major components. Achilicin has been identified as one of the pro-azulenes. Besides this, guaianolides and germacranolides are also present, polyalkynes (pontica epoxide), flavonoids (apigenin, luteolin and their glycosides), phenolic acids, triterpenes, sterols, cyanogenic glycosides, coumarins, tannins, etc. (Wichtl 1994).

**Cynodonii rhizoma**

The drug is represented by dried underground part of the plant *Cynodon dactylon* (L.) Pers., Poaceae. It contains saponins, mucilages, sugars, triticin and other components (Petkov 1982).

**Hyperici herba**

*Hyperici herba* is dried herbaceous part of St. John’s wort (*Hypericum perforatum* L., Hypericaceae) collected in flowering stage.

The major characteristic constituents of the drug include: 0.05-0.30 % naphthodianthrones (hypericin, pseudohypericin and related components); 2-4% flavonoids, derivatives of quercetin (hyperoside, quercitrin, isoqueritin, rutin) and apigenin (biapigenin), up to 3% hyperforin and related phloroglucinols, structurally close to the bitter substances of hops, up to 0.3% essential oil, up to more than 10% tannins, small amounts of procyanidins, etc. (Wichtl 1994).
2.2 Specific Pharmacodynamics

2.2.1 Laxative effect

The laxative effect of Varumin 1+2 is due to the component Aloe. Anthraquinone glycosides from Aloe are responsible for the activity. After oral administration, anthraquinone glycosides under the influence of the intestinal bacterial flora and the enzyme glycosidase are hydrolyzed to the active anthrone which stimulates colonic motility over the inhibition of Na⁺/K⁺-pump and chloride channels. This leads to increased secretion of the liquids in the colon happening because of the stimulation of mucosa and chloride secretion (De Witte 1993, Ishii 1990).

The laxative effect of Aloe is tested on rats. Nine hours after the administration of aloe, diarrhea was caused in different dosages such as 5g/kg (20%) and 20g/kg (100%) (Barnes 2002, PDR for Herbal medicines 2000, WHO 1999, Izzo 1999). Research has shown that the influence of a larger number of anthraquinones and anthrones (23 different constituents) over the activation of Cl⁻-channels in Ehrlich tumor cells leads to inhibition of the activity, especially in the case of aloe-anthrone or emodin-anthrone (Hoenig 1992). In many cases, these anthraquinones reduce the chloride cell permeability even more than the Cl⁻-channel block 130B does it. On the other hand, both components do not show inhibiting action over Na⁺/K⁺-ATPase (Hoenig 1992). Rhein, frangula-emodin and other anthraquinones with additional phenol function show inhibition also (Hoenig 1992).

Research has shown that the laxative effect of the aloein and 1.8-anthraquinones can relatively depend on the synthesis of the prostaglandines in the intestinal tissue (Capasso 1983). Nitric oxide (NO) may possibly be the mediator of the laxative effect over the anthraquinone products (Izzo 1999).

The effect of the rein and aloe-emodin is compared with the effect of the ricinoleic acid and calcium ionophore A23187 over the release of the thromocyte-activating factor (PAF) from human gastrointestinal piece in vitro. It is confirmed that the rhein does not have any activity and that the activity of aloe-emodin is determined by the activity of the other components (Tavares 1996). Later, it was confirmed that the inhibition of Na⁺/K⁺-ATPase and the release of NO are relevant in stimulating secretion of electrolytes and relaxation of smooth intestinal mucosa and that NO plays significant pathophisiological newly-confirmed role in relation to PAF, which provokes contractions of the smooth muscles (Longo 2002). Although the above mentioned data comes from experimental animal studies, no general conclusion can be made that biological factors PAF and NO have their role in stimulating the colon (Assement report of HMPC for Aloe 2007).
2.2.2. Anti-neoplastic activity (cytotoxic activity)


Antitumor effects of 5 Aloe components (aloins A and B, aloesin, aloeresin, aloe- emodin) were studied on human K562 leukaemia cells and on the multidrug resistant b(MDR) variant cell line, k562/R. Only the aglycone aloe- emodin produced reproducible antitumor effects. Aloe- emodin caused mainly cytostasis and accumulation of the cells in S and G2-M phases of the cell cycle during the first 48h of treatment. In another study, chemopreventive role of aloe- emodin in human promyelocytic leukaemia HL-60 cells in vitro was evaluated. It was concluded that aloe- emodin appeared to exert its anticancerogenesis properties by inhibiting proliferation and inducing cell cycle arrest, and apoptosis underwent activation of caspase-3 in human leukaemia HL-60 cells (Chen 2004).

