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TABLE OF CONTENTS

FLULAVAL.....	PAGE 02
Vitamin K, an example of triage theory: is micronutrient inadequacy linked to diseases of aging?.....	PAGE 17
Tks5-Dependent, Nox-Mediated Generation of Reactive Oxygen Species Is Necessary for Invadopodia Formation.....	PAGE 18
Regulation of Cancer Invasion by Reactive Oxygen Species and Tks Family Scaffold Proteins.....	PAGE 19
Aqueous Extract of Black Maca (Lepidium meyenii) on Memory Impairment Induced by Ovariectomy in Mice.....	PAGE 20
Beneficial effects of Lepidium meyenii (Maca) on psychological symptoms and measures of sexual dysfunction in postmenopausal women are not related to estrogen or androgen content.....	PAGE 21
Antagonistic effect of Lepidium meyenii (red maca) on prostatic hyperplasia in adult mice.....	PAGE 22
Hypocotyls of Lepidium meyenii (maca), a plant of the Peruvian highlands, prevent ultraviolet A-, B-, and C-induced skin damage in rats.....	PAGE 23
Maca (Lepidium meyenii) and yacon (Smallanthus sonchifolius) in combination with silymarin as food supplements: in vivo safety assessment.....	PAGE 23
The influence of maca (Lepidium meyenii) on antioxidant status, lipid and glucose metabolism in rat.....	PAGE 24
Dose-response effect of Red Maca (Lepidium meyenii) on benign prostatic	

hyperplasia induced by testosterone enanthate.....PAGE 25

Medicinal plants from Peru: a review of plants as potential agents
against cancer.....PAGE 25

Inhibitory effect of a defensin gene from the Andean crop maca
(Lepidium meyenii) against Phytophthora infestans.....PAGE 26

Effect of three different cultivars of Lepidium meyenii (Maca) on
learning and depression in ovariectomized mice.....PAGE 27

Effect of ethanol extract of Lepidium meyenii Walp. on osteoporosis
in ovariectomized rat.....PAGE 28

Toxicological aspects of the South American herbs cat's claw
(Uncaria tomentosa) and Maca (Lepidium meyenii) : a critical synopsis.....PAGE 29

Red maca (Lepidium meyenii) reduced prostate size in rats.....PAGE 30

Smallanthus sonchifolius and Lepidium meyenii - prospective Andean
crops for the prevention of chronic diseases.....PAGE 31

Imidazole alkaloids from Lepidium meyenii.....PAGE 32

Investigation of the tuber constituents of maca (Lepidium meyenii Walp.).....PAGE 32

Composition of the essential oil of Lepidium meyenii (Walp).....PAGE 33

Constituents of Lepidium meyenii 'maca'.....PAGE 33

Nutritional evaluation of Lepidium meyenii (MACA) in albino mice
and their descendants.....PAGE 34

http://us.gsk.com/products/assets/us_flulaval.pdf

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use FLULAVAL safely and effectively. See full prescribing information for FLULAVAL.

FLULAVAL® (Influenza Virus Vaccine)

Suspension for Intramuscular Injection

2009-2010 Formula

Initial U.S. Approval: 2006

-----INDICATIONS AND USAGE-----

- FLULAVAL is an inactivated influenza virus vaccine indicated for active immunization of adults 18 years of age and older against influenza disease caused by influenza virus subtypes A and type B contained in the vaccine. (1)
- This indication is based on immune response elicited by FLULAVAL, and there have been no controlled trials demonstrating a decrease in influenza disease after vaccination with FLULAVAL. (14)

-----DOSAGE AND ADMINISTRATION-----

A single 0.5-mL intramuscular injection. (2.2)

-----DOSAGE FORMS AND STRENGTHS-----

- FLULAVAL is a suspension in 5-mL multi-dose vials containing 10 doses (each dose is 0.5 mL). (3)
- Each 0.5-mL dose contains 15 micrograms (mcg) of influenza virus hemagglutinin (HA) of each of the following 3 strains: A/Brisbane/59/2007, IVR-148 (H1N1), A/Uruguay/716/2007, NYMC X-175C (H3N2) (an A/Brisbane/10/2007-like virus), and B/Brisbane/60/2008. (3, 11)
- Thimerosal, a mercury derivative, is added as a preservative. Each 0.5 mL dose contains 25 mcg mercury. (3)

-----CONTRAINDICATIONS-----

Known systemic hypersensitivity reactions to egg proteins, or any other component of FLULAVAL, or life threatening reaction to previous influenza vaccination. (4.1)

-----WARNINGS AND PRECAUTIONS-----

- If Guillain-Barré syndrome has occurred within 6 weeks of receipt of a prior influenza vaccine, the decision to give FLULAVAL should be based on careful consideration of the potential benefits and risks. (5.1)
- Immunocompromised persons may have a reduced immune response to FLULAVAL. (5.2)

-----ADVERSE REACTIONS-----

- Most common ($\geq 10\%$) local adverse events were pain, redness, and/or swelling at the injection site. (6.1)
- Most common ($\geq 10\%$) systemic adverse events were headache, fatigue, myalgia, low grade fever, and malaise. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or VAERS at 1-800-822-7967 and www.vaers.hhs.gov.

-----DRUG INTERACTIONS-----

- Do not mix with any other vaccine in the same syringe or vial. (7.1)
- Immunosuppressive therapies may reduce immune responses to FLULAVAL. (7.2)

-----USE IN SPECIFIC POPULATIONS-----

- Safety and effectiveness of FLULAVAL have not been established in pregnant women, nursing mothers, and children. (8.1, 8.3, 8.4)
- Geriatric Use: Antibody responses were lower in geriatric subjects than in younger subjects. (8.5)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: July 2009

FLV:5PI

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 Preparation for Administration

2.2 Recommended Dose and Schedule

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

4.1 Hypersensitivity

5 WARNINGS AND PRECAUTIONS

5.1 Guillain-Barré Syndrome

5.2 Altered Immunocompetence

5.3 Persons at Risk of Bleeding

5.4 Preventing and Managing Allergic Vaccine Reactions

5.5 Limitations of Vaccine Effectiveness

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

6.2 Postmarketing Experience

6.3 Adverse Events Associated With Influenza Vaccines

7 DRUG INTERACTIONS

7.1 Concomitant Administration With Other Vaccines

7.2 Immunosuppressive Therapies

7.3 Warfarin, Theophylline, and Phenytoin

8 USE IN SPECIFIC POPULATIONS

P8.1 Pregnancy

8.3 Nursing Mothers

8.4 Pediatric Use

8.5 Geriatri Use

c11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

13 NONLINICAL TOXICOLOGY

C13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

FLULAVAL is an inactivated influenza virus vaccine indicated for active immunization of adults (18 years of age and older) against influenza disease caused by influenza virus subtypes A and type B contained in the vaccine.

This indication is based on immune response elicited by FLULAVAL, and there have been no controlled trials demonstrating a decrease in influenza disease after vaccination with FLULAVAL [see Clinical Studies (14)].

2 DOSAGE AND ADMINISTRATION

2.1 Preparation for Administration

Shake the multi-dose vial vigorously each time before withdrawing a dose of vaccine. Inspect the vial visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Inspect visually for cracks in the vial prior to administration. If any of these conditions exist, the vaccine should not be administered.

Between uses, return the multi-dose vial to the recommended storage conditions, between 2° and 8°C (36° and 46°F). Do not freeze. Discard if the vaccine has been frozen. Once entered, a multi-dose vial, and any residual contents, should be discarded after 28 days.

It is recommended that small syringes (0.5-mL or 1-mL) be used to minimize any product loss.

2.2 Recommended Dose and Schedule

FLULAVAL should be administered as a single 0.5-mL injection by the intramuscular route preferably in the region of the deltoid muscle of the upper arm.

The vaccine should not be injected in the gluteal area or areas where there may be a major nerve trunk. A needle length of ≥ 1 inch is preferred because needles < 1 inch might be of insufficient length to penetrate muscle tissue in certain adults.

Do not administer this product intravenously, intradermally or subcutaneously.

3 DOSAGE FORMS AND STRENGTHS

FLULAVAL is a suspension available in 5-mL multi-dose vials containing 10 doses.

Each 0.5-mL dose contains 15 micrograms (mcg) hemagglutinin (HA) of each of the following 3 influenza viruses: A/Brisbane/59/2007, IVR-148 (H1N1), A/Uruguay/716/2007, NYMC X-175C (H3N2) (an A/Brisbane/10/2007-like virus), and B/Brisbane/60/2008. Thimerosal, a mercury derivative, is added as a preservative. Each 0.5 mL dose contains 25 mcg mercury.

