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# *Coriolus versicolor* – Assessment of the Effects on Patients Infected with Low-risk and High-risk HPV Subtypes


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## SUMMARY
*Coriolus versicolor* is a nutrient adjuvant with immunostimulating properties. An assessment study carried out in Bulgaria showed that *Coriolus* supplementation could be beneficial for elimination of most subtypes of HPV virus.

## INTRODUCTION
*Coriolus versicolor* (Coriolus - MRL) is a fungus whose biomass acts as a non-specific immunomodulator[1]. Coriolus-MRL is a nutrient adjuvant which is appropriate for immune deficiency patients after illness and after surgical intervention, for prevention from cancer-inducing viruses as well as in cancer patients for the strengthening of the immune system, especially after chemotherapy and radiotherapy.

The immunostimulating effect of Coriolus-MRL is due to the beta-glucanes and proteoglucanes it contains – polysaccharide K (PSK) and polysaccharopeptide (PSP) - that stimulate the effect of natural killer cells and increase the number of T-lymphocytes. The enzyme activity prevents oxidative stress due to the presence of Coriolus 10Kd peptide which mimics the activity of the superoxide dismutase enzyme (SOD). Protease activity inhibits the proliferation of the tumour cells and the role of cytochrome P-450 is related to the detoxification of the organism. The immunostimulating effect is strengthened by the content of some secondary metabolites (lectines, terpenoids and chelates) which also have fibrinolytic effects[2].

Human papillomavirus (HPV) infection is the most common sexually transmitted infection which affects approximately 70% of the reproductive-age population. It has been established during the last years that *Coriolus versicolor* has a positive effect in prevention of HPV patients from developing cervical cancer-[3, 4].

## MATERIALS AND METHODS
An assessment study was carried out in Bulgaria during the period 2009-2010 concerning the evaluation of *Coriolus versicolor* supplementation in 100 patients (aged 16-50 years) which were positive for low-risk and high-risk HPV subtypes.

Conservative treatment was applied in 73 patients (Coriolus 2 x 3 tablets (500 mg) for a period of 6 months) and the rest of the patients (27) were subjected to a combined treatment (surgical intervention + Coriolus 2 x 3 tablets (500 mg). Patients' status was determined by cervical cytology exams and HPV tipification. Colposcopy was performed in 53 patients and 51 % of them were subjected to biopsy as well.

## RESULTS
The results showed that after application of the combined treatment all PAP group IIIa and PAP group IIIb patients reverted to group I and/or group II. Persistent infection was established in 3 IIId PAP group patients (Table 1).

The results showed that 64 (88%) out of 73 patients subjected to a conservative treatment were HPV-negative.

Ninety-three percent (93%) of the patients (25 out of 27) who took Coriolus-MRL after surgical intervention were also HPV-negative.

## CONCLUSIONS
*Coriolus versicolor* supplementation boosted the patient's immune system naturally which led to a virus elimination. The beneficial effect of this supplement against most subtypes of HPV is important in modern virus infection treatment (both combined and conservative).*

*****Coriolus versicolor* used was supplied by Mycology Research Laboratories Ltd www.mycologyresearch.com

**Table 1**. Results of a 6-month study: number of the patients and the PAP smears in the respective groups. Four patients out of 100 were positive for low-risk HPV subtypes and 96 were diagnosed to have high-risk HPV subtypes. At the end of the study (after 6 months) only 11 patients were still positive for 1 or more HPV subtypes (Table 2).

| 1st Month | | 6th Month | | |
|---|---|---|---|---|
| | | PAP 1 | PAP II | PAP III a |
| **47** | PAP 1 / PAP II | 47 | | - |
| **29** | PAP III a | 9 | 20 | - |
| **9** | PAP III b | 3 | 6 | - |
| **15** | PAP III d | 6 | 6 | 3 |

**Table 2.** Results of a 6-month study: patients who were found to carry high-risk or low-risk HPV subtypes.

| | 1st month | 6th month | |
|---|---|---|---|
| | | Negative | Positive |
| **Low-risk HPV subtypes** | 4 | 4 | - |
| **High-risk HPV subtypes** | 96 | 85 | 11 |

**Table 3.** shows that 8 out of 11 patients were negative concerning several HPV subtypes which were established at the beginning of the study. Two patients carried new HPV subtypes and were negative concerning the subtypes established first.

