Natural Toxins in Plants and Fungi: The Ecological Biochemistry of Food

Food Toxicology
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Learning Objectives

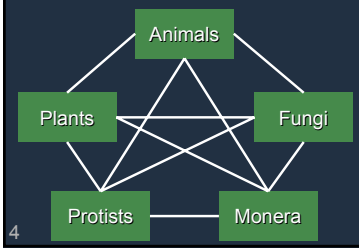
- Understand the relationship between ecology and the human food chain.
- Define ecological biochemistry.
- Explain biochemical adaptation and the roles of secondary compounds in plants.
- Examine the impacts of plant toxicants in the human food chain.
- Survey examples of plant toxicants.
- Review a range of toxic plant-based supplements.
- Review a range of poisonous mushrooms.

Ecology and The Human Food Chain

- Ecology: the scientific study of the distribution and abundance of living organisms and interactions between the organisms and their environment.
  - Derived from the Greek οικος (oikos, "household") and λόγος (logos, "study"); the "study of the household [of nature]".
- "Who eats who" and "what eats what" in the human food chain can be described as "The Ecology of Food."
- Molecular level analysis of this "Ecology of Food" is an aspect of food toxicology.

Ecological Biochemistry

- Coupling of the observational science of ecology with the molecular science of biochemistry.
- Ecological interaction in the food chain.



Ecological Biochemistry

- Synthesis and transformation of chemicals in the environment, as the result of biochemical processes in an organism, to aid in species survival.
- Includes:
  1. Biochemical adaptation.
     - Biosynthesis.
  2. Detoxification.
     - Biodegradation, biomineralization.
  3. Bioaccumulation, biomagnification.
  4. Ecological biochemical interaction.

Biochemical Adaptation

- The metabolic flexibility of a living organism to fit into a changing environment, improving chances for survival and reproduction.
  - Evolution
    - Many generations.
  - Acclimatization.
    - Lifetime of an individual.
- Our challenge: decipher the strategy of the natural world.
  - Example: Toxic plants

Competitive and Symbiotic Interactions

- Plant ↔ Plant ↔ Animal…
  - Secondary plant compounds.
- Animal ↔ Animal…
  - Venoms, toxins.

Monarch Butterfly and Milkweed

Toxins and Survival Strategy

- Organisms often synthesize or use toxins in their survival strategy.
  - The most conspicuous non-event in the history of the angiosperms is the failure of insects and other herbivores to attack plants on a wide-scale (Feeny, 1975).
    - Plants dominate the landscape, hence plants must be "broadly repellent" to animals as food and "toxic" in the widest sense.
    - Overcoming the defense strategy of plants by insects and herbivores is a part of their survival strategy.

Secondary Plant Compounds: Phytochemicals

- Hypothesis:
  developed in plants as survival mechanism.
  - Offensive and defensive biosynthesis
  - Bio-chemical warfare(?)

- Chemical defense
- Palatability
- Variable structures, properties, MOA
- Concentrations vary
  - Part of plant
  - Stage of maturity
  - Species
  - Env. conditions

Nitrogen Compounds

	Number of structures	Physiological activity
Alkaloids	6,500	Toxic, bitter
Amines	100	Repellent, hallucinogenic
Amino acids	400	Many toxic
Cyanogenic glycosides	30	Poisonous (as HCN)
Glucosinolates	75	Acrid, bitter

Terpenoids

	Number of structures	Physiological activity
Monoterpenes	1,000	Pleasant smells
Sesquiterpene lactones	1,500	Some bitter & toxic
Diterpenoids	2,000	Some toxic
Liminoids	100	Bitter
Cucurbitacins	50	Bitter & toxic
Cardenolides	150	Toxic & bitter
Carotenoids	500	Color

Phenolics

	Number of structures	Physiological activity
Simple phenols	200	Anti-microbial
Flavinoids	4,000	Often colored
Quinones	800	Colored, sometimes toxic

Example: The Walnut Tree

- Allelopathy: "biochemical interactions between all types of plant" (Molisch, 1937).
- Since the time of ancient Greece, the walnut tree *(Juglans nigra)* has been observed to kill nearby vegetation.
  - Moderately toxic to some insects, horses, dogs, humans.
  - 1500s physician's "Doctrine of Signatures"
    - Walnut = brain
- Produces a bound form of a toxin, which deposits in nearby soil through leaves, nut shells, stems and roots.