4 CONTRAINDICATIONS

4.1 Hypersensitivity

FLULAVAL should not be administered to anyone with known systemic hypersensitivity reactions to egg proteins (eggs or egg products), to chicken proteins, or to any component of FLULAVAL, or who has had a life threatening reaction to previous influenza vaccination.

5 WARNINGS AND PRECAUTIONS

5.1 Guillain-Barré Syndrome

If Guillain-Barré syndrome has occurred within 6 weeks of receipt of a prior influenza vaccine, the decision to give FLULAVAL should be based on careful consideration of the potential benefits and risks.

5.2 Altered Immunocompetence

If FLULAVAL is administered to immunocompromised persons, including individuals receiving immunosuppressive therapy, the expected immune response may not be obtained.

5.3 Persons at Risk of Bleeding

As with other intramuscular injections, FLULAVAL should be given with caution in individuals with bleeding disorders such as hemophilia or on anticoagulant therapy to avoid the risk of hematoma following the injection.

5.4 Preventing and Managing Allergic Vaccine Reactions

Prior to administration, the healthcare provider should review the patient's immunization history for possible vaccine sensitivity and previous vaccination-related adverse reactions. Appropriate medical treatment, including epinephrine, and supervision must be available to manage possible anaphylactic reactions following administration of the vaccine.

5.5 Limitations of Vaccine Effectiveness

Vaccination with FLULAVAL may not protect all susceptible individuals.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse event rates observed in the clinical trials of a vaccine cannot be directly compared to rates in the clinical trials of another vaccine, and may not reflect the rates observed in practice. As with any vaccine, there is the possibility that broad use of FLULAVAL could reveal adverse events not observed in clinical trials.

In clinical trials, the most common ($\geq 10\%$) local and systemic adverse events were pain, redness, and/or swelling at the injection site, headache, fatigue, myalgia, low grade fever, and malaise.

Safety information for FLULAVAL was collected in 2 randomized, controlled clinical trials, one in the United States (IDB707-105) and the second in Canada (SPD707-104). The safety population from these trials includes 1,049 adults 18 years of age and older vaccinated with products representative of the licensed formulation of FLULAVAL. The US study included subjects 18 to 64 years of age who were randomized to receive FLULAVAL (N = 721) or a US-licensed trivalent, inactivated influenza virus vaccine (FLUZONE) (N = 279). The Canadian study compared 4 vaccine groups: FLULAVAL, a similar investigational formulation of FLULAVAL with reduced thimerosal, and 2 Canadian-licensed trivalent influenza vaccines.

Among recipients of FLULAVAL, 56.6% were women; 92.4% of subjects were White, 6.5% Black, 2.7% Native American, and 1.0% Asian. In the US study, 74.8% of the recipients of FLULAVAL were Hispanic/Latino. The mean age of subjects in the US study was 38 years (range 18-64 years) and 19% of subjects were 50 to 64 years of age. In the Canadian study, the mean age was 63 years (range 50-92 years), and 46.6% were 65 years of age and older.

A series of symptoms and/or findings were specifically solicited by a diary/memory aid used by subjects for at least the day of vaccination and 3 days post-treatment (Table 1). Subjects were actively queried about changes in their health status through 42 days post-vaccination in the US trial, and six months post-vaccination in the Canadian study. In addition, spontaneous reports of adverse events were also collected (Table 2).

Table 1. Solicited Adverse Events in the First 4 Days After Administration of FLULAVAL or Comparator Influenza Vaccine

US Trial

Adults 18 to 64 years of age

(80% <50 years of age) Canadian Trial

Adults 50 years of age and older

FLULAVAL Comparator Influenza Vaccinea FLULAVALb

Adverse Events N = 721 N = 279 N = 328

Local

Pain 174 (24%) 85 (31%) 70 (21%)

Redness 76 (11%) 28 (10%) 48 (14%)

Swelling 71 (10%) 29 (10%) 21 (6%)

Systemic

Headache 127 (18%) 48 (17%) 34 (10%)

Fatigue 123 (17%) 43 (15%) 33 (10%)

Myalgia 93 (13%) 44 (16%) 35 (11%)

Feverc 79 (11%) 28 (10%) 1 (1%)

Malaise 73 (10%) 28 (10%) 13 (4%)

Sore throat 64 (9%) 26 (9%) 17 (5%)

Reddened eyes 44 (6%) 15 (5%) 10 (3%)

Cough 44 (6%) 19 (7%) 11 (3%)

Chills 38 (5%) 6 (2%) 10 (3%)

Chest tightness 24 (3%) 4 (1%) 6 (2%)

Facial swelling 7 (1%) 1 (1%) 1 (1%)

Results >1% reported to nearest whole percent; results >0 but ≤1 reported as 1%.

a US-licensed trivalent, inactivated influenza virus vaccine (FLUZONE).

b Includes subjects who received FLULAVAL and a similar investigational formulation of FLULAVAL with reduced thimerosal.

c Fever defined as ≥37.5°C in the US study, and ≥38.0°C in the Canadian study.

Local adverse events occurred with similar frequency in the 2 trials. In the US study, the only significant difference between FLULAVAL and a US-licensed trivalent, inactivated influenza virus vaccine was an increased frequency of chills in subjects receiving FLULAVAL.

Table 2 summarizes the most common adverse events in the 2 clinical trials; adverse events were reported, either spontaneously or in response to queries about changes in health status. The most common events were headache and cough in both studies. These, as well as throat pain, were the only adverse events reported by >1% of subjects in the US trial. The Canadian trial featured a longer safety follow-up (6 months vs. 42 days) and enrolled a population exclusively 50 years of age and older. Therefore, spontaneous adverse event reports were more frequent in this trial. As indicated in Table 2, upper respiratory infection, arthralgia, myalgia, nasopharyngitis, back pain, injection site erythema, diarrhea, fatigue, nausea, and nasal congestion were each reported by ≥5% of the recipients of FLULAVAL in the Canadian study.

Table 2. Adverse Events Reported Spontaneously by ≥5% of Subjects in Either Clinical Trial of FLULAVAL

US Trial

(safety follow-up 42 days)

Adults 18 to 64 years of age

(80% <50 years of age) Canadian Trial

(safety follow-up 6 months)

Adults 50 years of age and older

FLULAVAL Comparator Influenza Vaccine^b FLULAVAL^c

Adverse Events N = 721 N = 279 N = 328

Headache 49 (7%) 18 (7%) 63 (19%)

Cough 16 (2%) 5 (2%) 48 (15%)

Pharyngolaryngeal pain 17 (2%) 9 (3%) 38 (12%)

Upper respiratory infection	3 (1%)	2 (1%)	30 (9%)
Arthralgia	5 (1%)	3 (1%)	27 (8%)
Myalgia	4 (1%)	2 (1%)	23 (7%)
Nasopharyngitis	1 (1%)	1 (1%)	23 (7%)
Back pain	5 (1%)	3 (1%)	19 (6%)
Injection site erythema	2 (1%)	1 (1%)	18 (5%)
Diarrhea	5 (1%)	0	18 (5%)
Fatigue	6 (1%)	2 (1%)	17 (5%)
Nausea	5 (1%)	1 (1%)	17 (5%)
Nasal congestion	7 (1%)	2 (1%)	16 (5%)

Results >1% reported to nearest whole percent; results >0 but ≤1 reported as 1%.

a Adverse events in this table were reported spontaneously or in response to queries about changes in health status.

b US-licensed trivalent, inactivated influenza virus vaccine (FLUZONE).

c Includes subjects who received FLULAVAL and a similar investigational formulation of FLULAVAL with reduced thimerosal.

6.2 Postmarketing Experience

The following additional adverse events have been identified during postapproval use of FLULAVAL in Canada since 2001. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their incidence rate or establish a causal relationship to vaccine exposure. Adverse events described here are included because: a) they represent reactions which are known to occur following immunizations generally or influenza immunizations specifically; b) they are potentially serious; or c) the frequency of reporting.

Blood and Lymphatic System Disorders: Lymphadenopathy.

Eye Disorders: Conjunctivitis, eye pain, photophobia.

Gastrointestinal Disorders: Dysphagia, vomiting.

General Disorders and Administration Site Conditions: Chest pain, injection site inflammation, rigors, asthenia, injection site rash, influenza-like symptoms, abnormal gait, injection site bruising, injection site sterile abscess.

Immune System Disorders: Allergic edema of the face, allergic edema of the mouth, anaphylaxis, allergic edema of the throat.

Infections and Infestations: Pharyngitis, rhinitis, laryngitis, cellulitis.

Musculoskeletal and Connective Tissue Disorders: Muscle weakness, back pain, arthritis.