| 1st month | 6th month |
|---|---|
| HPV 56; 59 | HPV 59 |
| HPV 56 | HPV 52 |
| HPV 31; 33; 35; 39; 59 | HPV 35 |
| HPV 16; 35; 56 | HPV 16; 56 |
| HPV 16;31;58 | HPV 16; 31 |
| HPV 16; 18 | HPV 16 |
| HPV 6; 11; 16; 18 | HPV 16; 18 |
| HPV 16; 31; 58 | HPV 16; 31 |
| HPV 56 | HPV 56 |
| HPV 6; 59 | HPV 6 |
| HPV 35; 56; 58 | HPV 39; 45 |


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**Abstract:** Coriolus-MRL is a nutrient adjuvant, which contains biomass of the fungus Coriolus versicolor and is studied to reverse early stages of cervical cancer and to reduce risk factors of reoccurring HPV virus. PMID:19449722 [PubMed - indexed for MEDLINE]

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* *Coriolus versicolor* used was supplied by Mycology Research Laboratories Ltd www.mycologyresearch.com

# Ongoing Research: The Role of MRL Fungal Biomass Products as Modulators of Toll Receptor-Mediated Immune Response Pathways


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## BACKGROUND

It is widely recognized that inflammation plays a role in disease processes as widely diverse as minor cuts and bruises, to cancer [1]. An inflammatory condition is very often provoked by environmental factors such as pathogenic microorganisms, food components and pollutants.

Inherent in the inflammatory process is the activation of the immune system. The immune system is composed of two fundamental elements; the production of immunoglobulin antibodies by B-lymphocytes and the activity of cells such as macrophages and natural killer cells (cell-mediated immunity or innate immune system). When an invading pathogen is detected, the cell-mediated immune system is at hand and this can be reinforced by the production of antibodies from B-lymphocytes.

For some individuals and by a mechanism that is not entirely understood, prior exposure to a pathogen or foreign substance can lead to a hypersensitivity reaction, when the individual is next exposed to the agent. This type of sensitivity, called type IV hypersensitivity, involves T-lymphocytes that have a memory of previous exposure to the agent. Type IV hypersensitivity can lead to an allergic reaction to food components, microorganisms, heavy metals and other environmental pollutants.

If it is suspected that an individual is sensitive to an environmental factor, a system called the Lymphocyte Transformation Test (LTT) can be used to test for this. This method uses a special centrifugation process to separate immune cells from whole blood. A cell fraction enriched for T lymphocytes is then exposed to a potential T-cell stimulating substance and after several days in culture, the number of T cells is determined by a quantitative labelling process and also by visual observation of cells under a microscope. The increase in the number of T-cells is recorded as a stimulation index (SI). Positive responses are usually taken to have an SI of 3.0 and above, where the number of T lymphocytes is three times that of the control.

## STUDY OBJECTIVE

Having established the sensitive LTT assay, studies in the laboratory are now demonstrating significant responses to a range of common environmental metals; in particular, nickel, mercury and molybdenum are proving to be potent activators of the conversion of resting T cells to lymphoblasts. This transformation from resting state to proliferation is fundamental in initiating a type IV allergic response and these changes observed in vitro have been shown to correlate with clinical response [2].

Although it has been known for some years that metals such as nickel (Ni) can activate inflammatory pathways[3], the mechanism by which this is achieved is not known. However, in the case of Ni, a publication last year in Nature Immunology sheds light on this. The work by Schmidt and colleagues in Mannheim, Germany, has provided evidence that Ni can directly activate Toll receptor-4 (TLR-4)[4]. These receptors are fundamental in signalling the presence of extraneous environmental factors, such as microorganisms, to the innate immune system.

**The importance of these new findings are several fold:**

**1)** Evidence is accumulating that Ni concentration in breast tumours are around 100 fold higher than in non-tumour tissue[5] and recently demonstrated functioning Toll receptors within breast cancer cells[6].

**2)** In addition to this, Toll receptors are expressed on macrophages and dendritic cells of the immune system and therefore, allergenic responses to Ni might be mediated by Toll-generated, macrophage signals.

For some five or more years it has been recognized that fungal polysaccharides have an ability to interact with the Toll receptor-signalling system[7].In view of the above mentioned work on breast cancer cells[6], these findings raise the possibility that fungal polysaccharides, via an interaction with Toll receptors, might have a role in preventing pre-neoplastic change via direct interaction at the breast cell Toll receptor (competitive with metal binding).

Fungal polysaccharides and antioxidant enzymes, present within fungal biomass preparations, might also be capable of reducing the state of activation of the immune system by:

**1)** blocking an in-situ hyper-reactive immune response to metals by pre-neoplastic breast tissue or blocking the effect of metals released from breast tumours (breast tumour tissue concentrates metals which are released on the death of tumour cells leading to an enhanced inflammatory process) and

**2)** modulating the activity of the systemic immune response to metal allergens, thereby reducing type IV hypersensitivity.

