Developing a sustainable source of Canada yew biomass for drug production: Plantation research in Ontario

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Yew Talk Outline

- Canada Yew background
- Canada Yew research project with preliminary results
- Summary

Canada Yew Background

- Canada yew evergreen shrub native to N. Amer.
- Height + spread 1.5 m
- Sweeping form to branches

Medicinal Properties of Yew

- Yew contains paclitaxel and two other potential anticancer compounds10-DAB and DHB (unique to Canada yew) in its foliage, bark, & roots
- Paclitaxel is the active ingredient in Taxol™ an anticancer drug sold by Bristol-Myers-Squibb (BMS)
- Taxol™ is one of the world's most valuable anti-cancer drugs -9 billion $US sales for BMS1993-2002
- Paclitaxel is also produced from English and Asian species of yew

Paclitaxel Uses and Activity

- Taxol ® is a chemotherapy drug registered for use on ovarian, breast, and non-small lung cancer.
- Paclitaxel coated coronary stents (Boston Sci.)
- Abraxane new form of taxol approved by FDA, may increase its usage in breast cancer treatment
- 28 % of '00 cancer clinical trials used taxanes
- Trials being conducted for taxane use in psoriasis, rheumatoid arthritis, multiple sclerosis, and fungal and viral diseases

Taxane Demand and Production

- Current worldwide taxane is ↑ at ~ 10% year
- 2006 demand was about 750 kg
- 15,000 kg foliage to extract 1 kg paclitaxel
- 11.3 million kg of foliage/yr for world supply in 2006
- 1 ha wild Canada yew produces from 90 to 400 kg foliage every 4th year (sustainably harvested)

Canada Yew Research Project

- "Canada Yew: Developing a new value added crop for Northern Ontario"
- Objectives:
  - To develop a northern Ontario source for cutting-propagated Canada yew plants.
  - To develop methods to grow Canada yew as a new crop for northern Ontario growers
  - To develop methods to maximize paclitaxel yield of yew.

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Yew Project Partners

- Thessalon First Nation BioCentre Nursery
- CFS-GLFC, Dr. Mamdouh Abou-Zaid
- CFS-AFC, Drs. R. Smith and S. Cameron
- Forest and Land Control, Blind River, ON
- Whelan Resources, Brian Whelan
- Bioxel Pharma
- ULERN
- MNR Bondar, Dr. Michael Irvine

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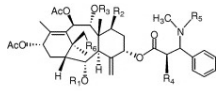
Why Canada yew?
Taxane content of yew species

Species	Paclitaxel	Baccatin III	10-deacetylbaccatin III	Total Taxanes ug/g
T. baccata	41	14	762	817
T. brevifolia	130	296	41	467
T. canadensis	285	224	2665	3,174
T. celebica	26	0	70	96
T. cuspidata	105	15	120	240
T. floridana	516	0	1689	2,205
T. globosa	433	168	1395	1,996
T. x hunnewalania	41	0	63	104
T. x media cv.	211	36	230	266
T. wallichiana	272	0	1092	1,364

Source: van Rozendaal *et al.* (2000).

Why Plantations?

- Why not synthesize paclitaxel?



R_1	R_2	R_3	R_4	R_5	R_6
H	H	H	H	H	H
H	H	Ac	H	Me	OH
H	OAc	Ac	OH	Me	H
Ac	H	H	H	Me	H

- Why not produce all paclitaxel through tissue culture?

Approach to Maximizing Paclitaxel Yield of Yew

- Screening 300 yew plants for growth and paclitaxel conentration
- Investigating growing conditions to optimize growth and paclitaxel content
- Choosing harvest time to maximize paclitaxel content

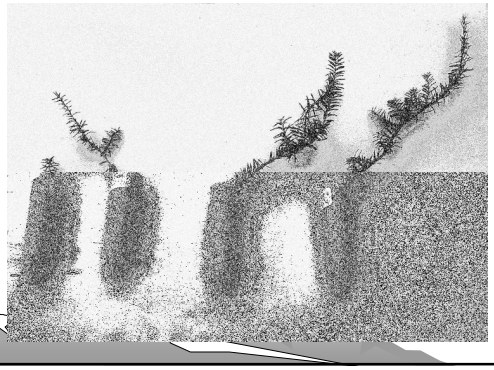
Selecting Yew for Paclitaxel Production

- Cuttings collected from 300 individual plants across northern Ontario
- Propagated at OFRI greenhouse and planted at arboretum
- Each monitored for paclitaxel and growth
- Best growth + paclitaxel individuals selected for further propagation

Greenhouse Growth of Individuals

Region Plant	Algoma RL	Neast 49	Algoma LWR
# of new shoots	3.2	11.0	28
New shoot growth mm	115	387	733
Growth Response	Lowest	Average	Maximum

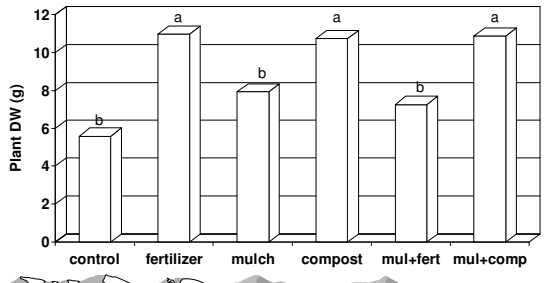
Greenhouse Growth of Yew Plants



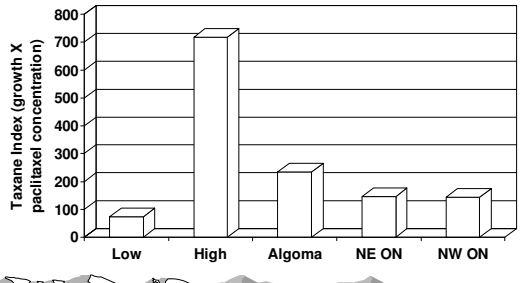
Plantations Established

- June 2004 – CFS plantation at OFRI arb
- August 2005
  - OFRI arboretum (loamy soil)
  - Thessalon First Nation BioCentre (sandy soil)
  - Brian Whelan Farm, Thessalon (clay soil)
- Treatments:
  - Fertilizer, mulch, Fert+mulch (CFS: compost + compost and mulch)
  - Spacing 30 + 45 cm
  - Herbicide trials with Princep and Goal

Treatment effects on Yew Growth



Taxane Production Index



Canada Yew Talk Summary

- Elite plantations will likely be one of the preferred taxane source of the future
- Plantation development will require 4 years for one time harvest or 5-8 years for continuous harvest
- Ontario-adapted elite material could lead to future plantations for 2nd generation taxane drug production (taxotere and abraxane)