Memorandum

Date: JUN 29 2000

From: Acting Division Director, Division of Standards and Labeling Regulations, Office of Nutritional Products, Labeling, and Dietary Supplements, HFS-820

Subject: 75-Day Premarket Notification for New Dietary Ingredients

To: Dockets Management Branch, HFA-305

New Dietary Ingredient: Kalanchoe pinnata (Lamarck) Persoon
Ruta Chalepensis L.

Firm: Isula Rain, Inc.
Date Received by FDA: April 19, 2000
90-Day Date: July 17, 2000

In accordance with the requirements of section 413(a) of the Federal Food, Drug, and Cosmetic Act, the attached 75-day premarket notification for the aforementioned new dietary ingredient should be placed on public display in docket number 95S-0316 after July 17, 2000.

Felicia B. Satchell
Felicia B. Satchell
This is in response to your letter to the Food and Drug Administration (FDA) dated April 19, 2000, making a submission for new dietary ingredients pursuant to 21 U.S.C. 350b(a)(2) of the Federal Food, Drug, and Cosmetic Act (the Act). Your letter notified FDA of the intent of Isula Rain, Inc. to market a product (Temporal Tension Extract) containing the new dietary ingredients Kalanchoe pinnata (Landmarck) Persoon and Ruta chalepensis L.

Under 21 U.S.C. 350b(a)(2), a manufacturer or distributor of a dietary supplement that contains a new dietary ingredient is required to submit to FDA, at least 75 days before the dietary ingredient is introduced or delivered for introduction into interstate commerce, information that is the basis on which the manufacturer or distributor has concluded that a dietary supplement containing such new dietary ingredients will reasonably be expected to be safe. FDA reviews this information to determine whether it provides an adequate basis for such a conclusion. Under section 350b(a)(2), there must be a history of use or other evidence of safety establishing that the dietary ingredient, when used under the conditions recommended or suggested in the labeling of the dietary supplement, will reasonably be expected to be safe. If this requirement is not met, the dietary supplement is deemed to be adulterated under 21 U.S.C. 342(f)(1)(B) because there is inadequate information to provide reasonable assurance that the new dietary ingredient does not present a significant or unreasonable risk of illness or injury.

FDA has carefully considered the information in your submission, and the agency has significant concerns about the evidence on which you rely to support your conclusion that the new dietary ingredients, Kalanchoe pinnata (Lamarck) Persoon and Ruta chalepensis L., will reasonably be expected to be safe. The information in your submission does not meet the requirements of 21 CFR 190.6(b)(3) because it does not contain a description of the dietary supplement that contains the new dietary ingredients including the level of the new dietary ingredients in the dietary supplement (see 21 CFR 190.6(b)(3)(i)), nor does it describe, in a quantitative manner, the amount to be consumed daily. The submission contains evidence of history of use and other information that you assert is an adequate basis to conclude that the dietary supplement containing the new dietary ingredients will reasonably be expected to be safe. However, the information in the submission is inadequate to make such a determination (see 21 CFR 190.6(b)(4)). Moreover, the submission provides no explanation or information that enables a determination to be
made that the citations in the submission are relevant to determining whether your product, as formulated and at the expected exposure when used as suggested in labeling, would reasonably be expected to be safe.

For the reasons discussed above, the information in your submission does not provide an adequate basis to conclude that *Kalanchoe pinnata* (Lamarck) Persoon and *Ruta chalepensis* L., when used under the conditions recommended or suggested in the labeling of your product, will reasonably be expected to be safe. Therefore, your product may be adulterated under 21 U.S.C. 342(f)(1)(B) as a dietary supplement that contain the new dietary ingredients specified for which there is inadequate information to provide reasonable assurance that such ingredients do not present a significant or unreasonable risk of illness or injury. Introduction of such products into interstate commerce is prohibited under 21 U.S.C. 331(a) and (v).

Please contact us if you have any questions concerning this matter.