Cytotoxic activity of mistletoe extract and isolated mistletoe glycoproteins has been investigated in vitro and in vivo studies. Significant antitumour activity has been observed in vivo for mistletoe extract against murine tumour, Lewis lung carcinoma, colon adenocarcinoma 38 and C3H mammary adenocarcinoma 16/C (Khwaja 1986). Sensitivity to mistletoe extract has been documented for acute lymphoblastic leukaemia (Newall 1986).

Cytotoxic activity in vitro and antitumour activity in vivo (against mouse Ehrlich carcinoma) have been documented for marigold extracts. The most active fractions in vivo were saponin-rich fraction (Boucard-Maitrey 1988).

Numerous in vitro studies have demonstrated that hypericin is a potent inhibitor of protein kinase C (Agostinis 1995, De Witte 1993, Zhang 1996). Hypericin treatment of glioma cell lines inhibited growth and induced cell death due to protein kinase C. Receptor tyrosine kinase activity of epidermal growth factor is also inhibited by hypericin and may be linked to its antiviral and antineoplastic effects (De Witte 1993, Panossian 1996). In vitro cytotoxicity against human colon carcinoma cells (CO 115) has been described for hyperforin-related constituents, isolated from Hypericum calycinum and H. revolutum (Newall 1996).

2.2.3. Immunostimulant and immunomodulatory effects

Extracts of mistletoe herb and isolated polysaccharides of the plant demonstrate non-specific immunostimulant activity, which depends on the frequency and the quantity of the applied extract (Newall 1996).

Nowadays, there is no more doubt about the effect of mistletoe extracts on immune reactions in vivo and in vitro and it is clear that different antigens presented in these extracts can modulate various cell types of the innate and adaptive immune system (Klein 2007). Mistletoe lectin (ML-1), especially, has shown itself to be responsible for a variety of
immunological reactions as well as other components such as viscotoxins, oligo- and polysaccharides, which exert immunostimulatory properties. Hence, analyzing the effect of mistletoe extracts on immune competent cells in vivo in tumor patients or healthy volunteers or even in vitro one is confronted with equation with many unknown variables (different components of the immune system altered immune system in tumor patients, different antigens in the mistletoe extracts, etc.). The modern techniques of immunology have made it possible to analyze the effect of different components of the extracts on specific cell subtypes such as natural killer (NK) cells, neutrophils, B-cells, or some T-cells. It became evident that antibodies of different kinds of antigens in these extracts are produced during therapy depending on the amount of these antigens in the respective extracts. The activation of antigen-presenting cells, NK-cells and T-cells is obvious and a release of different cytokines may be responsible for the various beneficial clinical effects but (although rarely observed) the adverse reactions during this kind of therapy. It is a fact that despite all efforts to analyze the effect of mistletoe extracts on immunocompetent cells during the last 20-30 years it is, however, still unknown whether the observed alterations of immunological reactions during mistletoe therapy have any effect indeed on the tumor defense and survival of tumor patients (Klein 2007).

Extracts of propolis and isolated components of propolis demonstrate activity on the immune system. Ethanol extract of propolis induces antibody production by mice spleen cells. Propolis modulated both in vivo and in vitro C1q production by macrophages as well as the action of complement system receptors on these cells (Dimov 1991, 1992). Some components of propolis (i.e. cinnamic acid) act on host defense, stimulating lymphocyte proliferation and inducing IL-1 and IL-2 production (Ivanovska 1995), and tend to inhibit H2O2 release by peritoneal macrophages or induce increased metabolic production. Other study shows that propolis action on natural killer cell activity increased its lytic capacity against tumor cells (Sforcin 1996). Some authors suggest that immunostimulant activity of propolis may be associated with macrophage activation and enhancement of macrophage phagocytic capacity (Scheller 1989, Tatefuji 1996).

Extract of marigold that contains some specific high molecular weight polysaccharides shows immunostimulant activity in granulocyte and carbon clearance tests (Wagner 1985).

2.2.4. Agglutinating activity

Lectin fraction of mistletoe herb shows agglutinating activity. Lectins are glycoproteins capable for binding to large number of cells including erythrocytes, lymphocytes, leucocytes, macrophages, glycoproteins and plasma proteins (Newall 1996).