Nervous System Disorders: Dizziness, paresthesia, hypoesthesia, hypokinesia, tremor, somnolence, syncope, Guillain-Barré syndrome, convulsions/seizures, facial or cranial nerve paralysis, encephalopathy, limb paralysis.

Psychiatric Disorders: Insomnia.

Respiratory, Thoracic, and Mediastinal Disorders: Dyspnea, dysphonia, bronchospasm, throat tightness.

Skin and Subcutaneous Tissue Disorders: Urticaria, localized or generalized rash, pruritus, periorbital edema, sweating.

Vascular Disorders: Flushing, pallor.

6.3 Adverse Events Associated With Influenza Vaccines

Anaphylaxis has been reported after administration of FLULAVAL. Although FLULAVAL contains only a limited quantity of egg protein, this protein can induce immediate hypersensitivity reactions among persons who have severe egg allergy. Allergic reactions include hives, angioedema, allergic asthma, and systemic anaphylaxis [see Contraindications (4.1)].

The 1976 swine influenza vaccine was associated with an increased frequency of Guillain-Barré syndrome (GBS). Evidence for a causal relation of GBS with subsequent vaccines prepared from other influenza viruses is unclear. If influenza vaccine does pose a risk, it is probably slightly more than 1 additional case/1 million persons vaccinated.

Neurological disorders temporally associated with influenza vaccination such as encephalopathy, optic neuritis/neuropathy, partial facial paralysis, and brachial plexus neuropathy have been reported.

Microscopic polyangitis (vasculitis) has been reported temporally associated with influenza vaccination.

7 DRUG INTERACTIONS

7.1 Concomitant Administration With Other Vaccines

There are no data to assess the concomitant administration of FLULAVAL with other vaccines. If FLULAVAL is to be given at the same time as another injectable vaccine(s), the vaccines should always be administered at different injection sites. FLULAVAL should not be mixed with any other vaccine in the same syringe or vial.

7.2 Immunosuppressive Therapies

Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs, and corticosteroids (used in greater than physiologic doses), may reduce the immune response to FLULAVAL.

7.3 Warfarin, Theophylline, and Phenytoin

Although it has been reported that influenza vaccination may inhibit the clearance of warfarin, theophylline, and phenytoin, controlled studies have yielded inconsistent results regarding pharmacokinetic interactions between influenza vaccine and these medications. Nevertheless, clinicians should consider the potential for an interaction when FLULAVAL is administered to persons receiving these drugs.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C.

Animal reproduction studies have not been conducted with FLULAVAL. It is also not known whether FLULAVAL can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. FLULAVAL should be given to a pregnant woman only if clearly needed.

8.3 Nursing Mothers

It is not known whether FLULAVAL is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when FLULAVAL is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness of FLULAVAL in pediatric patients have not been established.

8.5 Geriatric Use

In the 2 clinical trials, there were 157 subjects who were ≥ 65 years of age and received FLULAVAL; 21 of these subjects were ≥ 75 years of age. Hemagglutination-inhibiting (HI) antibody responses were lower in geriatric subjects than younger subjects after administration of FLULAVAL. Solicited adverse events were similar in frequency to those reported in younger subjects [see Adverse Reactions (6.1)].

11 DESCRIPTION

FLULAVAL is a trivalent, split-virion, inactivated influenza virus vaccine prepared from virus propagated in the allantoic cavity of embryonated hens' eggs. Each of the influenza virus strains is produced and purified separately. The virus is inactivated with ultraviolet light treatment followed by formaldehyde treatment, purified by centrifugation, and disrupted with sodium deoxycholate.

FLULAVAL is a homogenized, sterile, colorless to slightly opalescent suspension in a phosphate-buffered saline solution. FLULAVAL has been standardized according to USPHS requirements for the 2009-2010 influenza season and is formulated to contain 45 mcg hemagglutinin per 0.5-mL dose in the recommended ratio of 15 mcg HA of each of the following 3 strains: A/Brisbane/59/2007, IVR-148

(H1N1), A/Uruguay/716/2007, NYMC X-175C (H3N2) (an A/Brisbane/10/2007-like virus), and B/Brisbane/60/2008. Thimerosal, a mercury derivative, is added as a preservative. Each dose contains 25 mcg mercury. Each dose may also contain residual amounts of egg proteins (≤ 1 mcg ovalbumin), formaldehyde (≤ 25 mcg), and sodium deoxycholate (≤ 50 mcg). Antibiotics are not used in the manufacture of this vaccine.

The vial stopper does not contain latex.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Influenza illness and its complications follow infection with influenza viruses. Global surveillance of influenza identifies yearly antigenic variants. For example, since 1977, antigenic variants of influenza A (H1N1 and H3N2) viruses and influenza B viruses have been in global circulation. Specific levels of HI antibody titer post-vaccination with inactivated influenza virus vaccines have not been correlated with protection from influenza illness but the antibody titers have been used as a measure of vaccine activity. In some human challenge studies, antibody titers of $\geq 1:40$ have been associated with protection from influenza illness in up to 50% of subjects.^{1,2} Antibody against one influenza virus type or subtype confers little or no protection against another virus. Furthermore, antibody to one antigenic variant of influenza virus might not protect against a new antigenic variant of the same type or subtype. Frequent development of antigenic variants through antigenic drift is the virological basis for seasonal epidemics and the reason for the usual change of one or more new strains in each year's influenza vaccine. Therefore, inactivated influenza vaccines are standardized to contain the hemagglutinins of strains (i.e., typically 2 type A and 1 type B), representing the influenza viruses likely to circulate in the United States in the upcoming winter.

Annual revaccination with the current vaccine is recommended because immunity declines during the year after vaccination, and because circulating strains of influenza virus change from year to year.³

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

FLULAVAL has not been evaluated for carcinogenic or mutagenic potential, or for impairment of fertility.

14 CLINICAL STUDIES

In 2 randomized, active-controlled trials of FLULAVAL, the immune responses, specifically HI antibody titers to each virus strain in the vaccine, were evaluated in sera obtained 21 days after administration of FLULAVAL. No controlled trials demonstrating a decrease in influenza disease after vaccination with FLULAVAL have been performed.

A 1,000-subject randomized, blinded, and controlled study was performed in the United States in 18- to 64-year-old healthy adults. A total of 721 subjects received FLULAVAL, and 279 received a US-licensed trivalent, inactivated influenza virus vaccine (FLUZONE); 959 subjects had complete serological data and no major protocol deviations. Among recipients of FLULAVAL, 57.4% were women. The mean age

of recipients of FLULAVAL was 37.9 years; 80.4% were 18 to 49 years of age and 19.6% were 50 to 64 years of age.

A second, randomized, blinded, and controlled study which enrolled 658 subjects 50 years of age and older (stratified by age <65 and ≥65 years) was conducted in Canada. This study included elderly persons with medically controlled chronic high-risk diagnoses who were clinically stable. This study compared 4 vaccine groups: FLULAVAL, a similar investigational formulation of FLULAVAL with reduced thimerosal, and 2 Canadian-licensed trivalent influenza vaccines. Results from the 2 groups that received FLULAVAL were submitted in support of the US licensure of FLULAVAL. Among these 2 groups, 54.9% of subjects were women. The mean age of recipients of FLULAVAL was 63 years; 53.4% were 50 to 64 years of age and 46.6% were 65 years of age and older.

For both studies, analysis of the following co-primary endpoints (Table 3) were performed for each HA antigen contained in the vaccine: 1) assessment of the lower bounds of 2-sided 95% confidence intervals for the proportion of subjects with HI antibody titers of ≥1:40 after vaccination, and 2) assessment of the lower bounds of 2-sided 95% confidence intervals for rates of seroconversion (defined as a 4-fold increase in post-vaccination HI antibody titer from pre-vaccination titer ≥1:10, or an increase in titer from <1:10 to ≥1:40). The pre-specified targets for the 2 endpoints varied by study because of age of subjects enrolled. The pre-specified target for endpoint 1) was 70% in the US study and 60% in the Canadian study. For endpoint 2) the pre-specified target was 40% in the US study and 30% in the Canadian study. For the Canadian study, the primary endpoints, as originally designed, were descriptive comparisons of immune response; therefore, a post-hoc analysis of the endpoints, as described above, was performed.

