

Volume 12, issue 2, June 2001 | Recherches

The effect of Sambucol, a black elderberry-based, natural product, on the production of human cytokines: I. Inflammatory cytokines

Abstract

Sambucus nigra L. products – Sambucol – are based on a standardized black elderberry extract. They are natural remedies with antiviral properties, especially against different strains of influenza virus. Sambucol was shown to be effective in vitro against 10 strains of influenza virus. In a double-blind, placebo-controlled, randomized study, Sambucol reduced the duration of flu symptoms

to 3-4 days. Convalescent phase serum showed a higher antibody level to influenza virus in the Sambucol group, than in the control group. The present study aimed to assess the effect of Sambucol products on the healthy immune system – namely, its effect on cytokine production. The production of inflammatory cytokines was tested using blood – derived monocytes from 12 healthy human donors. Adherent monocytes were separated from PBL and incubated with different Sambucol preparations i.e., Sambucol Elderberry Extract, Sambucol Black Elderberry Syrup, Sambucol Immune System and Sambucol for Kids. Production of inflammatory cytokines (IL-1b, TNF-a, IL-6, IL-8) was significantly increased, mostly by the Sambucol Black Elderberry Extract (2-45 fold), as compared to LPS, a known monocyte activator (3.6-10.7 fold). The most striking increase was noted in TNF-a production (44.9 fold). We conclude from this study that, in addition to its antiviral properties, Sambucol Elderberry Extract and its formulations activate the healthy immune system by increasing inflammatory cytokine production. Sambucol might therefore be beneficial to the immune system activation and in the inflammatory process in healthy individuals or in patients with various diseases. Sambucol could also have an immunoprotective or immunostimulatory effect when administered to cancer or AIDS patients, in conjunction with chemotherapeutic or other treatments. In view of the increasing popularity of botanical supplements, such studies and investigations in vitro, in vivo and in clinical trials need to be developed.

Full text

INTRODUCTION

There is a growing interest in medicinal botanicals as complementary medicine all over the world.

Sambucus species were reported to have been used for years by native Americans, mostly against rheumatism and fever [1, 2]. Sambucol is a natural remedy with antiviral properties, especially against the human influenza virus. The main ingredient of the formulation is an extract of the black elderberry (*Sambucus nigra* L.) [1]. The preparation also contains smaller amounts of Echinacea and Propolis. The black elderberry, which is widely used in Europe for juices and preserves, and designated as a "natural antibiotic product" contains high levels of three bioflavonoids and anthocyanins [3, 4]. Bioflavonoids possess a wide spectrum of biological activities, including antioxidant

properties. The antioxidant and prooxidant activities of an elderberry extract on low density lipoproteins have been demonstrated [5]. Antioxidants disarm free radicals, thus decreasing tissue damage. They also prevent damage caused by irradiation [6, 7]. Extracts of plants containing bioflavonoids and purified flavonoids were active against *Herpes* virus Type 1, respiratory syncytial virus, parainfluenza and influenza viruses [7]. Sambucol was shown to inhibit the hemagglutination and the replication of different human influenza viruses, both type A and B. It was also shown *in vitro* to be effective against 10 strains of the influenza virus [8]. In a double-blind, placebo-controlled, randomized study, Sambucol reduced the duration of flu symptoms to 3-4 days. Convalescent phase serum antibodies showed higher antibody levels to influenza virus in the group treated with Sambucol, as compared to the control group [8]. The prevention of flu like symptoms by Sambucol was demonstrated as well in a colony of chimpanzees in the Jerusalem Zoo [9].

Echinacea, the purple coneflower, is used as a herbal medicine against the common cold and bronchitis [1, 10]. Studies have shown that preparations of this plant affect the phagocytic immune system but not the acquired immune system or the production of cytokines [11-13].

Propolis is produced by the honey bee from plant resins. It has been used as an anti-bacterial material for wound cleaning and as an anti-inflammatory remedy for over 2,000 years. Propolis is considered to be an anti-oxidant, having a protective effect on the liver [14]. It has also been shown to reduce damage caused by irradiation [15].

The aim of the present study was to determine the immune enhancing potency of Sambucol preparations by studying their effect on the production of inflammatory cytokines by human peripheral blood monocytes of healthy individuals.