Sincerely yours,

Felicia B. Satchell
(Acting) Division Director
Division of Standards and Labeling Regulations
Office of Nutritional Products, Labeling and Dietary Supplements
April 11, 2000

Division of Food and Dietary Supplement Safety
Standards and Labeling
Office of Special Nutritionals
Center for Food Safety and Applied Nutrition
Food and Drug Administration
200 C Street, S.W. (HFS-450)
Washington, DC 20204

Dear Food and Drug Administration:

Pursuant to 21 CFR Section 190.6, requirement for premarket notification, Isula Rain Inc. wishes to notify the Food and Drug Administration that it will market the following list of herbs as dietary supplements:

<table>
<thead>
<tr>
<th>Scientific Name</th>
<th>Common Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kalanchoe pinnata (Lamarck) Persoon</td>
<td>Q'ora Wayra</td>
</tr>
<tr>
<td>Ruta chalepensis L.</td>
<td>Ruta</td>
</tr>
</tbody>
</table>

These herbs will be distributed by Isula Rain Inc., 12 Skylark Drive, Unit 31, Larkspur, California 94939.

Attached please find a summary and reports which establish that these dietary ingredients, when used under ordinary recommended conditions, are reasonably expected to be safe. These reporting studies include:
(1) The history of use or other evidence of safety establishing that the dietary ingredient will reasonably be expected to be safe.
(2) Any citations to published articles and their reprints that support that the dietary ingredient will reasonably be expected to be safe.

Respectfully,

Lawrence J. Brucia
President
Isula Rain, Inc.
Common Names: qora wayra, air-plant

Latin Name: Kalanchoe pinnata (Lam.) Pers.
   Synonym: Bryophyllum calycinum Salisb.
Botanical Family: Crassulaceae

Geographical Distribution: Mexico, Madagascar, Mauritius

Related Species:

Food Use History:

Drug Use History: Leaves used in the healing or treating of wounds. (Vulnerary)

Toxicity: None found.

Remarks:

References: KewCD 1993, Lyons 1907, RHSDG 1992
Common Names: ruta, fringed rue

Latin Name: Ruta chalapensis Linn.
   Synonym: Ruta angustifolia Pers.

Botanical Family: Rutaceae

Geographical Distribution: Mediterranean

Related Species:

Food Use History:

Drug Use History: Juice of plant used for sore eyes and as antihelmintic, emmenagogue, and abortive.

Toxicity: None found.

Remarks:

References: KewCD 1993
Scientific name: *Kalanchoe pinnata* (Lamarck) Persoon  
(Common name: Q'ora Wayra, Coirama)

The botanical characteristics are described in the Analysis Certificate attached. (1) Ethnobotanical record is made of the internal use of this herb by South American populations (2,3,4,5,6).

The chemical composition of *Kalanchoe pinnata* through analysis includes alkoloids, flavonoids, tannins, steroid triterpenoids, and foam.

No ill-effects from its usage have been recorded.


These documents appear in this order under "Literature"

**Parts Used:** leaves

**Level**

The level of *Kalanchoe pinnata* in the product “Temporal Tension Extract” (see below for entire ingredient listing) is

<table>
<thead>
<tr>
<th>Common name</th>
<th>Scientific name</th>
<th>Parts of the plant used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q'ora Wayra</td>
<td><em>Kalanchoe pinnata</em></td>
<td>leaves</td>
</tr>
<tr>
<td>Ruda</td>
<td><em>Ruta chalepensis</em></td>
<td>Stem, leaves and flowers</td>
</tr>
</tbody>
</table>
Other ingredients: distilled water, ethyl alcohol derived from sugar cane

Condition of use:
The normal use recommended on the label of “Temporal Tension Extract” is:

Directions: Take one teaspoon mixed in a glass of hot or cold water as needed. Add honey if a sweetener is desired. If you’d like to avoid the consumption of alcohol, yet still enjoy the benefits of this product, add one teaspoon to a glass of hot, boiled water and let sit for 5 minutes. Do not exceed 4 teaspoons per day. DO NOT USE THIS PRODUCT IF YOU ARE PREGNANT OR LACTATING KEEP OUT OF THE REACH OF CHILDREN.
ANALYSIS CERTIFICATE
N° 229 - 98