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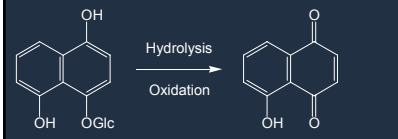
Example: The Walnut Tree

- Leaching causes hydrolysis and oxidation, releasing jugalone, a powerful quinone herbicide.



Bound form of toxin

Jugalone (5-Hydroxynaphthoquinone)

Harborne

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The Human Food Chain

Virtually all foods and food animal feeds contain some potential naturally-occurring toxicant.

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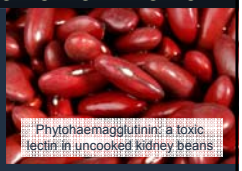
What Differentiates Nontoxic from Toxic?

- DOSE
  - Sufficient concentration?
    - Dose response curve: Where is NOAEL?
- HAZARD / RISK
  - Minimized by crop breeding
  - Deactivated in cooking/processing
  - Modified by dietary habits
  - Genetic factors
  - Adaptation



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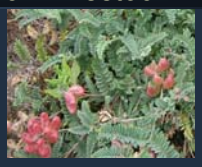
Impact: Plant Toxicants on Livestock

- Estimated $350-400 million loss annually to livestock producers – direct exposure to plant
  - Death
  - Illness – clinical disease
  - Loss in body weight
  - Reproductive failures
  - Abortions



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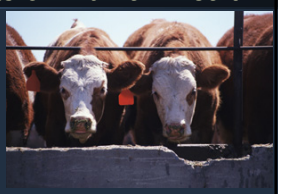
Impact: Plant Toxicants on Human Health

- Consumption of toxin-contaminated meat
  - Risk low – dilution
  - Most large-scale events recognized and corrected



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Impact: Plant Toxicants on Human Health

- Consumption of toxin-contaminated milk
  - Risk low – dilution through bulk handling
  - Management practices of large dairies

J. Anim. Sci. 1990. 68:892-904

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Plant Toxin-Contaminated Milk

Wetzlich, 1991

- Excretion of plant toxicants into milk by lactating animals is minor when compared to other routes of elimination.
- Plant toxins have been detected in the milk of animals grazing on toxic plants
- Human health risk is generally small for commercial milk because of diluting in bulk handling and controlled grazing.
  - Increased risk from animals raised in poisonous plant areas and where these animals are a sole source for milk.

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Plant Toxin-Contaminated Milk

- Milk is an emulsion of lipids in an aqueous solution of proteins.
- Virtually any plant toxin or metabolite that is circulating in the body can enter milk.
  - Most toxicants cross the mammary cell membranes by simple diffusion, thus chemicals bound to plasma proteins, associated with circulating lipids, or free in the plasma can cross through the mammary cells.
    - Lipo-proteineic "Blood-Milk Barrier"
  - Basic compounds, such as alkaloids, can become concentrated in milk because milk, with a pH of 6.5, is more acidic than plasma.
  - Lipophilic compounds can also concentrate in milk.

21 Wetzlich, 1991

Plant Toxin-Contaminated Milk

- Plant toxicants excreted via milk:
  - **Tremetol (or tremetone)** in white snakeroot (Eupatorium rugosom) and rayless goldenrod (Haplopappus heterophyllus)
  - **Pyrrolizidine alkaloids** in Senecio, Crotalaria, Heliotropium, Echium, Amsinckia, Symphytum (comfrey), Cynoglossum (Hounds Tongue), and Festuca (tall fescue)
  - **Piperidine alkaloids** in Conium and tobacco
  - **Quinolizidine alkaloids** in Lupinus
  - **Glucosinolates** in Amoracia (horseradish), Brassica (cabbage, broccoli, etc.), Limnanthes (meadowfoam), Nasturtium (watercress), Raphanus (radish) and Thlaspi (stinkweed).

22 Wetzlich, 1991

Human Health Risk Factors: Milkborne Toxins

- Susceptibility of infants and very young children
  - Dietary loading and immature enzyme systems
- Consumption of milk produced by lactating mothers who use potentially toxic herbal remedies
- Availability of toxic plants to grazing dairy animals
- Long-term health effects from low levels of plant toxicants
- Consumption of milk from individual animals grazing on toxic plants.