## STUDY DESIGN

In order to partially address these issues raised above, the LTT system will be used to study the effect of MRL mushroom nutrition products on the response of T-lymphocytes to Ni and other metals such as mercury and molybdenum. As a first step, it is proposed that experiments are established where aqueous extracts of MRL products are incubated with T-lymphocytes in the absence and presence of metals. These experiments will address the immuno-modulatory properties of the extracts at the cellular level.

## STUDY RATIONALE

It is believed by the author of this proposal that studies to date on MRL products have focused on establishing in vivo parameters of response. Therefore, evidence has accumulated to show that MRL products alter the Th1 to Th2 balance in favour of a cell-mediated 'anti-tumour' response. As yet, these responses have not been confirmed in an in vitro cell culture system and the LTT assay provides an ideal experimental system.

These previous in vivo observations support a role for components of the MRL biomass products as activators of monocyte/macrophage/dendritic cell-directed antitumour pathways. Whilst this is important for an existing neoplastic condition, as agents that might block an

*continued...*

inflammatory response that could lead to tumour formation, it would be necessary for the biomass component to block Toll receptor-mediated inflammatory pathways. A rationale for this has recently been provided by a study showing that ligands for Toll receptor 2 can inhibit pro-inflammatory stimuli[8].

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# Abstract of CytoGenex Research in Collaboration with the Max-Planck Institute, Munich, on Bacteria Activating Immune Receptors on Cancer Cells

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Blood-borne bacteria, fungi and viral agents can activate cells of the innate immune system by interacting with pattern-recognition or Toll receptors on the surface of immune cells.

It was demonstrated that mRNA for Toll receptors is ubiquitously expressed in a range of transformed and normal cell types. These findings raise the possibility that infection could induce an inflammatory response in somatic tissues and this might,

**1)** provide a milieu for changes in normal cells that lead to neoplastic growth and/or

**2)** provide conditions suitable for enhancing the growth of an existing neoplastic lesion.

As a preliminary step to investigate this, the response of breast tumour MCF-7 cells to a sonicate of a mixed population of bacteria was investigated. Using quantitative PCR (QPCR) and primers for Toll receptors 1 to 10, it was shown that 24 h exposure to the bacterial cell sonicate up-regulates the expression of mRNA for Toll-2 and Toll-4 by between 5 and 8 fold.

The expression of other Toll receptors was not significantly altered. Given that the cytokine IL-6 is induced in immune cells by ligands of Toll receptor 4, it was further demonstrated by QPCR, that mRNA for this inflammatory cytokine is markedly induced in MCF-7 cells by exposure to the sonicated bacteria and that this effect is blocked by prior exposure of the MCF-7 cells to dexamethasone.

These findings strongly suggest that the full Toll-mediated inflammatory system is present in breast tumour cells and they provide a rationale for tumour therapy, targeted to the Toll receptors. They also suggest that infection by bacteria or mycoplasma may play a role in tumour formation or that infection may enhance the growth of an existing lesion.

**Ref:** Newton CJ, Bilko D, Stalla G and Renner U. Endocrine Abstracts 25: P172 (2011)

# Detoxification - The Role of Mushroom Nutrition

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A number of pathological damages including carcinogenesis and cellular degeneration related to aging are due to reactive oxygen species (ROS), or superoxide radicals. These reactive oxygen species are produced by sunlight, ultraviolet radiation, chemical reactions, as well as by metabolic processes, and are toxic to living cells since they oxidize and degrade important biological macromolecules such as lipids and proteins[1]. Health maintenance and the avoidance of chronic degenerative conditions therefore depends to a large extent on the body's ability to neutralise, in other words detoxify, such ROS.

Central to the body's battle against ROS are a number of enzyme systems, prominent among which is superoxide dismutase (SOD), which catalyses the destruction of superoxide radicals and hence protects oxygen–metabolizing cells from the harmful effect of these free radicals. Several research workers have shown that SOD is involved in diseases such as Parkinson´s disease, cancer and anemia[1,2]. Another important enzyme system is cytochrome "P-450" which is located in the endoplasmic reticulum and plays an important role in metabolism and detoxification of endogenous substances[3]. In addition, enzyme therapy has been shown to play an important role in several clinical conditions including cancer, malignant lymphomas and cardiovascular disorders[4,5].