Table 3. Serum Hemagglutination-Inhibiting (HI) Antibody Responses to FLULAVAL in 2 Clinical Trialsa (Per Protocol Cohort)b

US Trial in Adults 18 to 64 years of age % of Subjects

(lower bound of 2-sided 95% confidence interval)c

FLULAVAL Primary endpoint met

post-vaccination

N = 692

HI titers ≥1:40 against: Pre-vaccination Post-vaccination

A/New Caledonia/20/99 (H1N1)	24.6	96.5 (94.9)	Yes
A/Wyoming/03/03 (H3N2)	58.7	98.7 (97.6)	Yes
B/Jiangsu/10/03	5.4	62.9 (59.1)	No

Seroconversiond to:

A/New Caledonia/20/99 (H1N1)	85.6 (82.7)	Yes
A/Wyoming/03/03 (H3N2)	79.3 (76.1)	Yes

B/Jiangsu/10/03	58.4 (54.6)	Yes	
Canadian Trial in Adults ≥ 50 years of age % of Subjects			
(lower bound of 2-sided 95% confidence interval) ^c			
FLULAVALE Primary endpoint met			
post-vaccination			
N = 324			
HI titers $\geq 1:40$ against: Pre-vaccination Post-vaccination			
A/New Caledonia/20/99 (H1N1)	39.5	86.4 (82.2)	Yes
A/Wyoming/03/03 (H3N2)	67.9	99.1 (97.3)	Yes
B/Jiangsu/10/03	10.2	57.1 (51.5)	No

Seroconversion^d to:

A/New Caledonia/20/99 (H1N1)	44.8 (39.3)	Yes
A/Wyoming/03/03 (H3N2)	69.1 (63.8)	Yes
B/Jiangsu/10/03	49.1 (43.5)	Yes

a Results obtained following vaccination with FLULAVALE manufactured for the 2004–2005 season.

b Per Protocol Cohort for immunogenicity included subjects with complete pre- and post-dose HI titer data and no major protocol deviations.

c Lower bounds were calculated using Clopper-Pearson method.

d Seroconversion = a 4-fold increase post-vaccination in HI antibody titer from pre-vaccination titer $\geq 1:10$, or an increase in titer from $<1:10$ to $\geq 1:40$.

e Includes subjects who received FLULAVALE and a similar investigational formulation of FLULAVALE with reduced thimerosal.

Across both studies, serum HI antibody responses to FLULAVALE met the pre-specified seroconversion criteria for all 3 virus strains, and also the pre-specified criterion for the proportion of subjects with HI titers $\geq 1:40$ for both influenza A viruses. In both trials, both FLULAVALE and the comparator vaccine did not meet the pre-specified criterion for the proportion of subjects with HI titers $\geq 1:40$ for the influenza B virus. The clinical relevance of this finding on vaccine-induced protection against illness caused by influenza type B strains is unknown.

15 REFERENCES

1. Hannoun C, Megas F, Piercy J. Immunogenicity and protective efficacy of influenza vaccination. *Virus Res* 2004;103:133-138.
2. Hobson D, Curry RL, Beare AS, et al. The role of serum haemagglutination-inhibiting antibody in protection against challenge infection with influenza A2 and B viruses. *J Hyg Camb* 1972;70:767-777.
3. Centers for Disease Control and Prevention. Prevention and control of influenza: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2006;55(RR-10):1-42.

16 HOW SUPPLIED/STORAGE AND HANDLING

FLULAVAL is supplied in a 5-mL multi-dose vial containing ten 0.5-mL doses. Once entered, the multi-dose vial should be discarded after 28 days.

Store refrigerated between 2° and 8°C (36° and 46°F). Do not freeze. Discard if the vaccine has been frozen. Store in the original package to protect from light.

NDC 19515-886-07 (package of 1 vial containing 10 doses)

17 PATIENT COUNSELING INFORMATION

The vaccine recipient or guardian should be:

- informed of the potential benefits and risks of immunization with FLULAVAL.
- educated regarding potential side effects, emphasizing that (1) FLULAVAL contains non-infectious killed viruses and cannot cause influenza and (2) FLULAVAL is intended to provide protection against illness due to influenza viruses only, and cannot provide protection against all respiratory illness.
- instructed to report any adverse events to their healthcare provider.
- given the Vaccine Information Statements, which are required by the National Childhood Vaccine Injury Act of 1986 to be given prior to immunization. These materials are available free of charge at the Centers for Disease Control and Prevention (CDC) website (www.cdc.gov/vaccines).
- instructed that annual revaccination is recommended.

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This Article

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ORIGINAL RESEARCH COMMUNICATION

Vitamin K, an example of triage theory: is micronutrient inadequacy linked to diseases of aging?

Joyce C McCann and Bruce N Ames

1 From the Children's Hospital Oakland Research Institute, Oakland, CA.

2 Supported by the Bruce and Giovanna Ames Foundation and by a generous donation from Elizabeth B and J Burgess Jamieson.

3 Address correspondence to JC McCann or BN Ames, Children's Hospital Oakland Research Institute, 5700 Martin Luther King Jr Way, Oakland, CA 94609. E-mail: jmccann@chori.org or bames@chori.org .

ESSENCE OF ARTICLE

“A triage perspective reinforces recommendations of some experts that much of the population and warfarin/coumadin patients may not receive sufficient vitamin K for optimal function of VKD proteins that are important to maintain long-term health. ‘

ARTICLE

The triage theory posits that some functions of micronutrients (the 40 essential vitamins, minerals, fatty acids, and amino acids) are restricted during shortage and that functions required for short-term survival take precedence over those that are less essential. Insidious changes accumulate as a consequence of restriction, which increases the risk of diseases of aging. For 16 known vitamin K–dependent (VKD) proteins, we evaluated the relative lethality of 11 known mouse knockout mutants to categorize essentiality. Results indicate that 5 VKD proteins that are required for coagulation had critical functions (knockouts were embryonic lethal), whereas the knockouts of 5 less critical VKD proteins [osteocalcin, matrix Gla protein (Mgp), growth arrest specific protein 6, transforming growth factor β -inducible protein (Tgfb1 or β ig-h3), and periostin] survived at least through weaning. The VKD -carboxylation of the 5 essential VKD proteins in the liver and the 5 nonessential proteins in nonhepatic tissues sets up a dichotomy that takes advantage of the preferential distribution of dietary vitamin K1 to the liver to preserve coagulation function when vitamin K1 is limiting. Genetic loss of less critical VKD proteins, dietary vitamin K inadequacy, human polymorphisms or mutations, and vitamin K deficiency induced by chronic anticoagulant (warfarin/coumadin) therapy are all linked to age-associated conditions: bone fragility after estrogen loss (osteocalcin) and arterial calcification linked to cardiovascular disease (Mgp).

There is increased spontaneous cancer in Tgfbi mouse knockouts, and knockdown of Tgfbi causes mitotic spindle abnormalities. A triage perspective reinforces recommendations of some experts that much of the population and warfarin/coumadin patients may not receive sufficient vitamin K for optimal function of VKD proteins that are important to maintain long-term health.

<http://stke.sciencemag.org/cgi/content/abstract/sigtrans;2/88/ra53>

Sci. Signal., 15 September 2009

Vol. 2, Issue 88, p. ra53

[DOI: 10.1126/scisignal.2000368]

RESEARCH

Tks5-Dependent, Nox-Mediated Generation of Reactive Oxygen Species Is Necessary for Invadopodia Formation

Begoña Diaz*, Gidon Shani*, Ian Pass, Diana Anderson, Manuela Quintavalle, and Sara A. Courtneidge

Tumor Microenvironment Program, Burnham Institute for Medical Research, 10901 North Torrey Pines Road, La Jolla, CA 92037, USA.

- The order of these authors was chosen by lot.

ESSENCE OF ARTICLE

“Invadopodia are actin-rich membrane protrusions of cancer cells that facilitate pericellular proteolysis and invasive behavior. We show here that reactive oxygen species (ROS) generated by the NADPH (reduced form of nicotinamide adenine dinucleotide phosphate) oxidase (Nox) system are necessary for invadopodia formation and function.”

ARTICLE

Abstract: Invadopodia are actin-rich membrane protrusions of cancer cells that facilitate pericellular proteolysis and invasive behavior. We show here that reactive oxygen species (ROS) generated by the NADPH (reduced form of nicotinamide adenine dinucleotide phosphate) oxidase (Nox) system are necessary for invadopodia formation and function. Knockdown of the invadopodia protein Tks5 [tyrosine kinase substrate with five Src homology 3 (SH3) domains], which is structurally related to the Nox component p47phox, reduces total ROS abundance in cancer cells. Furthermore, Tks5 and p22phox can associate with each other, suggesting that Tks5 is part of the Nox complex. Tyrosine phosphorylation of Tks5 and Tks4, but not other Src substrates, is reduced by Nox inhibition. We propose that Tks5 facilitates the production of ROS necessary for invadopodia formation, and that in turn ROS modulate Tks5 tyrosine phosphorylation in a positive feedback loop.