23 Wetzlich, 1991

Impact: Plant Toxicants on Human Health

- Consumption of toxin-contaminated eggs
  - Risk low – little known transfer to egg
  - Not recognized as a vector of toxin exposure due to commercial production standards
  - Larger problem is infectious diseases

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Plant Toxins in the Human Food Chain



Examples

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Eupatorium rugosum (white snakeroot)

- Perennial herb
- Eastern US, Mississippi and Ohio river valleys / moist, shaded uncultivated
- 'Milk sickness'
- Early 1800's – ¼ to ½ of deaths in IN, OH
- Abraham Lincoln's family

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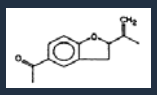
Eupatorium rugosum (white snakeroot)

- 1910: identified toxins: tremetol, tremetone - interferes with TCA cycle and glucose metabolism
- Still sporadic problem in rural areas
- Cumulative problem: fat soluble



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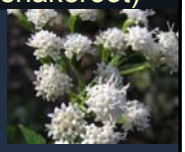
Eupatorium rugosum (white snakeroot)

- Risks
  - Milk – toxins excreted – cow not affected – not destroyed during pasteurization
  - Butter – fat soluble
  - Meat – long $T_{½}$
- Clinical signs
  - Weight loss, listlessness, weakness, tremors, collapse, death within days to weeks – heart, liver



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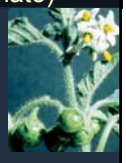
Solanum, *Lycopersicon* (nightshades, potato, eggplant, tomato)

- Food / noxious weeds / ornamentals / herbal medicines
- Annual or perennials
- Over 100 species worldwide
- Poisonings in people
  - Consumption of berries
  - Consumption of tubers with sprouts, leaves, stem



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Solanum, *Lycopersicon* (nightshades, potato, eggplant, tomato)

- Toxins: glycoalkaloids, anticholinergics, saponins
  - Solasodine, tomatidine, solanidine, tomatine, chaconine, solanine
  - Heat stable
  - Flowers>sprouts>peel and eyes>shoot>tuber
  - Increase with greening, decrease with maturity

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Solanum, *Lycopersicon* (nightshades, potato, eggplant, tomato)

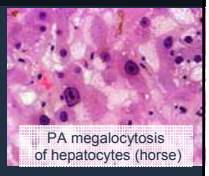
- Digestive and neurological problems
  - Nausea, vomiting, abdominal pain, diarrhea
  - Muscle tremors, staggering, weakness
- Consumption of blighted potatoes by pregnant women in Ireland – fetal deformities
  - Teratogenic

Pyrrolizidine Alkaloids

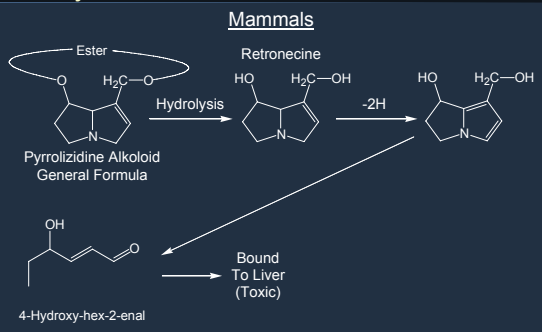
- Genera: *Senecio*, *Cynoglossum*, *Amsinckia*, *Symphytum* (comfrey)
- Hepatotoxic PA
  - Meat residues
  - Milk residues
  - Honey residues
  - Herbal teas, dietary supplements
- Risk: typically low
  - Home slaughter
  - Chronic

Pyrrolizidine Alkaloids

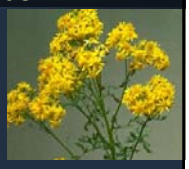
- Hepatotoxicity
  - Veno-occlusive disease
    - Herbal teas
    - Wound healing – external use only (astringent)
    - Dietary supplements – anticancer, cough remedy
    - Contaminant of cereal grains, bread products



Pyrrolizidine Alkaloid Metabolism

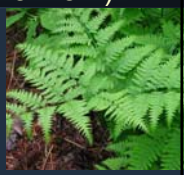


Pyrrolizidine Alkaloids



- Mutagenic
- Teratogenic
- Fetotoxic
- Carcinogenic
  - Association between *Senecio* and liver neoplasia in populations of South Africa