2.2.5. Hypotensive effects

The hypotensive effect of mistletoe herb is attributed to various biologically active constituents. The exact nature of the hypotensive effect remains unclear, although it has
been reported that the activity is mainly due to an inhibitory action on the excitability of the vasomotor centre in the medulla oblongata (Petkov 1979, Newall 1986). In addition, it has been stated that the hypotensive action of mistletoe is mainly of a reflex character, exerting a normalizing effect on both hypertensive and hypotensive states (Petkov 1979). The effect of different mistletoe plant parts and host-plant on the hypotensive activity has been studied with highest activity reported for mistletoe leaves parasitizing on willow (Petkov 1979).

Sesquiterpene lactones from elecampane root show hypotensive effect (Newall 1996).

Sesquiterpene lactones from yarrow show hypotensive activity (PDR for herbal Medicines 2000, Barnes 2002).

2.2.6. CNS effects

Water extract of elecampane root shows sedative effect on CNS (Newall 1996).

Extracts of St. John’s wort (hypericin, xanthines and flavonoids) show antidepressive, antineurotic and anxiolitic activity (Barnes 2002, Evans 2002, Petkov 1982, Newall 1996). Anti-depressive activity of St. John’s wort has been demonstrated in many studies in vitro. The European commission categorizes St. John’s wort as MAO-inhibiting plant. Results obtained from in vivo studies revealed that MAO-inhibiting action has very low intensity and it is due to hyperforin, flavonoids (aglycons and quercitrin), less to hypericin. All of the mentioned components act as anxyolitics by inhibition of type A MAO. Extracts of St. John’s wort, due to their CNS activity, are used for treating insomnia, epilepsy, middle neurotic states, etc. (WHO 1999, Barnes 2002, PDR for Herbal Medicines 2000, Bruneton 1999, Dewick 1997, Newall 1996).

A commercial extract of St. John’s wort has exhibited psychotropic and antidepressant activities in mice (Okpanyi 1987). It has been suggested that biflavonoids may be sedative principal in the extract (Berghofer 1987, 1989), while for hypericin is stated that in small quantities it has tonic and tranquilising action in human (Newall 1996).

2.2.7. Antibacterial and antiviral activity

Anthraquinone derivatives from Aloe show antibacterial activity, which is confirmed in vitro on Mycobacterium tuberculosis and Bacillus subtilis (MICs 0.125 mg/ml and 0.25 mg/ml respectively). Aloe-emodin is considered to be particularly active component that in certain doses inhibited growth of Helicobacter pylori and four different species of Staphylococcus aureus, which demonstrated resistance to methicillin (Barnes 2002, PDR for Herbal Medicines 2000, Heinrich 2004). Aloe-emodin shows direct antiviral activity on Herpes simplex virus type 1 and 2, Varicella zoster virus, Pseudorabies virus and Influenza virus (Barnes 2002, PDR for Herbal Medicines 2000).

Extracts of elecampane root and isolated sesquiterpene lactones (alantolaktone, isoalantolaktone and other lactones) show antimicrobial and antifungal effects (Newall 1996).

Extracts of marigold (flavonoids and essential oil) show antibacterial and fungicidal activity (Barnes 2002).

Ethanol extracts of yarrow demonstrate middle antimicrobial activity on *Staphylococcus aureus*, *Bacillus subtiliss*, *Mycobacterium smegmatis*, *Escherichia coli*, *Shigella sonnei* and *Schigella flexneri* (Moskalenko 1986). Sesquiterpene lactones are confirmed to be the components responsible for the activity (Chandler 1982).

Phenolic components of St. John’s wort show antimicrobial activity (Barnes 2002, Evans 2002, Newall 1996). In the older literature, some authors cited that St. John’s wort isolates such as novomain, water-soluble imanin and imanin were strong antimicrobial agents (Newall 1996). It is also published that novomanin is potent topical antimicrobial agent against *Staphylococcus aureus*, with activity better than that of sulphanalamide (Newall 1996). Extract of St. John’s wort are active on staphylococci, shigelleae, Escherichia coli (Sakar 1986, Koesnikova 1986). The fractions that contain flavonoids and catechins show antiviral activity on Influenza virus in range 83-100 % (Mishenkova 1975). Antiviral activity is published for hypercin against HIV and hepatitis (Newall 1996).