To whom correspondence should be addressed. E-mail: courtneidge@burnham.org

Citation: B. Diaz, G. Shani, I. Pass, D. Anderson, M. Quintavalle, S. A. Courtneidge, Tks5-Dependent, Nox-Mediated Generation of Reactive Oxygen Species Is Necessary for Invadopodia Formation. *Sci. Signal.* 2, ra53 (2009).

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In Science Signaling

PERSPECTIVES

CANCER

Regulation of Cancer Invasion by Reactive Oxygen Species and Tks Family Scaffold Proteins

Alissa M. Weaver (15 September 2009)

Sci. Signal. 2 (88), pe56. [DOI: 10.1126/scisignal.288pe56]

[Abstract](#) » [Full Text](#) » [PDF](#) »

REVIEWS

BIOCHEMISTRY

Localizing NADPH Oxidase–Derived ROS

Masuko Ushio-Fukai (22 August 2006)

Sci. STKE 2006 (349), re8. [DOI: 10.1126/stke.3492006re8]

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D. Gianni, B. Diaz, N. Taulet, B. Fowler, S. A. Courtneidge, and G. M. Bokoch (2009)

Science Signaling 2, ra54

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PMID: 18955369 [PubMed - as supplied by publisher]

Evid Based Complement Alternat Med. 2008 Oct 9. [Epub ahead of print]

Related Articles, Links

PMID: 18955369 [PubMed - as supplied by publisher]

Aqueous Extract of Black Maca (*Lepidium meyenii*) on Memory Impairment Induced by Ovariectomy in Mice.

Rubio J, Qiong W, Liu X, Jiang Z, Dang H, Chen SL, Gonzales GF.

Research Center for Pharmacology & Toxicology, Institute of Medicinal Plant Development, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100193, P.R. China.
liuxinminuae@yahoo.com.cn.

ESSENCE OF ARTICLE

” Black maca (0.5 and 2.0 g/kg) increased step-down latency when compared to OVX control mice. Black maca decreased MDA and Ache levels in OVX mice; whereas, no differences were observed in MAO levels. Finally, black maca improved experimental memory impairment induced by ovariectomy, due in part, by its antioxidant and Ache inhibitory activities.”

ARTICLE

The present study aims to test two different doses of aqueous extract of black maca on learning and memory in ovariectomized (OVX) mice and their relation with malonaldehyde (MDA), acetylcholinesterase (Ache) and monoamine oxidase (MAO) brain levels. Female mice were divided into five groups: (i) naive (control), (ii) sham, (iii) OVX mice and OVX mice treated with (iv) 0.50 g kg(-1) and (v) 2.00 g kg(-1) black maca. Mice were orally treated with distilled water or black maca during 35 days starting 7 days after surgery. Memory and learning were assessed using the water Morris maze (from day 23-27) and the step-down avoidance test (days 34 and 35). At the end of each treatment, mice were sacrificed by decapitation and brains were dissected out for MDA, Ache and MAO determinations. Black maca (0.5 and 2.0 g/kg) increased step-down latency when compared to OVX control mice. Black maca decreased MDA and Ache levels in OVX mice; whereas, no differences were observed in MAO levels. Finally, black maca improved experimental memory impairment induced by ovariectomy, due in part, by its antioxidant and Ache inhibitory activities.

PMID: 18955369 [PubMed - as supplied by publisher]

PMID: 18784609 [PubMed - indexed for MEDLINE]

Menopause. 2008 Nov-Dec;15(6):1157-62.

Related Articles, Links

Beneficial effects of *Lepidium meyenii* (Maca) on psychological symptoms and measures of sexual dysfunction in postmenopausal women are not related to estrogen or androgen content.

Brooks NA, Wilcox G, Walker KZ, Ashton JF, Cox MB, Stojanovska L.

School of Biomedical and Health Sciences, Victoria University, St. Albans, Victoria, Australia.

ESSENCE OF ARTICLE

“CONCLUSIONS: Preliminary findings show that *Lepidium meyenii* (Maca) (3.5 g/d) reduces psychological symptoms, including anxiety and depression, and lowers measures of sexual dysfunction in postmenopausal women independent of estrogenic and androgenic activity.”

ARTICLE

OBJECTIVE: To examine the estrogenic and androgenic activity of *Lepidium meyenii* (Maca) and its effect on the hormonal profile and symptoms in postmenopausal women. **DESIGN:** Fourteen postmenopausal women completed a randomized, double-blind, placebo-controlled, crossover trial. They received 3.5 g/day of powdered Maca for 6 weeks and matching placebo for 6 weeks, in either order, over a total of 12 weeks. At baseline and weeks 6 and 12 blood samples were collected for the measurement of estradiol, follicle-stimulating hormone, luteinizing hormone, and sex hormone-binding globulin, and the women completed the Greene Climacteric Scale to assess the severity of menopausal symptoms. In addition, aqueous and methanolic Maca extracts were tested for androgenic and estrogenic activity using a yeast-based hormone-dependent reporter assay. **RESULTS:** No differences were seen in serum concentrations of estradiol, follicle-stimulating hormone, luteinizing hormone, and sex hormone-binding globulin between baseline, Maca treatment, and placebo ($P > 0.05$). The Greene Climacteric Scale revealed a significant reduction in scores in the areas of psychological symptoms, including the subscales for anxiety and depression and sexual dysfunction after Maca consumption compared with both baseline and placebo ($P < 0.05$). These findings did not correlate with androgenic or alpha-estrogenic activity present in the Maca as no physiologically significant activity was observed in yeast-based assays employing up to 4 mg/mL Maca extract (equivalent to 200 mg/mL Maca). **CONCLUSIONS:** Preliminary findings show that *Lepidium meyenii* (Maca) (3.5 g/d) reduces psychological symptoms, including anxiety and depression, and lowers measures of sexual dysfunction in postmenopausal women independent of estrogenic and androgenic activity.

Publication Types:

- Randomized Controlled Trial
- Research Support, N.I.H., Extramural

PMID: 18784609 [PubMed - indexed for MEDLINE]

ADDITIONAL RESEARCH ON MACA, SHOULD YOU WISH

3: *Andrologia*. 2008 Jun;40(3):179-85.

Related Articles, Links

Antagonistic effect of *Lepidium meyenii* (red maca) on prostatic hyperplasia in adult mice.

Gonzales GF, Gasco M, Malheiros-Pereira A, Gonzales-Castañeda C.

Faculty of Sciences and Philosophy, Instituto de Investigaciones de la Altura, Universidad Peruana Cayetano Heredia, Lima, Peru. ggr@upch.edu.pe

The plants from the *Lepidium* gender have demonstrated to have effect on the size of the prostate. *Lepidium meyenii* (Maca) is a Peruvian plant that grows exclusively over 4000 m above sea level. The present study was designed to determine the effect of red maca (RM) in the prostate hyperplasia induced with testosterone enanthate (TE) in adult mice. Prostate hyperplasia was induced by administering TE, and then these animals (n = 6, each group) were treated with RM or Finasteride (positive control) for 21 days. There was an additional group without prostate hyperplasia (vehicle). Mice were killed on days 7, 14 and 21 after treatment with RM. Testosterone and oestradiol levels were measured on the last day of treatment. Prostatic stroma, epithelium and acini were measured histologically. RM reduced prostate weight at 21 days of treatment. Weights of seminal vesicles, testis and epididymis were not affected by RM treatment. The reduction in prostate size by RM was 1.59 times. Histological analysis showed that TE increased 2-fold the acinar area, effect prevented in the groups receiving TE + RM for 14 (P < 0.05) and 21 (P < 0.05) days and the group receiving TE + Finasteride for 21 days (P < 0.05). TE increased prostatic stroma area and this effect was prevented by treatment with RM since 7 days of treatment or Finasteride. The reduction in prostatic stroma area by RM was 1.42 times. RM has an anti-hyperplastic effect on the prostate of adult mice when hyperplasia was induced with TE acting first at prostatic stromal level.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 18477205 [PubMed - indexed for MEDLINE]

4: *Photodermatol Photoimmunol Photomed*. 2008 Feb;24(1):24-31.

Related Articles, Links

Hypocotyls of *Lepidium meyenii* (maca), a plant of the Peruvian highlands, prevent ultraviolet A-, B-, and C-induced skin damage in rats.

Gonzales-Castañeda C, Gonzales GF.

Department of Biological and Physiological Sciences, Faculty of Sciences and Philosophy, Universidad Peruana Cayetano Heredia, Lima, Peru.