MATERIALS AND METHODS

Healthy donors blood monocyte cultures

Twelve donors (young, healthy students with no inflammatory conditions and currently receiving no medication) participated in this study. Heparinized peripheral blood (50 ml) was obtained from each subject and diluted 1:1 with

phosphate-buffered saline (PBS). The mononuclear cells were separated by Ficoll-Hypaque sedimentation (400 g, 30 min) and washed three times in PBS (175 g, 10 min) to remove platelets. An aliquot of cells was counted in a hemocytometer, and viability was checked using the trypan blue exclusion method. The adherent cells were > 90% monocytes by beta-naphthyl acetate non-specific esterase staining [16]. The cells were suspended in RPMI 1640 media, supplemented to a final concentration of 1 mM sodium pyruvate, 50 U/ml penicillin, 50 mg/ml streptomycin, 2 mM L-glutamine, 1/100 MEM-vitamins and 2% inactivated human AB serum. The cells were plated in 24-well culture dishes at a concentration of 4×10^6 cells per well and incubated for 90 min at 37° C in a humidified atmosphere containing 5% CO_2. Non-adherent cells were removed by aspiration and the wells washed three times with PBS. The adherent cells were cultured for 24 hours in RPMI media without the addition of serum. Different Sambucol formulations (1/10 dilution, 10 mul/well) or LPS (100 ng/ml) as a control monocyte stimulator, were added to the monocytes. At the end of the culture period (24 hours), the supernatants were harvested, centrifuged (300 g, 10 min) and stored at - 70° C until assayed for cytokines, as previously reported [17, 18].

Sambucol preparations

A standardized extract of the black elderberry, (E.Ex.) is the main ingredient of different Sambucol preparations. *Sambucol Black Elderberry Syrup* (B.E.) contains 38% E.Ex., glucose, raspberry extract, citric acid and honey. *Sambucol Active Defense* (A.D.), in the USA known under the name *Immune System Formula*, contains also 38% E.Ex., glucose, raspberry extract, citric acid, honey, *Echinacea angustifolia, Echinacea purpurea*, propolis, ascorbic acid and zinc gluconate. *Sambucol for Kids* (Kids) contains half the amount of E.Ex. (19%) used in the other formulations and in addition - glucose, raspberry extract, citric acid*, E. angustifolia, E. purpurea* and propolis.

The anthocyanin content of the Sambucol formulations was assessed by measuring the absorbance at 526 nm (not less than 0.6 for B.E, A.D. and 0.3 for Kids [1, 7].

Cytokine assays

Levels (pg/ml) of inflammatory cytokines (IL-1beta, IL-6, IL-8 and TNF-alpha) in supernatants of monocyte cultures were measured by a solid phase ELISA (R&D,

Minneapolis, USA). This assay employs the quantitative "sandwich" enzyme immunoassay technique. A monoclonal antibody specific for the cytokine molecule was pre-coated onto the polystyrene microtiter plate. Standards and samples were introduced into the wells where the immobilized specific antibodies bind the cytokines. After washing away any unbound proteins, the second enzyme-linked polyclonal or monoclonal antibody specific for the cytokine was added to the wells to "sandwich" the cytokine immobilized during the first incubation. Following a wash to remove any unbound antibody-enzyme reagent, a substrate solution was added to the wells, causing the development of a color that was proportional to the amount of cytokine bound in the initial step. The color development was stopped and the intensity of the color was measured. A standard curve plotting the optical density *versus* the concentration of a given cytokine was prepared, and used to determine the concentration of the cytokine in unknown samples, as previously reported [17-20].

Evaluation of Sambucol's effect

The effect of the different formulations of Sambucol on the induction of inflammatory cytokines production (in pg/ml) was also expressed as:

$$\text{Stimulation index} = \frac{+\text{ Sambucol cytokine production}}{-\text{ Sambucol}}$$

Statistical analysis

Comparison between groups was performed by Mann-Whitney's test. A value of $p < 0.05$ was considered significant.

RESULTS

The Sambucol E.Ex. and its three formulations (B.E., A.D., Kids) significantly stimulated the production of the inflammatory cytokines IL-1beta, IL-6, IL-8 and TNF-alpha by normal human monocytes.

The effects of the Sambucol formulations and of LPS (the well known positive control for monocyte activation) expressed as range (minimum and maximum induction levels) and as mean ± SE of stimulation indesces, for each of the

cytokines tested by 12 healthy donors' monocytes, are presented in Table 1: IL-1beta (Table 1a), TNF-alpha (Table 1b), IL-6 (Table 1c) and IL-8 (Table 1d).