CERTIFICATE OF VEGETABLE KIND

I. DATA OF THE REQUESTING

Name: INTERNATIONAL CORPORATION HEALTH AND LIFE E.I.R.L.
Address: Alfonso Cobian cooperative Mr. H. Li I - Chucacayo

II. DATA OF THE SERVICE

Service request: N° 1216 - 98
Date of service request: 98-09-08.
Requested service: Certificate of vegetable kind

III. NAME OF THE PRODUCT

QORR HUAYRA

IV. DATA OF THE SAMPLE

Type: 1 bag
Other characteristics: Containing folious stem

V. USED LABORATORY

Le Molina Calidad Total Laboratorio

VI. RESULTS

Of agreement to the Trial report Co. V- 165 - 98, that work in the files and reports the following:
The sample (stem folious) of “Qora Huayra”, has been identified by orthodox method as: Licteroides perua L., which botanical classification according to A. Cronquist (1982) is:

KINGDOM
PLANTAE

DIVISION
MAGNOLIOPHYTA

CLASS
MAGNOLIOPSIDA

SUBCLASS
RODAE

ORDER
ROSEPUSHES

FAMILY
CRAESSULACEAE

GENUS
Crasu

SPECIES
E.prunata

METHOD USED IN THE LABORATORY
(Orthodox method, according to A. Cronquist 1982)

The certified present is referred exclusively to the analyzed sample, the one that is provided by the solicitor.
Any alteration or manipulation invalidates the present document.
The owner of the present document is authorized to issue certificates of its own.
All reproductions of this document that it will not be authorized by LMP TL is its official value.
The present document, the emblem and name of our institution can not be used for advertising and, unless previous authorization.

October 5th, 1998 Le Molina
ANALYSIS CERTIFICATE
N° 839 - 98

PHYTOCHEMIST TRIAL RUN CERTIFICATE

II. DATA OF THE REQUESTING

Name: INTERNATIONAL CORPORATION
Address: HEALTH AND LIFE E.I.R.L.
        Alfonso Cobian cooperative Mz.
        H 11 J - Chalacayo

III. DATA OF THE SERVICE

Service request: N° 1216 - 98
Date of service request: 98 09 98
Requested service: Phytochemist trial run

III. NAME OF THE PRODUCT

QORAHUAYRA

IV. DATA OF THE SAMPLE

Size: 01 plant
Other characteristics: Containing folius stem

V. USED LABORATORY

SERVICIOS PROFESIONALES

VI. RESULTS

Of agreement to the Trial report N° 165 - 98, that work in the files and reports the presence of the following components:
Alkaloids, flavonoids, tannin, steroids-terpenoids, foam.

METHOD USED IN THE LABORATORY
Ludm. de Ugaz OIga PHYTOCHEMIST investigation Method 1994

October 9th, 1998 La Molina
**EthnobotDB**

**Taxon : Kalanchoe pinnata**

**[PhytochemDB]**

Family Crassulaceae  
Genus Kalanchoe  
Species pinnata  
Species_author (LAM.) PERS.  
Common_name Sedingin  
Other_info Ethnobotany_Use Ache(Head) Kalanchoe pinnata Philippines  
Asthma Kalanchoe pinnata Bahamas  
Chest-Cold Kalanchoe pinnata Bahamas  
Ear Kalanchoe pinnata Bahamas  
Sore Kalanchoe pinnata Philippines  
Strain Kalanchoe pinnata Bahamas  
Fever Kalanchoe pinnata Malaya  
Headache Kalanchoe pinnata Malaya
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DOCKETS MANAGEMENT BRANCH
FOOD AND DRUG ADMINISTRATION
5630 FISHERS LANE, ROOM 1061
ROCKVILLE, MD 20852
Scientific name: *Ruta chalepensis* L.  
(Common name: Ruta)

The botanical characteristics are described in the Analysis Certificate attached. (1) Ethnobotanical record is made of the internal use of this herb by South American and North American Indians as well other populations around the world (1,2,3,4,5,6).