2.2.8. Anti-inflammatory effect

Water extract of Aloe inhibits releasing of histamine from peritoneal mast cells in animal models (rats) in which the releasing of histamine was induced by antigen stimulation (Yamamoto 1993, Barnes 2002, PDR for Herbal Medicines 2000).

Extracts and isolated components of elecampane root show antiflogistic effects (Evans 2002, Newall 1996).

Some components of propolis like caffeic acid methyl ester and flavonoids (galangin) are pointed out as components responsible for the extensive anti-inflammatory effects of propolis, performed via inhibition of COX II enzymes, which are important for production of inflammatory prostaglandins and for inhibition of NF-kB (Capasso 2003). It was found that
propolis promotes local leukocytosis (Capasso 2003). Anti-inflammatory and analgesic effects of a standard ethanolic extract of propolis were tested on mice (Paulino 2003). The extract inhibited abdominal contortions with an ID$_{50}$ = 7.4 mg/kg. In the formalin test the extract caused a significant reduction of pain in mice treated with 100 mg/kg of extract during the neurogenic phase and for the inflammatory phase with all doses of the extract, with an ID$_{50}$ = 2.5 mg/kg. Ethanol extract of propolis inhibited also the capsaicin-induced ear edema in mice. The analgesic effect of the extract was associated with the inhibition of inflammatory responses and not to a simple irritation of nervous terminals (Paulino 2003). In other study, inhibition of dyhydropfolat-reductase was found, due to the activity of caffeic acid (Strehl 1994).

Anti-inflammatory activity has been documented for aqueous extract of yarrow using mouse and rat paw oedema models, with inflammation induced by yeast and various inflammatory substances including histamine, carageenan and prostaglandin (Barnes 2002, Newall 1996). In general, anti-inflammatory properties are associated with components of the essential oil of yarrow, particularly for azulenenes (Evans 2002, Newall 1996, Miller 1998).

Alcohol extract of marigold acts as an anti-inflammatory agent (Mills and Bone, 2000). The activity is probably due to the triterpenoid esters (Barnes 2002, Newall 1996). In experimental models on rat marigold extracts in combined products was effective in dextran and burn edemas and in acute lymphoedema. Activity against lymphoedema was primarily attributed to an enhancement of macrophage proteolytic activity (Casley-Smith 1983).

St. John’s wort extract prepared with vegetable oil has a long reputation as an anti-inflammatory and wound healing agent (Samuelsson 1999, Bruneton 1999, WHO 1999, Bombardeli 1995). The anti-inflammatory effect is probably due to the activity of hypericin which demonstrates protein kinase C inhibition as well as inhibition of releasing of arachidonic acid and leucotriene B$_4$ (Panossian 1996). St. John’s wort extract was found to suppress inflammation in mice induced by carageenan and PGE1 (Schipochliev 1981). Anti-inflammatory and antiulcerogenic properties have been documented for amentoflavone, a biapigenine derivative (Berghofer 1989).

2.3. Interaction

Long-term use of product containing Aloe with product containing cardiac glycosides or medicines for cardiac disorders (arrhythmia) can lead to excessive loss of potassium and can accentuate the effect of cardiac glycosides and arrhythmia medicines. Simultaneous use of product containing Aloe and thiazide diuretics and corticosteroids increases the possibility of potassium loss (Newall 1996).

Product containing extracts of Viscum album can accentuate the effect of cardiac glycosides, medicines for hypo-hypertension, antidepressants and anticoagulants (Newall 1996).
Simultaneous use of products containing elecampane extract with hypoglycemic and antihypertensive medicines may cause interactions (Newall 1996).

Overdose of yarrow may interfere with anticoagulant and antihypertensive therapy (Newall 1996).

No data is published on interactions of marigold, cynodon or cornel-tree.

Product containing St. John’s wort extract may decrease the effects of theophylline, cardiac glycosides, cyclosporine and warfarin (Nebel 1999, Johne 1999, WHO 2002). FDA has reported serious interaction between St. John’s wort extract and indinavir, a protease inhibitor, used in treatment of HIV infections (Piscitelli 2000).