BACKGROUND: *Lepidium meyenii* (maca) is a plant that grows exclusively in the Peruvian Central Andes, where ultraviolet radiation (UVR) is predominant. **Objective:** Determine if two extracts of maca can provide dermal protection against UVR. **METHODS:** We have administered two maca extracts (0.13 mg/ml), one obtained after boiling and the other without boiling, on the dorsal surface of male Holtzman rats exposed to UVC radiation once a week during 3 consecutive weeks. A dose-response effect of an aqueous extract of maca after a boiling process under exposure of rats to UVA, UVB, or UVC was also studied. A commercial sunscreen was used as a positive control. **RESULTS:** UVR caused significant increase in skin epidermal thickness. The epidermal height in animals treated with maca was similar to those who did not receive UVR. The aqueous extract of maca after a boiling process had better effect than maca extract without a boiling process. A dose-response effect was observed with increasing doses of aqueous extract of maca after a boiling process. Maca extract had benzyl glucosinolates and polyphenols. **CONCLUSIONS:** Maca extracts protect the skin of rats against UV irradiations and can be suggested as an alternative means of solar protection.

Publication Types:

- Research Support, N.I.H., Extramural
- Research Support, Non-U.S. Gov't

PMID: 18201354 [PubMed - indexed for MEDLINE]

5: Food Chem Toxicol. 2008 Mar;46(3):1006-13. Epub 2007 Nov 1.

Related Articles, Links

Maca (*Lepidium meyenii*) and yacon (*Smallanthus sonchifolius*) in combination with silymarin as food supplements: in vivo safety assessment.

Valentová K, Stejskal D, Bartek J, Dvořáková S, Kren V, Ulrichová J, Simánek V.

Department of Medical Chemistry and Biochemistry, Palacký University, Olomouc, Czech Republic.
kata.valentova@email.cz

Yacon and maca are native Andean crops with growing popularity as food supplements often in combination with other components, e.g. silymarin. There are however no published data on their toxicity and safety in humans. The aim of our randomized placebo-controlled 90-day study was to evaluate the effects of yacon and maca in combination with silymarin on plasma and lipoprotein lipids, serum glucose

and safety parameters in patients suffering from the metabolic syndrome. No adverse effects were found in volunteers using silymarin (0.8 g/day), silymarin+yacon (0.8+2.4 g/day) and silymarin+maca (0.6+0.2 g/day). A moderate AST level and diastolic blood pressure increase was found in volunteers using maca (0.6 g/day). In conclusion, the combination silymarin+yacon appears to be promising as a nutraceutical in the prevention of diseases with a proatherogenic lipoprotein profile and liver steatosis. The effect of maca on AST level and blood pressure must be considered when using high doses of maca powder. This effect could be reversed by supplementation with silymarin.

Publication Types:

- Randomized Controlled Trial
- Research Support, Non-U.S. Gov't

PMID: 18054420 [PubMed - indexed for MEDLINE]

7: Plant Foods Hum Nutr. 2007 Jun;62(2):59-63.

Related Articles, Links

The influence of maca (*Lepidium meyenii*) on antioxidant status, lipid and glucose metabolism in rat.

Vecera R, Orolin J, Skottová N, Kazdová L, Oliyarnik O, Ulrichová J, Simánek V.

Institute of Pharmacology, Medical Faculty, Palacký University, Hnevotínská 3, 775 15, Olomouc, Czech Republic. vecera@seznam.cz

This work focused on the effect of Maca on lipid, anti-oxidative, and glucose parameters in hereditary hypertriglyceridemic (HHTg) rat. Maca (1%) was administered to rats as a part of a high-sucrose diet (HSD) for 2 weeks. Rosiglitazone (0.02%) was used as a positive control. Maca significantly decreased the levels of VLDL (very low density lipoproteins), LDL (low density lipoproteins), and total cholesterol, and also the level of TAG (triacylglycerols) in the plasma, VLDL, and liver. Maca, as well as rosiglitazone, significantly improved glucose tolerance, as the decrease of AUC (area under the curve) of glucose showed, and lowered levels of glucose in blood. The activity of SOD (superoxide dismutase) in the liver, the GPX (glutathione peroxidase) in the blood, and the level of GSH (glutathione) in liver increased in all cases significantly. Results demonstrate that maca seems to be promising for a positive influence on chronic human diseases (characterized by atherogenous lipoprotein profile, aggravated antioxidative status, and impaired glucose tolerance), and their prevention.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 17333395 [PubMed - indexed for MEDLINE]

8: Phytomedicine. 2007 Aug;14(7-8):460-4. Epub 2007 Feb 7.

Related Articles, Links

Dose-response effect of Red Maca (*Lepidium meyenii*) on benign prostatic hyperplasia induced by testosterone enanthate.

Gasco M, Villegas L, Yucra S, Rubio J, Gonzales GF.

Department of Biological and Physiological Sciences, Universidad Peruana Cayetano Heredia, Lima, Peru. 05931@upch.edu.pe

The main goal of this study was to determine the effect of a freeze-dried aqueous extract of the red variety of *Lepidium meyenii* (Red Maca) on testosterone-induced benign prostatic hyperplasia (BPH) in adult rats of the Holtzman strain. Rats were treated with freeze-dried aqueous extract of Red Maca at doses of 0, 0.01, 0.05, 0.1, and 0.5 g/kg body wt. A positive control group received Finasteride (0.6 mg/kg body wt.). After treatment, the animals were sacrificed, and the ventral prostate was extracted, and weighed. HPLC was used to determine the presence of glucosinolates in Red Maca. The prostate weight diminished in a dose-dependent fashion in rats treated with Red Maca. The effect of Red Maca was better than that observed with Finasteride. Finasteride, but not Red Maca, reduced seminal vesicles weight. Analysis of the HPLC indicated the presence of benzyl glucosinolate (Glucotropaeolin) with a content of 0.639%. Serum testosterone levels were not affected by Red Maca. Moreover, serum testosterone levels were not related to prostate or seminal vesicles weight in rats treated with vehicle and Red Maca. In conclusion, Red Maca administered orally in rats seems to exert an inhibitory effect at a level post DHT conversion, on the BPH-induced experimentally, although a direct measure of reductase action would still be required.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 17289361 [PubMed - indexed for MEDLINE]

9: Anticancer Agents Med Chem. 2006 Sep;6(5):429-44.

Related Articles, Links

Medicinal plants from Peru: a review of plants as potential agents against cancer.

Gonzales GF, Valerio LG Jr.

Department of Biological and Physiological Sciences, Faculty of Sciences and Philosophy and Instituto de Investigaciones de la Altura, Universidad Peruana Cayetano Heredia, Lima, Peru. iiad@upch.edu.pe

Natural products have played a significant role in drug discovery and development especially for agents against cancer and infectious disease. An analysis of new and approved drugs for cancer by the United States Food and Drug Administration over the period of 1981-2002 showed that 62% of these cancer drugs were of natural origin. Natural compounds possess highly diverse and complex molecular structures compared to small molecule synthetic drugs and often provide highly specific biological activities likely derived from the rigidity and high number of chiral centers. Ethnotraditional use of plant-derived natural products has been a major source for discovery of potential medicinal agents. A number of native Andean and Amazonian medicines of plant origin are used as traditional medicine in Peru to treat different diseases. Of particular interest in this mini-review are three plant materials endemic to Peru with the common names of Cat's claw (*Uncaria tomentosa*), Maca (*Lepidium meyenii*), and Dragon's blood (*Croton lechleri*) each having been scientifically investigated for a wide range of therapeutic uses including as specific anti-cancer agents as originally discovered from the long history of traditional usage and anecdotal information by local population groups in South America. Against this background, we present an evidence-based analysis of the chemistry, biological properties, and anti-tumor activities for these three plant materials. In addition, this review will discuss areas requiring future study and the inherent limitations in their experimental use as anti-cancer agents.

Publication Types:

- Review

PMID: 17017852 [PubMed - indexed for MEDLINE]

10: J Plant Physiol. 2007 Aug;164(8):1071-82. Epub 2006 Aug 17.

Related Articles, Links

Inhibitory effect of a defensin gene from the Andean crop maca (*Lepidium meyenii*) against *Phytophthora infestans*.

Solis J, Medrano G, Ghislain M.

International Potato Center, Applied Biotechnology Laboratory, P.O. Box 1558, Lima 12, Peru.