The chemical composition of *Ruta chalepensis* through analysis includes essence containing metilnonilcetone, metil-heptil cetone 90%, pineno, eucalyptus, metile solicitate, azuleno, glycosilated flavonoids, alkoloids, coumarins, chalepensin, chalepin, and rutamarin.

No ill-effects from its usage have been recorded.

1. Analysis Certificate, No. 053-98, La Molina Calidad Total Laboratorio. 1998
4. Plants for a future: database. [http://www.scs.leeds.ac.uk/cgi-bin/pfaf/arr](http://www.scs.leeds.ac.uk/cgi-bin/pfaf/arr)
5. Native American Ethnobotony Database. [http://www.umd.umich.edu/cgi-bin/herb/](http://www.umd.umich.edu/cgi-bin/herb/)

These documents appear in this order under "Literature"

Parts used: leaves, stem, flowers

Level

The level of *Ruta chalepensis* in the product "Temporal Tension Extract" (see below for entire ingredient listing) is

<table>
<thead>
<tr>
<th>Common name</th>
<th>Scientific name</th>
<th>Parts of the plants used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ruda</td>
<td><em>Ruta chalepensis</em></td>
<td>stem, leaves, flowers</td>
</tr>
<tr>
<td>Q'ora Wayra</td>
<td><em>Kalanchoe pinnata</em></td>
<td>leaves</td>
</tr>
</tbody>
</table>

Other ingredients: distilled water, ethyl alcohol derived from sugar cane.

Condition of use:

The normal use recommended on the label of "Temporal Tension Extract" is:
Directions: Take one teaspoon mixed in a glass of hot or cold water as needed. Add honey if a sweetener is desired. If you'd like to avoid the consumption of alcohol, yet still enjoy the benefits of this product, add one teaspoon to a glass of hot, boiled water and let sit for 5 minutes. Do not exceed 4 teaspoons per day.

DO NOT USE THIS PRODUCT IF YOU ARE PREGNANT OR LACTATING.

KEEP OUT OF THE REACH OF CHILDREN.
ANALYSIS CERTIFICATE
Nº 053 - 98
CERTIFICATE OF VEGETABLE KIND

I. DATA OF THE REQUESTING
   Name: INTERNATIONAL CORPORATION
   Address: HEALTH AND LIFE E.I.R.L.
            Alfonso Cobian cooperative Mz
            H LI I - Chacacayo

II. DATA OF THE SERVICE
   Service request: Not 285 - 98
   Date of service request: 98-05-06
   Requested service: Vegetable kind

III. NAME OF THE PRODUCT
     RUE

IV. DATA OF THE SAMPLE
    Size: 50 g aprox.
    Other characteristics: Packed to bulk

V. USED LABORATORY
    Professional services

VI. RESULTS
    Of agreement to the Trial report No Co-V- 061 - 98 that work in the files the results are:

    PHYSICAL DETERMINATION:

    1. Specimen identification: Ruta chalepensis
       Family specie RUTACEAE

    METHOD USED IN THE LABORATORY:
    Classic method, orthodox.

    VII. CONCLUSIONS:
    Of agreement to the result obtained the sample from RUE corresponds to Ruta chalepensis.

- The certified present is referred exclusively to the analyzed sample, the one that is provided by the solicitor.
- Any alteration or emendation nullifies the present document.
- The force of the present expires to 90 given calendar of its emission.
- All reproduction of this document that it will not be authorized by LMCIL lacks official value.
- The present document, the emblems and names of our institution can not be used for advertising end, unless previous authorization.