3. Pharmacokinetics/ Bioavailability

No pharmacokinetic data is available for water extracts of herbal drugs: aloe, mistletoe herb, propolis, elecampane root, marigold, yarrow, cornel-tree bark, Cynodonii rhisoma, and St. John’s wort. Certain number of data could be found considering pharmacokinetics of some active constituents of above mentioned drugs, obtained in animal studies for aloins from aloe, lectins and voscotoxins from mistletoe and hypericin, hyperforin and quercetin from St. John’s wort, etc. No pharmacokinetic data is available for the active constituents from elecampane, marigold, cynodon or cornel-tree. The following data may be considered as corresponding to this report:

Aloins A and B, hydroxyaloins and aloinosides A and B are not absorbed in the upper gut. In humans, they pass into the colon unmodified after oral ingestion. Human intestinal flora are able to break down O-glycosides easily but only to some extent C-glycosides of most anthranoides. Experimental studies on rats resulted positively only in gnotobiotic rats mono-associated with the Eubacterium sp. BAR in which administration of barbaloin causes severe diarrhea. Only in those rats, barbaloin was transformed to aloe-emodin athrone, which is responsible for the laxative effect. In contrast, another study showed that aloe-emodin-9-anthrone was produced in the rat large intestine, as main active metabolite, which acts specifically on the colon (Assessment report on Aloe barbadensis and aloe HMPC, 2007). After oral administration of 4.5 mg/kg 14C-aloe-emodin to rats, 20-30% of the dose was excreted in urine and the rest in faeces. Aloe-emodin was quickly metabolized to rhein, to an unknown metabolite and to conjugates of all three. In the plasma 10% of 14C-activity was identified as free aloe-emodin. Maximum plasma values were reached 1.5-3 h p.a. with 248 (male) and 441 (female) ng equivalents aloe-emodin/ml. Maximum concentrations in plasma were about 3 times higher than those in ovaries and 10 times higher than those in testes. Only liver, kidney and intestinal tract showed higher concentrations than plasma. Terminal half-life (for radioactivity) in blood was about 50 h (Assessment report on Aloe barbadensis
and aloe HMPC, 2007). The ESCOP monograph mentioned research report of a human pharmacokinetic study, in which after oral administration of aloe (equivalent to 16.4 mg of hydroxyanthracene derivatives) for 7 days, aloe-emodin was detected as a metabolite in the plasma only sporadically and with maximum concentrations of less than 2 ng/ml. In the same study rhein was detected in the plasma in concentrations ranging from 6-28 ng/ml after single dose administration. There was no evidence of accumulation of rhein (Assessment report on Aloe barbadensis and aloe HMPC, 2007).

The pharmacokinetics of mistletoe lectins from whole plant mistletoe extract is still unknown. Studies with intravenous application of a recombinant type II ribosome inactivating protein analogous to mistletoe lectin revealed a short half-life of about 13 min in cancer patients (Huber 2007).

Limited summary information is available on the pharmacokinetics of hypericin and pseudohypericin in mice and humans. After oral administration of 14C-labelled hypericin and pseudohypericin to mice, these substances are absorbed to 80% and 60%, respectively. In humans, after oral administration of hydromethanolic extract of Hypericum perforatum, containing 0.1% total hypericin (300 to 1800 mg per person) a plasma half-life of approximately 6 h was observed for hypericin. After administration of an extract containing 0.3% total hypericin, the plasma half-life was approximately 25 h for hypericin and 16 to 36 h for pseudohypericin (Summary report on Hypericum perforatum, EMEA/MRL 1999).

4. **Toxicology**

4.1. Side-effects

Possible side effects of Varumin 1 + 2 can be expected from active ingredients such as Aloe. The side effects of this drug are well documented in literature: abdominal spasms and pain may occur after even one single dose of Aloe. Overdose can lead to colicky abdominal spasms and pain, as well as formation of thin, watery stool. Prolonged use of anthraquinone laxative (aloe) may lead to electrolyte disturbances (hypokalaemia, hypocalcaemia) in more serious cases metabolic acidosis, malabsorption, weight loss, albuminuria and haematuria. Weakness and orthostatic hypotension may be exacerbated in elderly patients when stimulant laxatives are repeatedly used. Melanotic pigmentation of the colonic mucosa has been observed in individuals taking anthraquinone laxatives for extended periods. The pigmentation is clinically harmless and usually reversible within 4 to 12 months after the drug is discontinued (Muller-Lissner 1993). Chronic abuse of anthraquinone laxatives may lead to hepatitis (Beuers 1991). Conflicting data exist on other toxic effects such as intestinal-neuronal damage after long-term use (Muller-Lissner 1993).