Mushrooms have been known to possess medicinal properties for thousands of years and higher basidiomycete mushrooms have been used in clinical nutrition for their anti-tumour, immune modulating, cardiovascular and anti-microbial effects[6]. As well as other complex substances of therapeutic interest, such as protein-bound polysaccharide complexes (i.e PSK, PSP and Lentinan) and secondary metabolites (i.e terpenes, alkaloids and lactones) we are now finding that mushrooms are rich sources of many enzymes. Several mushrooms have been shown to contain substances which mimic SOD activity[7] and the "P450" cytochrome enzyme system has also been found in some higher basidiomycete fungi. Other enzymes present in clinically used mushrooms include laccase, glucose oxidase and peroxidase[8].

It is likely that the potent enzymatic and ROS detoxifying properties of mushrooms are in large part due to the harsh environments colonized by mushroom mycelia with high concentrations of free radicals that the mushrooms have to protect themselves against.

In this connection it is worth noting that these enzymes are found almost exclusively in the mushroom mycelia and hence preparations derived from the fruiting bodies of mushrooms are likely to have far lower levels of enzymatic activity than those derived from mushroom mycelia.

In the present work, we investigated the levels of SOD, cytochrome "P450", cytochrome "P450" reductase (NADPH dependent) and secondary thrombin inhibiting metabolites in the following mushrooms: *Coriolus versicolor*, *Cordyceps sinensis*, *Ganoderma lucidium* (Reishi) and *Grifola frondosa* (Maitake).

There are a number of secondary metabolites in mushrooms which play an important role as thrombin inhibitors[10] and since thrombin is an important protease of the coagulation system it is a suitable target for inhibition of blood coagulation, which is desirable in combating many age related conditions.

In order to simulate the human intestinal tract we treated the mushrooms with the following proteolytic enzymes:

**1.** Pepsin (500IU/g biomass) at pH2 for 30 min. at 37°C in an incubator with orbital shaking.

**2.** Trypsin (500IU/g biomass) at pH 7.6 for 30 min. at 37°C in an incubator with orbital shaking.

The analysis of SOD, cytochrome "P450", cytochrome "P450" reductase (NADPH dependent) and secondary thrombin inhibiting metabolites in *Coriolus versicolor*, *Cordyceps sinensis*, *Ganoderma lucidium* (Reishi) and *Grifola frondosa* (Maitake) produced the following results:

**Table 1. In the Absence of Proteolytic Enzymes***

| Enzymes and secondary metabolites | Maitake (Grifola frondosa) | Reishi (Ganoderma lucidum) | Coriolus versicolor | Cordyceps sinensis |
|---|---|---|---|---|
| **Analysis Per Tablet (500 mg)*** | | | | |
| 1 Superoxide dismutase (SOD) activity | 70.2U | 50.4U | 77.1U | 77.1U |
| 2 Cytochrome "P450" | 0.60 nmoles | 0.66 nmoles | 0.51 nmoles | 0.25 nmoles |
| 3 Cytochrome "P450" reductase | 7.14 mU | 7.05 mU | 11.9mU | 4.14mU |
| 4 Secondary metabolites (Thrombin inhibitors) | 49% | 4.4% | 59% | 56% |

Table 2. In the Presence of Pepsin*

| Enzymes and secondary metabolites | Maitake (Grifola frondosa) | Reishi (Ganoderm frondosa) | Coriolus versicolor | Cordyceps sinensis |
|---|---|---|---|---|
| **Analysis Per Tablet (500 mg)*** | | | | |
| 1 Superoxide dismutase (SOD) activity | 58.7U | 41.3U | 61.2U | 49.5U |
| 2 Cytochrome "P450" | 0.48 nmoles | 0.53 nmoles | 0.49 nmoles | 0.24 nmoles |
| 3 Cytochrome "P450" reductase | 6.06mU | 5.92mU | 9.52mU | 3.80mU |
| 4 Secondary metabolites (Thrombin inhibitors) | 46.5% | 3.7% | 54.2% | 50.9% |

Table 3. In the Presence of Trypsin*

| Enzymes and secondary metabolites | Maitake (Grifola frondosa) | Reishi (Ganoderm frondosa) | Coriolus versicolor | Cordyceps sinensis |
|---|---|---|---|---|
| **Analysis Per Tablet (500 mg)*** | | | | |
| 1 Superoxide dismutase (SOD) activity | 69.5U | 51.4U | 68.5U | 90.6U |
| 2 Cytochrome "P450" | 0.58 nmoles | 0.63 nmoles | 0.52 nmoles | 0.24 nmoles |
| 3 Cytochrome "P450" reductase | 7.03mU | 6.98mU | 11.1mU | 4.02mU |
| 4 Secondary metabolites (Thrombin inhibitors) | 46% | 3.7% | 52% | 57% |

The data presented in these tables reveal that simulation of the intestinal tract with pepsin and trypsin decreased the enzyme and secondary metabolite levels by 15-20%

**Conclusions:**

Mushrooms contain several important enzymes involved in detoxification process (i.e cytochrome "P450") and destruction of superoxide free radicals (i.e SOD activity) as well as secondary metabolites which act as thrombin inhibitors. Further research is required to study the effect of mushroom nutrition on the levels of some key proteins and enzymes in vivo which are involved in several clinical conditions including cardiovascular diesases, cancer, HIV and neurological disorders.