In addition, the effect of Sambucol preparations on the actual amounts of cytokines produced (expressed as pg/ml) in comparison to the untreated control monocytes, which represent physiological levels, are presented in Table 2: IL-1beta (Table 2a), TNF-alpha (Table 2b), IL-6 (Table 2c) and IL-8 (Table 2d).

The highest stimulation index was observed with the E.Ex., followed by B.E. and A.D. which contain the same amount of elderberry extract (E.Ex.) and had similar stimulatory effect on these cytokines. Kids, which contains the lowest amount of extract, showed indeed the lowest stimulation index. For the E.Ex., the highest mean stimulation index (44.9) was observed for the induction of TNF-alpha, followed by IL-6 (19.5), IL-1beta (6.4) and IL-8 (3.3).

The effect of Sambucol preparations and of LPS (tested in 7 out of 12 donors) expressed as mean stimulation indexes, on the production of inflammatory cytokines for all individual donors, are shown in Figures 1-4:

IL-1beta (Figure 1), TNF-alpha (Figure 2), IL-6 (Figure 3) and IL-8 (Figure 4).

E.Ex. was the strongest activator for all 4 cytokines and was statistically significantly different from the other Sambucol formulations, except for IL-8 ($p < 0.05$). However, there were no statistically significant differences between effects of B.E., A.D. and Kids. LPS induction of all cytokines was lower than that induced by E.Ex ($p < 0.05$). For IL-8, the effect of LPS was similar to that of E.Ex. and a little higher than the other 3 formulations. For IL-6, the effect of LPS was higher than B.E., A.D. and Kids. For IL-1beta, the effect of LPS was higher then B.E., A.D. and Kids. For TNF-alpha the effect of LPS was a little higher than that of B.E., A.D. and Kids. There was no significant difference between levels of cytokines activated by B.E. and A.D.

A representative assay performed on monocytes from one single donor (K.L.) showing cytokine production is presented in Figure 5.

When the Sambucol preparations were mixed together with LPS to activate the monocytes, a synergistic effect was found, especially for E.Ex. (data not shown).

DISCUSSION

The results of this study show that all Sambucol elderberry formulations have a strong stimulatory effect on inflammatory cytokine production by human normal monocytes. With the exception of IL-8, the stimulatory activity was dose-dependent, *i.e.*, the E.Ex. with the highest extract concentration of Sambucol showed the highest cytokine stimulation, while the less concentrated B.E. and A.D. caused a less pronounced stimulation. The less concentrated formulation, Kids, had the lowest effect on the production of inflammatory cytokines. The most impressive effect of E.Ex. was on TNF-alpha production. The extremely high amounts of TNF-alpha produced by Sambucol, were even higher than those produced by LPS. TNF-alpha is a multipotential mediator of cellular immune responses with a wide variety of biological activities. Under different conditions, TNF-alpha can exhibit favorable or unfavorable effects on the host immune response. The unfavorable effects may occur with high concentrations of TNF-alpha or with low concentrations - for longer periods [21]. The Sambucol preparations, especially the E.Ex., when added together with LPS, had a synergistic inducing effect.

Echinacea, propolis, ascorbic acid and zinc gluconate, which are included in the A.D. formulation, but not in the B.E., did not enhance the stimulatory effect of the E.Ex. and even appeared to reduce it (data not shown).

Our results are in accordance with the studies which showed that the extracts of *Echinacea* are not able to induce increased cytokine production [10, 11]. Levels of the cytokines (IL-1alpha, IL-1beta, IL-2, IL-6, TNF-alpha and IFN-gamma) were measured in culture supernatants of stimulated whole blood cells derived from 23 tumor patients undergoing a 4-week oral treatment with an *Echinacea* complex. No significant alteration in the production of cytokines was detected [11]. In healthy volunteers, two out of five studies performed with different preparations of *Echinacea* showed an enhancement in the phagocytic activity of polymorphonuclear neutrophil granulocytes [21].

Propolis was shown to enhance murine macrophage spreading and mobility [22]. Its influence on the production of cytokines has not yet been reported.