In this study, we report the isolation of a defensin gene, *Im-def*, isolated from the Andean crop 'maca' (*Lepidium meyenii*) with activity against the pathogen *Phytophthora infestans* responsible of late blight disease of the potato and tomato crops. The *Im-def* gene has been isolated by polymerase chain reaction (PCR) using degenerate primers corresponding to conserved regions of 13 plant defensin genes of the Brassicaceae family assuming that defensin genes are highly conserved among cruciferous species. The *Im-def* gene belongs to a small multigene family of at least 10 members possibly including pseudogenes

as assessed by genomic hybridization and nucleotide sequence analyses. The deduced mature Lm-Def peptide is 51 amino acids in length and has 74-94% sequence identity with other plant defensins of the Brassicaceae family. The Lm-Def peptide was produced as a fusion protein using the pET-44a expression vector and purified using an immobilized metal ion affinity chromatography. The recombinant protein (NusA:Lm-Def) exhibited in vitro activity against *P. infestans*. The NusA:Lm-Def protein caused growth inhibition and hyphal damage at concentration not greater than 0.4 microM. In contrast, the NusA protein alone expressed and purified similarly did not show any activity against *P. infestans*. Therefore, these results indicate that the lm-def gene isolated from maca belong to the plant defensin family with activity against *P. infestans*. Its expression in potato, as a transgene, might help to control the late blight disease caused by *P. infestans* with the advantage of being of plant origin.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 16919367 [PubMed - indexed for MEDLINE]

11: BMC Complement Altern Med. 2006 Jun 23;6:23.

Related Articles, Links

Effect of three different cultivars of *Lepidium meyenii* (Maca) on learning and depression in ovariectomized mice.

Rubio J, Caldas M, Dávila S, Gasco M, Gonzales GF.

Department of Biological and Physiological Sciences, Faculty of Sciences and Philosophy and Instituto de Investigaciones de la Altura, Universidad Peruana Cayetano Heredia, Lima, Peru. 09008@upch.edu.pe

BACKGROUND: *Lepidium meyenii* Walp. (Brassicaceae), known as Maca, is a Peruvian hypocotyl growing exclusively between 4000 and 4500 m altitude in the central Peruvian Andes, particularly in Junin plateau and is used traditionally to enhance fertility. Maca is a cultivated plant and different cultivars are described according to the color of the hypocotyls. **METHODS:** The study aimed to elucidate the effect of Yellow, Red and Black Maca on cognitive function and depression in ovariectomized (OVX) mice. In all experiments OVX mice were treated during 21 days and divided in four groups: control group, Yellow Maca, Red Maca and Black Maca. Latent learning was assessed using the water finding task and the antidepressant activity of the three varieties of Maca was evaluated using the forced swimming test. Animals were sacrificed at the end of each treatment and the uterus were excised and weighed. **RESULTS:** Black Maca was the variety that showed the best response in the water finding task, particularly in the trained mice. The three varieties were effective to reduce finding latency in non trained and trained mice ($P < 0.05$). In the force swimming test, all varieties assessed reduced the time of immobility and increased uterine weight in OVX mice. **CONCLUSION:** Black Maca appeared to

have more beneficial effects on latent learning in OVX mice; meanwhile, all varieties of Maca showed antidepressant activity.

Publication Types:

- Comparative Study
- Research Support, Non-U.S. Gov't

PMID: 16796734 [PubMed - indexed for MEDLINE]

PMCID: PMC1534053

12: J Ethnopharmacol. 2006 Apr 21;105(1-2):274-9. Epub 2006 Feb 8.

Related Articles, Links

Effect of ethanol extract of *Lepidium meyenii* Walp. on osteoporosis in ovariectomized rat.

Zhang Y, Yu L, Ao M, Jin W.

School of Life Science & Technology, Huazhong University of Science & Technology, 430074 Wuhan, PR China.

Maca (*Lepidium meyenii* Walp.) is a cruciferous plant from the Andes of Peru. The root of Maca is traditionally employed for its supposed properties in aphrodisiacs and improving fertility, it also has been widely used to help alleviate the symptoms of menopause. The purpose of this study was to evaluate the effect of ethanol extract of Maca on postmenopausal osteoporosis in ovariectomized rats. Female Sprague-Dawley rats were divided into four groups: Sham-operated and ovariectomized groups were fed with equivolume of distilled water, and the remaining ovariectomized groups were orally administrated with ethanol extract of Maca at 0.096 and 0.24 g/kg for 28 weeks. The findings derived from the basis of bone mineral density, biomechanical, biochemical and histopathological parameters indicated that higher dose of ethanol extract of Maca was effective in the prevention of estrogen deficient bone loss.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 16466876 [PubMed - indexed for MEDLINE]

14: Toxicol Rev. 2005;24(1):11-35.

Related Articles, Links

Toxicological aspects of the South American herbs cat's claw (*Uncaria tomentosa*) and Maca (*Lepidium meyenii*) : a critical synopsis.

Valerio LG Jr, Gonzales GF.

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Recent exceptional growth in human exposure to natural products known to originate from traditional medicine has led to a resurgence of scientific interest in their biological effects. As a strategy for improvement of the assessment of their pharmacological and toxicological profile, scientific evidence-based approaches are being employed to appropriately evaluate composition, quality, potential medicinal activity and safety of these natural products. Using this approach, we comprehensively reviewed existing scientific evidence for known composition, medicinal uses (past and present), and documented biological effects with emphasis on clinical pharmacology and toxicology of two commonly used medicinal plants from South America with substantial human exposure from historical and current global use: *Uncaria tomentosa* (common name: cat's claw, and Spanish: uña de gato), and *Lepidium meyenii* (common name: maca). Despite the geographic sourcing from remote regions of the tropical Amazon and high altitude Andean mountains, cat's claw and maca are widely available commercially in industrialised countries. Analytical characterisations of their active constituents have identified a variety of classes of compounds of toxicological, pharmacological and even nutritional interest including oxindole and indole alkaloids, flavonoids, glucosinolates, sterols, polyunsaturated fatty acids, carbolines and other compounds. The oxindole alkaloids from the root bark of cat's claw are thought to invoke its most widely sought-after medicinal effects as a herbal remedy against inflammation. We find the scientific evidence supporting this claim is not conclusive and although there exists a base of information addressing this medicinal use, it is limited in scope with some evidence accumulated from in vitro studies towards understanding possible mechanisms of action by specific oxindole alkaloids through inhibition of nuclear factor (NF)- κ B activation. Although controlled clinical studies have demonstrated reduction in pain associated with cat's claw intake in patients with various chronic inflammatory disorders, there is insufficient clinical data overall to draw a firm conclusion for its anti-inflammatory effects. An important observation was that experimental results were often dependent upon the nature of the preparation used. It appears that the presence of unknown substances has an important role in the overall effects of cat's claw extracts is an important factor for consideration. The available animal toxicological studies did not indicate severe toxicity from oral intake of cat's claw preparations but rather were suggestive of a low potential for acute and subacute oral toxicity, and a lack of evidence to demonstrate genotoxic potential and mutagenic activity. Maca is a clear example of a herb with substantial medicinal use in traditional herbal medicine by indigenous cultures in South America since the first recorded knowledge of it in the seventeenth century. The hypocotyls of maca are the edible part of the plant used for nutritional and proposed fertility-enhancing properties. Maca has been described to possess many other medicinal properties in traditional herbal medicine but only a few of them have been well studied scientifically. Published clinical studies of maca seem to be related to its property as a nutrient, for male fertility and for energy. There are inadequate data regarding the precise mechanism of action of maca. Some studies suggest that secondary

metabolites found in maca extracts are important constituents responsible for its physiological effects. Maca has been reported in the scientific literature to have a low degree of acute oral toxicity in animals and low cellular toxicity in vitro. An important finding unveiled by this review is the importance of standardisation in quality and additional basic and clinical research to scientifically validate and understand composition, biological activity, safety and risk. Development of a comprehensive pharmacological and toxicological profile through critical evaluation of existing and future experimental data, especially carefully conducted clinical studies would facilitate the scientific evidence-based approach to understanding potential biological effects of these major traditionally based herbals in current global use.

Publication Types:

- Review

PMID: 16042502 [PubMed - indexed for MEDLINE]

15: *Reprod Biol Endocrinol*. 2005 Jan 20;3:5.

Related Articles, Links

Red maca (*Lepidium meyenii*) reduced prostate size in rats.