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*Mushroom samples (in tablet form) were composed of the mycelium and primordia of the respective mushrooms and were provided by Mycology Research Laboratories Ltd. www.mycologyresearch.com

# Evaluation of the Efficacy of *Coriolus versicolor* in the Treatment of HPV Lesions (LSIL)*

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*Coriolus versicolor* (biomass) is a mushroom with immuno-stimulant properties used in traditional Asian cultures, namely in China and Japan, as a dietary supplement.

## Objectives

With the aim of evaluating the therapeutical effects in patients with cervical Low-grade Squamous Intraepithelial Lesions (LSIL) caused by HPV (Human Papillomavirus) infection, a group of 43 LSIL patients (confirmed by citology, colposcopy and biopsy) was randomly divided into 2 sub-groups: the first group received treatment with *Coriolus versicolor* for 1 year (6 tablets/day-3 g). The control group did not receive any treatment. In neither group was any therapeutic procedure performed (cryotherapy, electrocoagulation or laser vaporization).

## Results

Thirty nine (39) patients already concluded one year of follow-up. The first time they were controlled, 22 patients had HPV+ High Risk.

Eighteen (18) patients took *Coriolus* supplementation, while the other 21 patients had no therapy (control), all being under clinical observation for 365 days.

Of the 22 patients who showed HPV+ High Risk typification, 10 patients took *Coriolus* supplementation and 12 patients did not.

Of the 18 patients who took *Coriolus* supplementation over one year, 13 (72,5%) still showed normal cervical citology, after one year of follow up.

Of the 21 patients who did not take any supplementation, 10 (47,5%) still showed normal cervical citology after one year of follow-up.

Regarding HPV typification, from 10 patients who had HPV+ High Risk and took *Coriolus* supplementation, 9 (90%) reverted to HPV - status after one year.

On the other hand, of the 12 HPV+ High Risk status patients who did not take *Coriolus* supplementation, only 1 (8,5%) reverted to HPV - status.

## Material and Methods

All patients were confirmed by citology to be LSIL carriers. In the first consultation patients underwent both citology and biopsy to confirm the LSIL. In the same consultation HPV typing was screened. With the confirmation of LSIL diagnosis a randomization of the group was undertaken. In the second consultation citology was essayed to assess the LSIL status of the patient and a questionnaire on side-effects was performed. In the third consultation the patients underwent citology and HPV typing.

**Table 1. Results of the treatment of Low-grade Squamous Epithelial Lesions (LSIL)**

| | With *Coriolus versicolor* | | Without supplementation | | Total |
|---|---|---|---|---|---|
| | Normal after 1 year | Positive after 1 year | Normal after 1 year | Positive after 1 year | |
| Citology | 13 (72,5%) | 5 (27,5%) | 10 (47,5%) | 11 (52,5%) | 39 |
| HPV | 9 (90%) | 1 (10%) | 1 (8,5%) | 11 (91,5%) | 22 |

**Low-grade Squamous Epithelial Lesions (LSIL)-% of regression (1 year)**

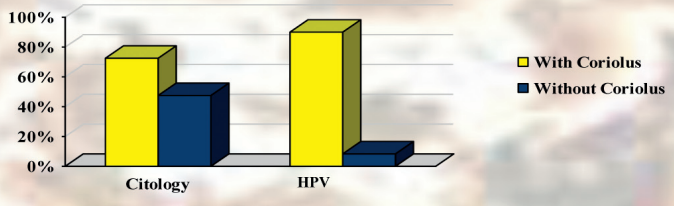


**Fig.1 - Percentage of regression of citologies LSIL and HPV + in LSIL patients**

*Coriolus MRL – Mycology Research Laboratories Ltd

## Conclusions

The use of *CORIOLUS VERSICOLOR* for 1 year revealed a great efficacy, whether in the regression of the displasia of Low-grade Squamous Intraepithelial Lesions (LSIL), or in the disappearance of the High Risk HPV.

It seems therefore, to be a very useful food supplementation with positive therapeutic impact, either in the reversion of LSIL (with High Risk HPV+), or in those HSIL patients, who have undergone surgery but experience continued High Risk HPV viral count.