In addition to Sambucol's antiviral properties [7, 8], the E.Ex. and the other Sambucol formulations were shown in this study to activate the immune system

by strongly increasing inflammatory cytokines production. In preliminary studies, we have shown that Sambucol formulations significantly induce the production of both Th1(IFN-gamma and sIL-2R) and Th2 (IL-10) cytokines, as well as the production of the hematopoietic growth factor GM-CSF by monocytes and lymphocytes from healthy individuals. (unpublished results).

Sambucol may therefore be beneficial to the stimulation of the immune system in healthy individuals, as well as in patients with influenza, cancer and HIV, which have decreased immune functions. As we have shown previously, breast cancer patients undergoing chemo/hormonotherapy and provided with an addition of interferons, which activated the immune system, had a better therapy response concomitant to changes in cytokine production [24]. We believe therefore, that Sambucol may be beneficial to cancer patients receiving chemotherapy. The immunoprotective or immunostimulatory effects of Sambucol, in various patients will be assessed in future clinical trials.

CONCLUSION

Acknowledgements. This study was not funded in any way by the company which produces and markets the product of Sambucol in Israel.

As the Israeli Cytokine Standartization Laboratory, we have performed many studies dealing with various activation pathways of human cytokines.

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Figures

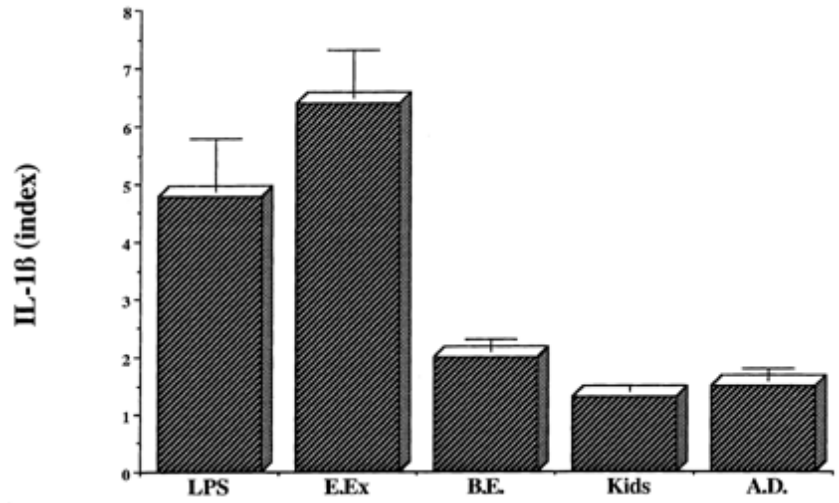


Figure 1

The effect of Sambucol on IL-1beta production (index).

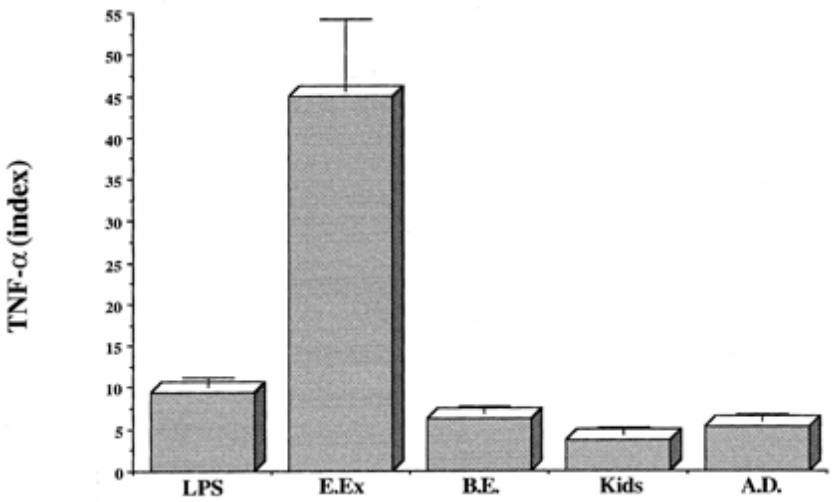


Figure 2

The effect of Sambucol on TNF-alpha production (index).