Products that contain extracts or isolated components of mistletoe can cause side effects such as headache, high fever, anginal problems, orthostatic circulatory disorders, and allergic reactions (German Commision E Monograph no. 228).
Propolis is considered relatively safe for usage. However, some data shows a familiar and an unfamiliar sensibilating activity during the use of propolis that is manifested as an allergic eczematous contact dermatitis in case of allergic predisposition on bee sting (Capasso 2003). There are some cases when acute oral mucosis was caused by the use of propolis-containing lozenges (Capasso 2003).

There is no data published indicating side effects from the use of cornel-tree (Petkov 1982).

There is no data published indicating side effects from the use of marigold (Newall 1996).

Yarrow may cause allergic reactions in individuals hypersensitive to other Asteraceae plants (Newall 1996).

There is no data published indicating side effects from the use of Cynodoni rhizoma (Petkov 1982).

St John’s wort, in the Monography of the German Commission E, is highlighted as the possible arouser of photosensitivity that occurs very rarely in people with fair complexion (Wichtl 1994, The Complete German Commission E Monographs 1998). This photosensitivity is demonstrated also in clinical studies in individuals that have been taking hypericin and have been exposed to ultraviolet A and B radiation (WHO 2002). A patient, who was treated with 600 mg of a hydroalcoholic extract of the herb (containing 0.24-0.32 % total hypericin) three times a day for 15 days, showed a significant increase in erythema due to the ultraviolet A irradiation. The plasma concentration of hypericin in this subjects was double that seen during normal therapeutic treatment of depression (WHO 2002). Monitoring studies have been done for products based on St John’s wort that show that the drug produces rare and mild types of side effects such as gastrointestinal irritation, allergic reactions, fatigue etc. (Linde 1996, WHO 2002, Capasso 2003).

4.2. Contra-indications, Warnings

Products containing Aloe should not be used by patients that suffer intestinal obstruction or stenosis, dehydratation or chronic constipation (WHO 1990), inflammatory intestinal diseases such as appendicitis, Crohn disease, ulcerative colitis, irritable bowel syndrome, etc. (Wichtl 1994). Aloe is not recommended for children under the age of 10. Women are not supposed to take Aloe during pregnancy and lactation unless it is recommended and supervised by a doctor (Wichtl 1994). Patient with cramps, colic, hemorrhoids, nephritis, or any undiagnosed abdominal symptoms such as pain, nausea or vomiting (WHO 1999) should not take aloe. Prolonged use of products containing Aloe can lead to hypersensitive reactions manifested in dermatitis and eczematous formations, loss of electrolytes (potassium) that may result in hiperaldosteronizam, inhibition of intestinal motility and
emphasize the effect of cardiac glycosides, gastrointestinal disorders, cardiac disorders and rarely nephropathy and albuminuria and haematuria (WHO 1999, Gooding 1976).

In animal studies, some chemical components of mistletoe (tyramin and cardioactive components) stimulated the uterus (Newall 1996). Due to lack of relevant data, taking into consideration the toxicity of the drug, the use of it during pregnancy and lactation is highly restricted (Newall 1996). Products containing extracts from mistletoe are not to be used together with cardiotonic, immunosuppressive, anti-hypertensive, antidepressive and anticoagulant therapy (Hulsen 1987). The use of mistletoe is contraindicated in cases of protein hypersensitivity and chronic progressive infections such as tuberculosis (German Commision E Monograph no. 228).

Products containing extract from the root of elecampane can cause allergic reactions (Newall 1986). The components of essential oil, alantolactone and isoalantolactone can lead to sensitivity (Stampf 1982, Newall 1986). Due to lack of toxicological data, the root of elecampane should not be used during pregnancy and lactation (Newall 1996).

Marigold is traditionally known as drug affecting the menstrual cycle. In vitro studies have shown uterotonic effects of the drug and triterpeoid constituents are reported to be effective as spermatocides and as antiblastocyst and abortion agent (Newall 1996). Due to lack of toxicological data, the use of marigold during pregnancy and lactation is not recommended (Newall 1996).

The use of propolis is contraindicated in cases when patients manifest allergic reactions due to bee sting (Capasso 2003).

Yarrow can cause allergic reactions in sensitive patients, especially those that are sensitive to the plants from Asteraceae (Mathias 1979). Patients sensitive to these plants should not take them in any form (Tyler 1993). Traditionally, yarrow is considered as abortive and drug that affects the menstrual cycle. Due to lack of toxicological data, the use of yarrow during pregnancy and lactation is not recommended (Newall 1996).