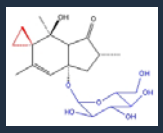
Pteridium aquilinum (bracken fern)

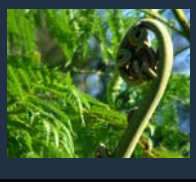


- Worldwide distribution
- Rhizomes – flour
  - Europe, New Zealand, Australia
- Fronds (croziers)
  - Fresh, cooked, preserved
  - Japan, Hawaii, Brazil
- Meat / milk contamination

Pteridium aquilinum (bracken fern)

- Toxin: ptaquiloside
  - Carcinogenic
    - Esophagus, stomach, white blood cells
  - Esophageal tumors
    - Japan





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Herbs and Supplements

- 1994 Dietary Supplement Health and Education Act (DSHEA)
- Drug manufacturers
  - Prove products safe
- DSHEA
  - Makes FDA prove products are unsafe
  - Takes years
- Individuals searching for "complementary and alternative medicine"
  - 36% of adults
  - 19% - use natural products
  - 1997: $36 to 47 billion on CAM therapies

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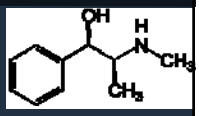
Ephedrine

- December 2003
  - FDA banned use of ephedra as weight loss aid
  - Steve Bechler, 23 yo MLB pitcher dies
- Previous 5 years
  - 14,684 adverse events
  - 18 heart attacks
  - 26 strokes
  - 43 seizures
  - 5 deaths



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Ephedra Replacements

- Other stimulants
  - Bitter orange (*Citrus aurantium*)
    - Synephrine
  - Green tea extract
    - Caffeine + catechins

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St. John's Wort (*Hypericum perforatum*)

- Used for centuries – mild to moderate depression
- Second most popular herb
  - Annual sales: $104 million
- Many active ingredients
  - Hypericin
  - Hyperforin

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St. John's Wort (*Hypericum perforatum*)

- Potential problems
  - "…when using this product, one should avoid prolonged excessive contact with sunlight…"
  - Interferes with metabolism of other drugs
    - Contraceptives
    - Heart medication
  - Induction of the cytochrome P450 metabolic pathway

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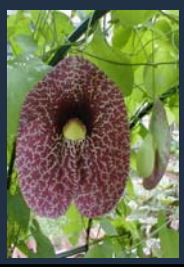
Plant Supplements to Avoid

- Aristolochic acid (*Aristolochia*)
  - Carcinogen, kidney failure
- Chaparral (*Larrea divaricata*)
  - Liver failure



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Plant Supplements to Avoid

- Lobelia (*Lobelia inflata*)
  - Respiratory, low bp and HR, diarrhea, dizziness, death
- Germander (*Teucrium chamaedrys*)
  - Liver damage

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Plant Supplements to Avoid

- Kava root (*Piper methysticum*)
  - Liver damage
- Pennyroyal oil (*Hedeoma pulegiodides*)
  - Liver and kidney damage

Your head is affected most pleasantly. Thoughts come cleanly. You feel friendly...never cross...You cannot hate with kava in you."
-Tom Harrison, Savage Civilization, 1937

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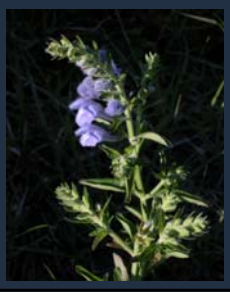
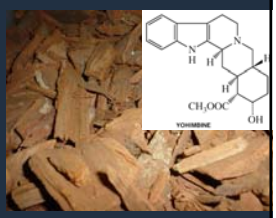
Plant Supplements to Avoid

- Skullcap (*Scutellaria lateriflora*)
  - Liver damage
- Yohimbe bark (*Pausinystalia yohimbe*)
  - Drop bp, heart arrhythmias, heart failure





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Mushroom Toxins

- Mushroom poisoning is caused by the consumption of raw or cooked fruiting bodies (mushrooms, toadstools) of a number of species of higher fungi.
  - The term toadstool is commonly given to poisonous mushrooms.
    - German Todesstuhl, death's stool
- No general rule for distinguishing edible mushrooms and poisonous toadstools.
  - Most mushrooms that cause human poisoning cannot be made nontoxic by cooking, canning, freezing, or any other means of processing.
  - Only way to avoid poisoning is to avoid consumption of toxic species.