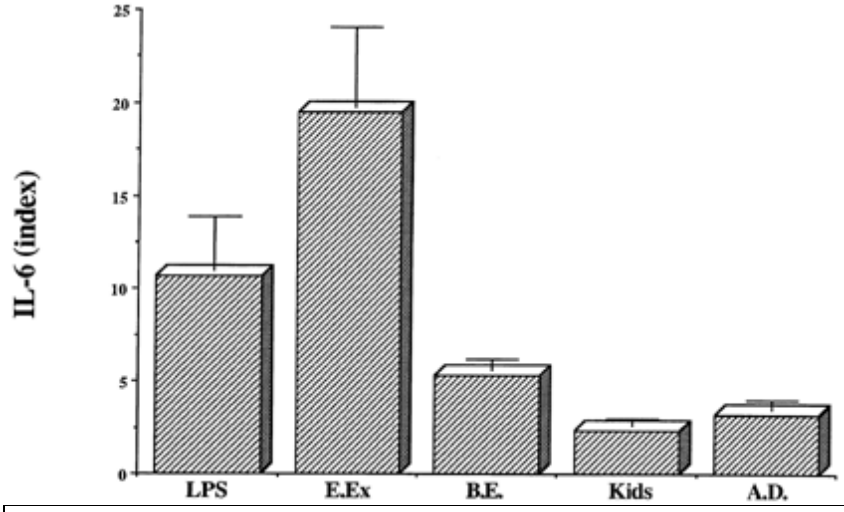


Figure 3

The effect of Sambucol on IL-6 production (index).

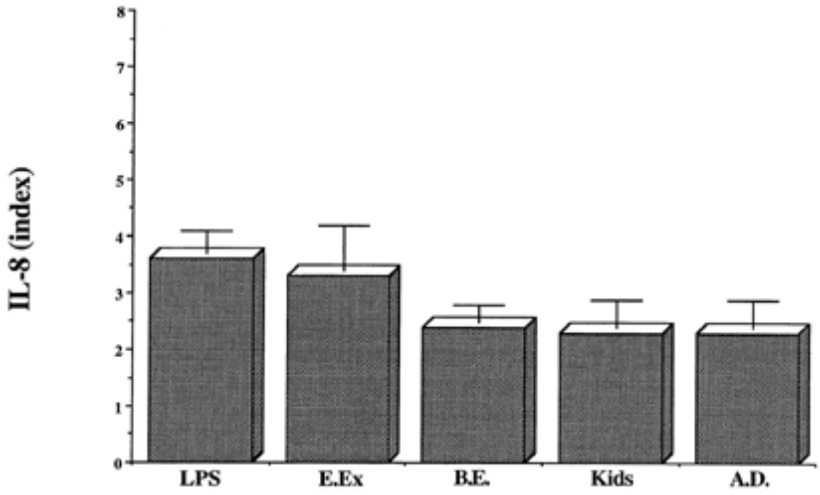


Figure 4

The effect of Sambucol on IL-8 production (index).