June 5th, 1998 La Molina
VI- MONOGRAPH OF THE VEGETABLE KIND: RUE

1. DESCRIPTION:

SUPRASPECIFIC CATEGORIES:
- KINGDOM : PLANTAE
- DIVISION : MAGNOLIOPHYTA
- CLASS : MAGNOLIOPSIDA
- SUBCLASS : ROSIDAE
- ORDER : SAPINDALES
- FAMILY : RUTACEAE
- Genus : Ruta
- Species : R. chalepensis

1.1 SCIENTIFIC NAME : Ruta chalepensis
1.2 SYNONYMY : Rue, fragrant rue.
1.3 BOTANICAL CHARACTERISTICS:

It is a perennial plant from 1 to 1.5 m heights. Its stem is herbaceous green color, very ramified, presents spherical prominents punctuations, it has not hair. Its leaves are alternate composite; it has a very disagreeable odor. Pedunculars flowers tetramerias and pentamerias.

It grows spontaneously or cultivated at coast, forest and jagged mountain range.

Root : Underground, herbaceous, pivotty, whitish yellow color.
Stem : Aerial, erect, very ramified from its base, green bluish, cylindrical, up to 1 m height.
Leaves: Alternate, peclobates, glaucescent, composites, with seed foliages.
Flowers: Cymose inflorescence, in umbel, little flowers, greenish yellow, calyx from 4 to 5 sepals, acute, corolla from 4 to 5 petals, slightly concave to the higher part.
Fruits : Capsule, from 4 to 5 salient rugged lobes.

1.4 DISTRIBUTION:
Native from Europe, widely known in Peru.

2. COMMERCIAL SOURCE:
Leaves

3. CHEMICAL COMPOSITION:
It has essence-containing metilnonilcetone, metil-heptil cetone 90%, in addition to pineno, eucalyptus, metile sotlicate, azuleno, and glycosilated flavonoids

4. THERAPEUTIC PROPERTIES:
5. Antispasmodic (painful menstruation)

**Used part**: Leaves

**Preparation**: Infusion 5 g with 250 mL of hot water. Let it settle for 10 minutes.

**Forms of use**: Drink: drink a cup after meals.

**Otitis**:

**Used part**: Leaves

**Preparation**: Plaster. 10 g of crushed leaves.

**Forms of use**: Soaking a clean cotton with the plaster and put it to the hearing all night long.

**Hearing pain and Headache**

**Used part**: Leaves

**Preparation**: Fresh leaves

**Ways of use**: Soaking the fresh leaves in the head, temple and behind hearing.

5. **BIBLIOGRAPHY**:

- "The plants cure", Alfonso Balbochas Publishing the present truth.
- "Catalogue of Medicinal Plants ", University of Lima Investigation center of the Industrial production CIPI 1944.
- Biologist Graciela Vilcapoma Segovia, according to A. Cronquist 1982.


Rollinia mucosa (Jaq.) Baill. Annonaceae. "Anona". Cultivated. Fruit edible. (Fig. 202)


Rosa centifolia L. Rosaceae. "Rosa del remedio", "Medicinal rose". Ornamental.


Roucheria punctata Ducke. Linaceae. "Puma caspi". Wood used for construction, beams, decks, and columns (RVM). "Taiwano" believe the bark decoction of the related R. culophylla Planch. is a "sure cure" for malaria (SAR).

Ruitzerania trichanthera (Spruce ex Warm.) Marcano-Berti. Vochysiaceae. "Quillo sisa", "Moena sin olor". Wood for lumber, general construction.


Ruta chalepensis L. Rutaceae. "Ruda", "Rue". Cultivated. Around Iquitos, tied to many superstitions; a little branch of rue dispels bad spirits, and attracts clientele. Some merchants carry a rue leaf on their ears. Rue tea mixed with castor oil is well known as an oxytocic (SOU). Powdered leaves used to treat otitis, opthalmia, and pediculosis. Leaf tea taken, perhaps dangerously, as antidysmenorrheic, antihysteric, cardiotonic, digestive, sedative, vermifuge. Vinegar decoction of leaves used for decongestant (FEO). Brazilians use the tea for stroke (BDS). Psoralens in the plant may render photoTOXIC (JAD).

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By JAMES DUKE & RODOLFO VASQUEZ
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