Prolonged insolation or exposion to UV-light should be avoided during the use of products containing extracts from St Jonh’s wort because it may lead to photosensitive reaction (Wichtl 1994). The use of St Jonh’s wort is contraindicated in cases when there is an allergy to the plants from Hypericaceae (WHO 2002).

4.3. Toxicity

Data on the carcinogenicity of Aloe are not available. While chronic abuse of anthranoid-containing laxatives was hypothesized to play role in colorectal cancer, no causal relationship between anthranoid laxative abuse and colorectal cancer has been demonstrated (Siegers 1992, WHO 1999). In animal studies on mice, administration of Aloe
50 mg/kg in a period of 12 weeks did not cause serious pathological disturbances; although it increased the concentration of sorbitol dehydrogenase, which may be connected with eventual hepatic damage (Barnes 2002, PDR for Herbal Medicines 2000).

Intravenous administration of viscotoxin (isolated from mistletoe) to cats (35 μg/kg) resulted in a negative inotropic effect on cardiac muscle, reflex bradycardia, and hypotension. Viscotoxin A₁ and B have caused muscle contracture and progressive depolarization in isolated smooth, skeletal or cardiac muscle preparation. Viscotoxin is toxic on paranthelial administration and an LD₅₀ value (mice, intraperitoneal injection) has been estimated as 0.7 mg/kg. Mistletoe lectins inhibit protein synthesis in cells and cell-free systems. In common with other known toxic lectins (e.g. ricin), mistletoe lectins bind to plasma proteins, are specific towards D-galactose, posses some cytotoxic activity and have caused macroscopic lesions in rats. An LD₅₀ (mice) value for mistletoe lectin fraction is reported as 80 μg/kg. In animal studies, the simulative effect on the uterus by tiramin was observed, isolated from mistletoe extract. Because of possible stimulation of the uterus, mistletoe is not recommended for use during pregnancy and lactation (Barnes 2002, PDR for Herbal Medicines 2000, Newall 1996).

Symptoms of toxicity documented following the ingestion of mistletoe include hypotension, coma, seizures, myosis, mydriasis and death (Barnes 2002, PDR for Herbal Medicines 2000, Newall 1996). One case of hepatitis is reported for woman who had ingested a mixed herbal preparation containing mistletoe (Barnes 2002).

Yarrow is considered non-toxic (Newall 1996). In mice LD₅₀ values have been reported of up to 3.65g/kg (by mouth), 3.1g/kg (by intraperitoneal injection), and greater than or equal to 1 g/kg (by subcutaneous injection). In the rat an LD₅₀ (subcutaneous injection) has been recorded as 16.86 g/kg, with corresponding LD₀ and LD₁₀₀ values reported as 12 and 20 g/kg, respectively (Newall 1996). For comparison, an ED₂₅ for anti-inflammatory activity has been estimated as about 0.43 g/kg (Shipochliev 1984). Terpenoid-rich essential oils are defined as irritant agents and the same may be implied for yarrow essential oil (Newall 1996). A toxic constituent of the oil (thujone) is presented in yarrow essential oil in concentration that could not be harmful for patients (Newall 1996).

The mutagenity of hydroalcoholic extracts of St. John’s wort containing 0.2-0.3 % hypericin and 0.35 % quercetin has been studied in various in vitro and in vivo systems. Although some positive results were observed in vitro, all the in vivo tests were negative, indicating that hydroalcoholic extract was not mutagenic in animals (Schimmer 1988, 1994). In a 26-week study, intragastric administration of a hydroalcoholic extract to rats and dogs (900 and 2700 mg/kg body weight) had no effect on fertility, development of the embryo, or prenatal or postnatal development (Leuschner 1996). According to EMEA report on St. John’s wort, there is no data on acute toxicity, reproductive toxicity or teratogenicity as well as for carcinogenity for St. John’s wort (Summary report on Hypericum perforatum EMEA 1999).
5. **Summary and conclusions**

5.1. Pharmacodynamics

Varumin 1+2 is a traditional herbal medicinal product (solutions for oral use) containing aloe, propolis and water extract from mistletoe in Varumin 1 and aloe and water extract from herbal drugs (mistletoe, elecampane, cornel-tree bark, marigold, yarrow, cynodon and St John’s wort) in Varumin 2. The product is used in the following manner: single Varumin 1 dose of 50ml is taken (the whole solution should be consumed) and 6 hours after the consummation of Varumin 1, Varumin 2 should be consumed by taking one soup-spoon on every 6 hours.