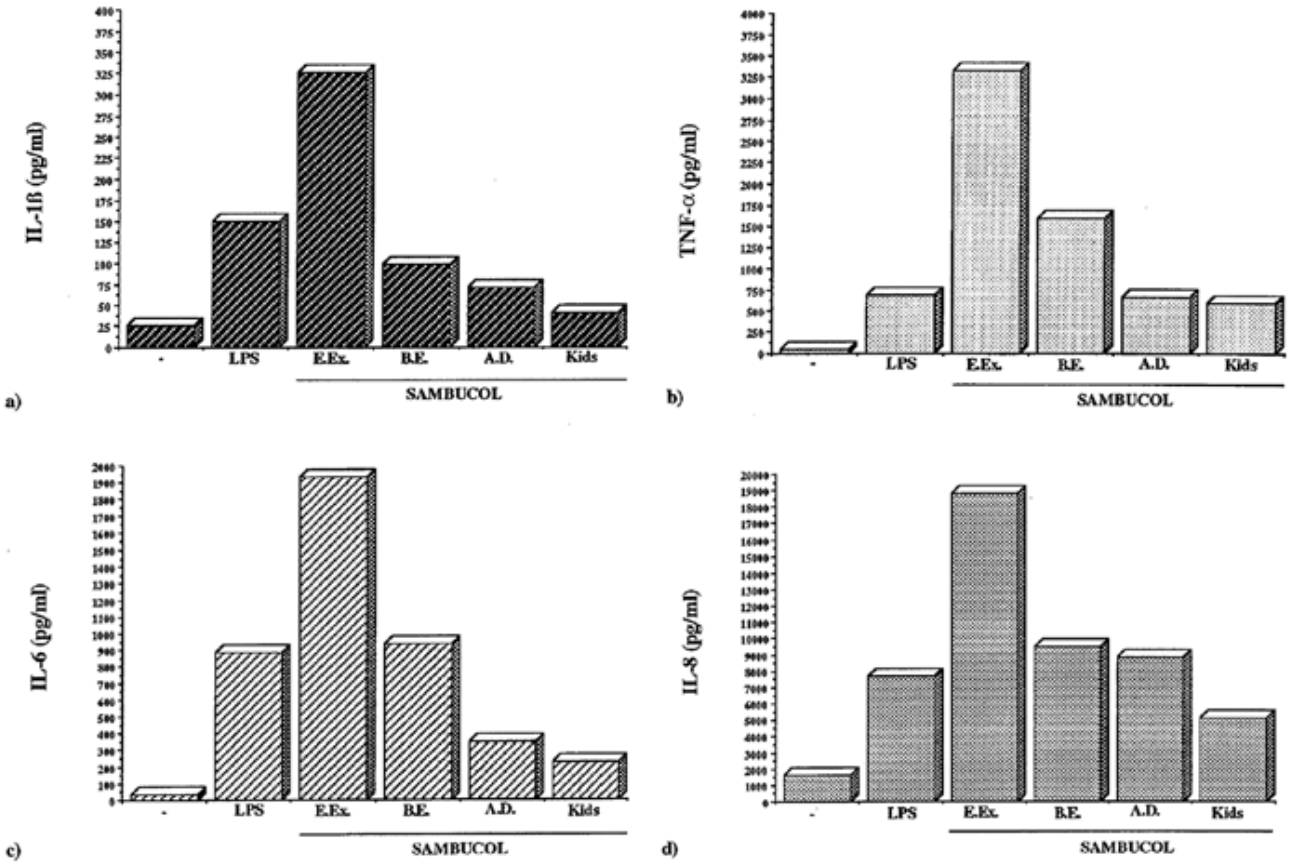


Figure 5

The effect of Sambucol and LPS on production of a) IL-1beta, b) TNF-alpha, c) IL-6, d) IL-8 in a donor (K.L.).

Table 1a
The effect of Sambucol preparations and LPS on production of inflammatory cytokines (index of activation): IL-1beta

IL-1beta	E.Ex.	B.E.	Kids	A.D.	LPS
Range (index)					
Minimum	1.6	1.2	0.8	0.9	1.7
Maximum	11.1	3.8	2.1	2.4	9.6
Mean (index)	6.4	2	1.3	1.5	4.8
± SE	0.8	0.2	0.1	0.2	0.9
No. of donors	10	12	10	10	7

E.Ex.: Sambucol elderberry extract; B.E.: Sambucol black elderberry syrup; Kids: Sambucol for kids; A.D.: Sambucol active defence.

Table 1b
The effect of Sambucol preparations and LPS on production of inflammatory cytokines (index of activation): TNF-alpha

TNF	E.Ex.	B.E.	Kids	A.D.	LPS
Range (index)					
Minimum	8.4	2.4	1.5	1.4	5.2
Maximum	95.1	10	7.6	8.7	14
Mean (index)	44.9	6.2	3.7	5.3	9.5
± SE	8.6	0.9	0.7	0.7	1.1
No. of donors	10	10	10	10	7

Table 1c
The effect of Sambucol preparations and LPS on production of inflammatory cytokines (index of activation): IL-6

IL-6	E.Ex.	B.E.	Kids	A.D.	LPS
Range (index)					
Minimum	5.7	1.9	1.2	1.5	2.7
Maximum	38.4	9	4.4	5.8	25.2
Mean (index)	19.5	5.3	2.3	3.2	10.7
± SE	4.3	0.6	0.4	0.5	2.9
No. of donors	10	11	10	10	7

Table 1d
The effect of Sambucol preparations and LPS on production of inflammatory cytokines (index of activation): IL-8

IL-8	E.Ex.	B.E.	Kids	A.D.	LPS
Range (index)					
Minimum	1.1	1.3	0.7	1.1	1.5
Maximum	10.4	9.1	6.1	5.7	4.8
Mean (index)	3.3	2.4	2.3	2.2	3.6
± SE	0.8	0.3	0.5	0.5	0.4
No. of donors	10	12	10	10	7