47 USFDA/CFSAN

Mushroom Poisoning Occurrence

- Occurs most commonly when hunters of wild mushrooms (especially novices) misidentify and consume a toxic species.
- When recent immigrants collect and consume a poisonous American species that closely resembles an edible wild mushroom from their native land.
- When mushrooms that contain psychoactive compounds are intentionally consumed by persons who desire these effects.

48 USFDA/CFSAN

Physiological Effects of Mushroom Toxins

USFDA/CFSAN

- Protoplasmic poisons
  - Result in generalized destruction of cells, followed by organ failure
- Neurotoxins
  - Cause neurological symptoms such as profuse sweating, coma, convulsions, hallucinations, excitement, depression, spastic colon
- Gastrointestinal irritants
  - Produce rapid, transient nausea, vomiting, abdominal cramping, and diarrhea
- Disulfiram-like toxins
  - Interact with alcohol

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Protoplasmic Poisons: ex. Cyclic Peptides

- *Amanita*, *Galerina*
- *Conocybe, Pholiotina, Lepiota*
- Many associated with roots of trees
- Amatoxins and phallotoxins – inhibit nuclear RNA polymerase – protein synthesis
- Delayed onset
- Targets: GIT, kidney, liver
- 50-90% death rate for large dose

Amanita phalloides (death cap)

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Poisoning by the Amanitins

- Long latent period (range 6-48 hours, average 6-15 hours) during which the patient shows no symptoms.
- Symptoms appear at the end of the latent period in the form of sudden, severe seizures of abdominal pain, persistent vomiting and watery diarrhea, extreme thirst, and lack of urine production.
- If this early phase is survived, the patient may appear to recover for a short time, but this period will generally be followed by a rapid and severe loss of strength, prostration, and pain-caused restlessness.
- Death in 50-90% of the cases from progressive and irreversible liver, kidney, cardiac, and skeletal muscle damage may follow within 48 hours (large dose), but the disease more typically lasts 6 to 8 days in adults and 4 to 6 days in children.
- Two or three days after the onset of the later phase, jaundice, cyanosis, and coldness of the skin occur.
- Death usually follows a period of coma and occasionally convulsions. If recovery occurs, it generally requires at least a month and is accompanied by enlargement of the liver. Autopsy will usually reveal fatty degeneration and necrosis of the liver and kidney.

51 USFDA/CFSAN

Neurotoxins: ex. Ibotenic Acid and Muscimol

- *Amanita, Tricholoma*
- Toxins: neurotransmitters
  - Ibotenic acid (GABA derivative)
  - Muscimol (false neurotransmitter)
  - Affects serotonin, noradrenalin, dopamine: similar to LSD
- Onset: 30-90 min; Peaks: 2-3 hrs
- Initial abdominal discomfort
- Chief symptoms are drowsiness and dizziness, followed by a period of hyperactivity, excitability, illusions, and delirium.
- Fatalities rarely occur in adults

Amanita muscaria (fly agaric)

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Gastrointestinal Irritants

- GI Irritants: Many types
  - Green Gill (*Chlorophyllum molybdites*), Gray Pinkgill (*Entoloma lividum*), Tigertop (*Tricholoma pardinum*), Jack O'Lantern (*Omphalotus illudens*), Naked Brimcap (*Paxillus involutus*), Sickener (*Russula emetica*), Early False Morel (*Verpa bohemica*), Horse mushroom (*Agaricus arvensis*) and Pepper bolete (*Boletus piperatus*),
- Rapid onset
- Signs: vomiting, diarrhea – short lived
- Rare fatalities: dehydration

Omphalotus illudens (Jack o'lantern)

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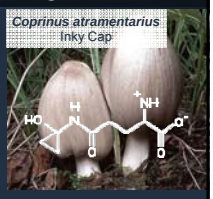
Disulfiram-Like Toxins

- No illness results when eaten in the absence of alcoholic beverages (like Antabuse®)
- Produces an unusual amino acid, coprine
  - Converted to cyclopropanone hydrate in the human body
  - Interferes with the breakdown of alcohol
  - Consumption of alcoholic beverages within 72 hours after eating it will cause headache, nausea and vomiting, flushing, and cardiovascular disturbances that last for 2 - 3 hours.



Coprinus atramentarius Inky Cap

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