Varumin 1+2 is intended for enhancing the general condition of the organism due to fatigue, for raising the strength and it is used as an additional help in the standard therapy for different acute and chronic diseases, malign diseases, anaemia and other conditions of the organism which are characterized by lowered immunity.

There is vast amount of data stating the traditional use of the drugs that are active ingredients in this product. They are used in both folk and scientific medicine. Different drugs, from whose water extracts this product is made of, may have laxative, anti-inflammatory, antimicrobial, immunostimulative and immunomodulatory effects as well as cytotoxic, antidepressive, antihypertensive and agglutinating influence. The pharmacodynamic characteristics are in accordance with the recommended uses of Varumin 1+2. Additionally, it is very important to mention that there has not been found any data about possible incompatibility or interaction between the componential drugs of this product.

5.2. Pharmacokinetics

There is no pharmacokinetic data about the water extracts from the drugs that are active components of Varumin 1+2. There is very limited data about the chemical constituents of some of the drugs such as anthraquinone glycosides of aloe, lectins of mistletoe as well as hypericin from St. John’s wort. However, the data is insufficient for any conclusion considering the pharmacokinetics of this product.

5.3. Toxicology

There is no data about acute and subacute toxicity of Varumin 1+2 as well as the active components of the product. However, there is limited data about the toxicity of some of the drugs such as aloe (indication of eventual hepatic damage in chronic abuse of athonoid laxatives) and for viscostoxins and crude extract of mistletoe (symptoms of hypertension, pireksia, leucocitosis, spasms, myosis, mydriasis, in very serious cases coma and death). The
testing of the eventual toxicity of extracts from yarrow and St Jonh’s wort has shown negative results concerning mutagenicity and teratogenicity.

In accordance with the temporarily available data, there are some precautions that need to be pointed out when using the product Varumin 1+2 such as possible hypersensitive reactions, electrolyte misbalance, abdominal difficulties, spasms, weakness, possible orthostatic hypotension (concerning elderly patients), cardiac disorders due to the loss of electrolytes etc.

The product Varumin 1+2 is not recommended for patients that are over-sensitive to some of the componential drugs of the product, suffer intestinal obstruction, inflammatory intestinal diseases (Crohn disease, ulcerative colitis), appendicitis or abdominal disorders.

The product should not be used during pregnancy and lactation. The product is not recommended for children under the age of 10.

5.4. **Expert Opinion**

Based on the above-mentioned data, I confirm that the product of Inter-Evrogeneks, Novo Selo, Republic of Macedonia, Varumin 1+2, satisfies the criteria both in terms of its structure and in terms of characteristics appropriate for a traditional herbal medicinal product in the stated indicative domain.
6. **Literature**


2. Bankova V., Recent trends and important developments in propolis research, eCAM 2 (1) 29-32, 2005.


8. British Herbal Pharmacopoeia (BHP), British herbal medicine association, 1996.


77. WHO monographs on selected medicinal plants, Volume 1, WHO, Geneve, 1999.


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1999 to 2007  Head of the Commission for marketing authorization of herbal medicinal products, Ministry of health, R Macedonia.

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Selection of scientific publication and project


Mihailo S. Ristic, Svetlana Kulevanova, Vlado Matevski, Trajce Stafilov, Building a databases for the fast chemical screening of essential oils of several Thymus species by LS/MS technique, Maced. pharm. bul., 49, 163, 2003


Tatijana Kadikova Panovska, Svetlana Kulevanova, Effect of some Teucrum species (Lamiaceae) on lipid peroksidation in rat liver microsoms, Fresenius Environmental Billetin, 14 (10), 957-959, 2005.

Projects:

- Chemical characterization of wild medicinal and aromatic plants of Lamiaceae family and assessment of the possibilities for their cultivation (2005-2006).
- Investigation of the plant species from macedonian flora from aspect of the antioxidant activity and possible hepatoprotective effects (2004-2006).
- COST action 926: Impact of new technologies on the health benefits and safety of bioactive plant compounds, 2005-2008;
- SEE-ERA.NET Research Project: Exploring the molecular biodiversity of medicinal and aromatic plants; 2007-2008;

Scientific collaboration on books and other publications


4. Radisa Jancic, BOTANICA PHARMACEUTICA, Nauka, Belgrad, 2003; Prof. d-r Svetlana Kulevanova, expert reviewer on the Macedonian language edition

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