Table 2a
The effect of Sambucol preparations on production of inflammatory cytokines (pg/ml) : IL-1beta

IL-1beta (pg/ml)					
Donors	–	E.Ex.	B.E.	Kids	A.D.
1	236	1,170	527	218	241
2	176	981	321	201	225
3	286	1,111	434	249	250
4	111	1,233	141	151	139
5	84.9	904	160	80	109
6	276	1,938	1,060	479	579
7	962	4,420	1,550	2,010	1,940
8	651	4,900	1,490	808	1,150
9	111		296		
10	235		319		
11	153	1,020	367	218	368
12	627	1,687	776	529	688

E.Ex.: Sambucol elderberry extract; B.E.: Sambucol black elderberry syrup; Kids: Sambucol for kids; A.D.: Sambucol active defence.

Table 2b
The effect of Sambucol preparations on production of inflammatory cytokines (pg/ml) : TNF-alpha

TNF-alpha (pg/ml)					
Donors	–	E.Ex.	B.E.	Kids	A.D.
1	139	5,960	1,390	501	870
2	75.7	2,560	252	115	215
3	262	24,918	2,215	567	1,457
4	228	14,563	2,272	1,571	1,988
5	204	14,107	1,313	521	1,194
6	249	13,770	2,063	1,887	1,719
7	931	7,860	2,220	3,230	2,320
8	861	19,761	3,710	2,000	4,060
9	164		1,600		
10	268		1,630		
11	174	8,290	1,210	1,000	1,380
12	448	4,660	932	777	615

Table 2c
The effect of Sambucol preparations on production of inflammatory cytokines (pg/ml) : IL-6

IL-6 (pg/ml)					
Donors	–	E.Ex.	B.E.	Kids	A.D.
1	730	4,740	2,240	917	1,150
2	845	7,140	4,430	1,400	1,980
3	329	8,524	1,645	653	1,008
4	179	6,866	1,611	787	974
5	151	4,338	820	341	570
6	1,214	6,972	4,006	2,355	2,717
7	2,660	25,670	8,140	7,500	8,880
8	3,320	30,267	18,121	5,190	9,750
9	231		2,021		
10	911		1,940		
11	368	7,390	1,740	1,490	2,130
12	1,480	9,600	2,750	1,810	2,200

Table 2d
The effect of Sambucol preparations on production of inflammatory cytokines (pg/ml) : IL-8

	IL-8 (pg/ml)				
Donors	–	E.Ex.	B.E.	Kids	A.D.
1	11,670	25,550	26,700	18,290	16,720
2	15,280	46,310	72,900	50,000	61,770
3	23,516	68,400	52,010	44,779	33,552
4	5,705	59,441	51,988	34,857	32,775
5	18,820	70,131	64,850	37,274	31,261
6	51,906	58,136	71,423	37,994	55,154
7	25,930	79,120	87,790	90,110	69,520
8	54,913	103,830	83,610	74,180	72,080
9	23,860		57,260		
10	55,060		68,960		
11	29,080	76,425	79,757	48,750	60,720
12	47,230	80,267	62,980	51,580	50,010

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In this issue

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immunotherapy, soft tissue sarcoma, interleukin-2, chemoresistance, anthracyclin.

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melanoma, tumor necrosis factor, apoptosis, cell cycle arrest, p38 MAPK.

Impaired interleukin-5 (IL-5) production by T cells as a prognostic marker of disease progression in human immunodeficiency virus type 1 (HIV-1)-infected children

S. Resino, S. Sanchez-Ramon, J.M. Bellon, J.L. Jimenez, M.A. Munoz-Fernandez
HIV-infected children, cytokine production, interleukin-5, PBMC, prognostic markers.

Cytokine-mediated inflammatory hyperalgesia limited by interleukin-13

B.B. Lorenzetti, S. Poole, F.H. Veiga, F.Q. Cunha, S.H. Ferreira
inflammatory hyperalgesia, interleukin-13, tumour necrosis factor alpha, interleukin-1b, interleukin-8, prostaglandin E2.

Expression of thrombopoietin by umbilical vein endothelial cells

A. El Andaloussi, P. Duchez, J. Rieffers, J. Ripoche, C. Grosset
thrombopoietin, umbilical vein endothelial cells.

Production of cytokines by immature erythroid cells derived from human embryonic liver

S.V. Sennikov, S.V. Krysov, T.V. Injelevskaya, A.N. Silkov, V.A. Kozlov
erythroid progenitor, IL-1b, IL-2, IL-4, IL-6, fetal liver.