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BACKGROUND: Epidemiological studies have found that consumption of cruciferous vegetables is associated with a reduced risk of prostate cancer. This effect seems to be due to aromatic glucosinolate content. Glucosinolates are known for have both antiproliferative and proapoptotic actions. Maca is a cruciferous cultivated in the highlands of Peru. The absolute content of glucosinolates in Maca hypocotyls is relatively higher than that reported in other cruciferous crops. Therefore, Maca may have proapoptotic and anti-proliferative effects in the prostate. **METHODS:** Male rats treated with or without aqueous extracts of three ecotypes of Maca (Yellow, Black and Red) were analyzed to determine the effect on ventral prostate weight, epithelial height and duct luminal area. Effects on serum testosterone (T) and estradiol (E2) levels were also assessed. Besides, the effect of Red Maca on prostate was analyzed in rats treated with testosterone enanthate (TE). **RESULTS:** Red Maca but neither Yellow nor Black Maca reduced significantly ventral prostate size in rats. Serum T or E2 levels were not affected by any of the ecotypes of Maca assessed. Red Maca also prevented the prostate weight increase induced by TE treatment. Red Maca administered for 42 days reduced ventral prostatic epithelial height. TE increased ventral prostatic epithelial height and duct luminal area. These increases by TE were reduced after treatment with Red Maca for 42 days. Histology pictures in rats treated with Red Maca plus TE were similar to controls. Phytochemical screening showed that aqueous extract of Red Maca has alkaloids,

steroids, tannins, saponins, and cardiogenic glycosides. The IR spectra of the three ecotypes of Maca in 3800-650 cm⁻¹ region had 7 peaks representing 7 functional chemical groups. Highest peak values were observed for Red Maca, intermediate values for Yellow Maca and low values for Black Maca. These functional groups correspond among others to benzyl glucosinolate. CONCLUSIONS: Red Maca, a cruciferous plant from the highland of Peru, reduced ventral prostate size in normal and TE treated rats.

Publication Types:

- Research Support, Non-U.S. Gov't

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17: Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2003 Dec;147(2):119-30.

Related Articles, Links

Smallanthus sonchifolius and Lepidium meyenii - prospective Andean crops for the prevention of chronic diseases.

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Smallanthus sonchifolius (yacon) and *Lepidium meyenii* (maca) were the traditional crops of the original population of Peru where they are also still used in folk medicine. These plants are little known in Europe and Northern America although at least yacon can be cultivated in the climatic conditions of these regions. This article deals with the botany and the composition, the structure of main constituents, biological activity of these plants and the cultivation of yacon in the Czech Republic. The potential of yacon tubers to treat hyperglycemia, kidney problems and for skin rejuvenation and the antihyperglycemic and cytoprotective activity of its leaves seems to be related mostly to its oligofructan and phenolic content, respectively. Maca alkaloids, steroids, glucosinolates, isothiocyanates and macamides are probably responsible for its aptitude to act as a fertility enhancer, aphrodisiac, adaptogen, immunostimulant, anabolic and to influence hormonal balance. Yacon and maca are already on the European market as prospective functional foods and dietary supplements, mainly for use in certain risk groups of the population, e.g. seniors, diabetics, postmenopausal women etc.

Publication Types:

- Research Support, Non-U.S. Gov't
- Review

PMID: 15037892 [PubMed - indexed for MEDLINE]

18: J Nat Prod. 2003 Aug;66(8):1101-3.

Related Articles, Links

Imidazole alkaloids from *Lepidium meyenii*.

Cui B, Zheng BL, He K, Zheng QY.

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Two new imidazole alkaloids (lepidiline A and lepidiline B) have been isolated from a root extract of *Lepidium meyenii* with the common name Maca and identified as 1,3-dibenzyl-4,5-dimethylimidazolium chloride (1) and 1,3-dibenzyl-2,4,5-trimethylimidazolium chloride (2), respectively. The structures of these two new compounds were determined by spectroscopic methods, as well as single-crystal X-ray diffraction performed on compound 1.

PMID: 12932133 [PubMed - indexed for MEDLINE]

19: J Agric Food Chem. 2002 Sep 25;50(20):5621-5.

Related Articles, Links

Investigation of the tuber constituents of maca (*Lepidium meyenii* Walp.).

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Lepidium meyenii, known in South America as maca, has received attention worldwide as a powerful energizer that improves physical and mental conditions and increases fertility. Because of these reports, we investigated the secondary metabolites of the tuber of maca. The methanol extract of the tuber of maca contained, in addition to free sugars and amino acids, the following: uridine, malic acid and its benzoyl derivative, and the glucosinolates, glucotropaeolin and m-methoxyglucotropaeolin. Because glucosinolates and their derived products have received increasing attention due to their biological activities, the occurrence of glucosinolate degradation products in the hexane extract was also investigated, and benzylisothiocyanate and its m-methoxy derivative were isolated. The two glucosinolates were semiquantified by HPLC, and benzylisothiocyanate was semiquantified by GC/MS. The methanol extract of maca tuber also contained (1R,3S)-1-methyltetrahydro-beta-carboline-3-carboxylic acid, a molecule which is reported to exert many activities on the central nervous system.

PMID: 12236688 [PubMed - indexed for MEDLINE]

20: Phytochemistry. 2002 Sep;61(2):149-55.

Related Articles, Links

Composition of the essential oil of *Lepidium meyenii* (Walp).

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The essential oil profile of maca (*Lepidium meyenii*) obtained from Lima, Peru, was examined. Steam distillates of the aerial parts of *L. meyenii* were continuously extracted with pentane and the pentane extracts analyzed by GC/MS. Retention indices and mass spectral data were used to identify 53 oil components. Phenyl acetonitrile (85.9%), benzaldehyde (3.1%), and 3-methoxyphenylacetonitrile (2.1%) were the major components of the steam distilled oil. The oil of *L. meyenii* was tested for phytotoxic, cyanobactericidal, and antitermite activity. The oil was selectively toxic towards the cyanobacterium *Oscillatoria perornata* compared to the green alga *Selenastrum capricornutum*, with complete growth inhibition at 100 microg/ml. Mortality of the Formosan subterranean termite, *Coptotermes formosanus*, was numerically, but not significantly, higher when held on filter paper treated with maca oil. At 1% (w/w), maca oil also appeared to act as a feeding deterrent to termites. Several minor components of the essential oil of maca including 3-methoxyphenylacetonitrile and benzylthiocyanate were significantly active against the Formosan termite. This is the first report on the essential oil composition of *L. meyenii*.

PMID: 12169308 [PubMed - indexed for MEDLINE]

21: Phytochemistry. 2002 Jan;59(1):105-10.

Related Articles, Links

Constituents of *Lepidium meyenii* 'maca'.

Muhammad I, Zhao J, Dunbar DC, Khan IA.

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The tubers of *Lepidium meyenii* contain the benzylated derivative of 1,2-dihydro-N-hydroxypyridine, named macaridine, together with the benzylated alkamides (macamides), N-benzyl-5-oxo-6E,8E-octadecadienamide and N-benzylhexadecanamide, as well as the acyclic keto acid, 5-oxo-6E,8E-octadecadienoic acid. The structure elucidation of the isolated compounds was based primarily on 1D and 2D NMR spectroscopic analyses, including 1H-1H COSY, 1H-13C HMQC, 1H-13C HMBC and 1H-1H NOESY experiments, as well as from 1H-15N NMR HMBC correlations for macaridine and N-benzylhexadecanamide.

Publication Types:

- Research Support, Non-U.S. Gov't
- Research Support, U.S. Gov't, Non-P.H.S.

PMID: 11754952 [PubMed - indexed for MEDLINE]

22: Arch Latinoam Nutr. 2000 Jun;50(2):126-33.

Related Articles, Links

Nutritional evaluation of *Lepidium meyenii* (MACA) in albino mice and their descendants

Canales M, Aguilar J, Prada A, Marcelo A, Huamán C, Carbajal L.

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The Maca (*Lepidium meyenii*) is a Peruvian hypocotyl that grows exclusively between the 3700 and 4500 masl at the Peruvian Andes. Traditionally it is attributed nutritional, energizing, fertilizing properties among others. With the purpose of evaluate scientifically the nutritional property of Maca, we carried out a controlled study in two generations of albino Swiss mice (parents and breeding). The parents were aleatorily assigned to one of three nutritional schedules. The food of each group was prepared based on powder from a commercial balanced food (CBF) of which 30% was replaced by raw or cooked Maca according to the corresponding group or pure CBF in the control group. The groups were this way: 1) Raw Maca Group; 2) Cooked Maca Group; and, 3) Control Group. The results showed that the curves of growth were similar and adequate for the three groups. However, the cooked Maca group showed the best curve. These data were better observable in the second generation of animals, with significant statistical difference ($p < 0.05$). The CBF group had a better growth than raw Maca group. No signs of malnutrition nor overweight were observed in none of the groups. The serum values of total proteins and albumin were statistically superior for the mice group eating cooked Maca than that of the raw Maca and CBF groups. This study demonstrates, in a scientific evaluation, one of the traditionally attributed properties of Maca, the nutritional capability.

Publication Types:

- Comparative Study
- English Abstract

PMID: 11048583 [PubMed - indexed for MEDLINE]