Inflammatory cytokine production in interferon-g-primed mice, challenged with lipopolysaccharide. Inhibition by SK&F 86002 and interleukin-1b-converting enzyme inhibitor

S. Spinelle-Jaegle, P. Devillier, S. Doucet, S. Millet, C. Banissi, A. Diu-Hercend, E. Ruuth
interferon-g, lipopolysaccharide, interleukin-1b, cytokine, interleukin-1b-converting enzyme inhibitors.

The effect of Sambucol, a black elderberry-based, natural product, on the production of human cytokines: I. Inflammatory cytokines

V. Barak, T. Halperin, I. Kalickman
Sambucol, inflammatory cytokines, IL-1b, TNF-a, IL-6, IL-8.

Interferon (IFN)-g and Herpes simplex virus/tumor necrosis factor-a synergistically induce nitric oxide synthase 2 in macrophages through cooperative action of nuclear factor-kB and IFN regulatory factor-1

S.R. Paludan, L. Malmgaard, S. Ellermann-Eriksen, L. Bosca, S.C. Mogensen
macrophages, NOS2, Herpes simplex virus, NF-kB, IRF-1.

Negative regulation of onconstatin M signaling by suppressor of cytokine signaling (SOCS-3)

F. Magrangeas, O. Boisteau, S. Denis, Y. Jacques, S. Minvielle
cytokine signaling, inhibition, Jak-STAT pathway.

Increased expression of interleukin-8 and aminopeptidase N by cell-cell contact: interleukin-8 is resistant to degradation by aminopeptidase N/CD13

A. Kehlen, I. Egbert, K. Thiele, K. Fischer, D. Riemann, J. Langner
cell co-culturing, leucine aminopeptidase, plasma membrane preparations, CD13, proteolysis of IL-8, interleukin-8.

Functional characterization of the mouse lymphotoxin-beta receptor promoter

P. Muller, D.N. Männel, T. Hehlgans
LTbR-promoter, transcriptional activation, dexamethasone.

Glucose potentiates interleukin-1b (IL-1b)-induced p38 mitogen-activated protein kinase activity in rat pancreatic islets of Langerhans

A.M.E. Sprinkel, N.A. Andersen, T. Mandrup-Poulsen
interleukin-1b, p38, ERK1/2, JNK, nitric oxide, diabetes mellitus.

Sustained parasite burden in the spleen of Leishmania infantum-infected BALB/c mice is accompanied by expression of MCP-1 transcripts and lack of protection against challenge

D. Rousseau, S. Demartino, F. Anjuère, B. Ferrua, K. Fragaki, Y. Le Fichoux, J. Kubar
murine leishmaniasis, acquired immunity, inflammation, chemokines, spleen cell subpopulations.

Effects of cytokines and prolactin on the replication of Toxoplasma gondii in murine microglia

N. Benedetto, A. Folgore, C. Romano-Carratelli, F. Galdiero
T. gondii, cytokine, PRL, MGC.

Strip test for bedside detection of interleukin-6 in cervical secretions is predictive for impending preterm delivery

H. Trébéden, F. Goffinet, G. Kayem, F. Maillard, E. Lemoine, D. Cabrol, B. Weill, F. Batteux
cytokine, IL-6, prematurity, cervicovaginal secretions, strip test.

Serum levels of interleukin-18 in patients with uncomplicated Plasmodium falciparum malaria

D. Torre, M. Giola, F. Speranza, A. Matteelli, C. Basilico, G. Biondi
interleukin-18, malaria, Plasmodium falciparum, gamma interferon.

The ecdysone inducible gene expression system: unexpected effects of muristerone A and ponasterone A on cytokine signaling in mammalian cells

S. Constantino, R. Santos, S. Gisselbrecht, F. Gouilleux
ecdysone, PI 3-kinase, AKT, survival.

Presence of estrogen receptors in human myeloid monocytic cells (THP-1 cell line)

M. Cutolo, B. Villaggio, A. Bisso, A. Sulli, D. Coviello, J.M. Dayer
THP-1 cells, macrophages, estrogen receptors, estrogens, monocytes.

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