applications in products such as chewing gums or breath fresheners. It is not toxic, not cariogenic, and it enhances aromas and flavors at low doses. At higher doses, it is an intense sweetener. Research efforts to come up with production methods that do not require using the plant (transgenic organisms) have not yet succeeded in achieving sufficient yields.

• Monellin

Monellin is found in the fruits of a Menispermaceae of tropical western Africa, *Dioscoreophyllum cuminsii* Diels. This tropical rain forest vine, with cordate leaves, bears tight bunches of up to a hundred little red berries. In spite of the fact that the seed is bitter (due to diterpenoids), the whitish mucilage that surrounds it is particularly "sweetening". This is due to monellin, a protein composed of two chains comprising 44 and 50 amino acids, respectively. Although it is particularly efficacious (2,000 times the sweetening potency of sucrose), monellin is unstable at extreme pHs, and does not resist heating, let alone the combination of the two (it is destroyed at 50°C at pH 3.2). Toxicological data are lacking, which seriously limits potential applications.

• Miraculin

This protein can be extracted from the fruit of a western African shrub: *Synsepalum dulcificum* Dan. (Sapotaceae). After about two and a half centuries in oblivion—since the first mention in 1725 of this fruit "which could mask the bitter taste of drugs"—the "miracle" fruit regained attention for its very curious properties: just about tasteless on its own, it transforms the acidic taste into a sweet taste and modifies the perception of numerous flavors. Its properties are linked to a glycoprotein, miraculin, composed of 473 amino acids. Its potential applications are of limited scope; moreover, it induces a risk for confusion due to the persistence (for two hours) of its ability to modify taste.

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Proteins

Lectins

Lectins, from the latin *lego, legere (lectum)* = to read, to choose, to se*lect*... are uninduced proteins or glycoproteins able to bind to saccharide residues on cell membranes, in a specific and reversible fashion, without displaying enzymatic activity. Most lectins of higher plants are located in the seeds: they form during ripening and disappear during germination. They are especially common in Fabaceae (peanut, soybean, lentil, *Canavalia*, green bean, and more).

Many lectins have the ability to agglutinate red blood cells—they are referred to as phytohemagglutinins—and several among them do so with blood group specificity. Some lectins are mitotic; a few can differentiate between normal and tumor cells; some are highly toxic.

Several lectins are currently available for numerous applications in the biological disciplines, but this aspect exceeds the scope of this text (see biochemistry, immunology, hematology texts).

VEGETABLES THAT ARE TOXIC DUE TO LECTINS

Although lectins are often toxic only by the parenteral route, some are not destroyed by the enzymes of the digestive tract: such is the case of abrin from jequirity seeds, phasin from green beans, and also ricin of castor seeds.

Intoxication by ingestion of this type of poison manifests itself 2-3 hours after consumption, by vomiting and hemorraghic diarrhea, loss of fluids, and a state of shock.

Lectins are in fact denatured by cooking: thus green beans are perfectly edible cooked, whereas ingesting raw seeds or pods results in severe gastric disturbances,

• JEQUIRITY, *Abrus precatorius*, Fabaceae

Also known as Indian licorice, this climbing tropical species is known for its ovoid, shiny, red and black seeds (jequirity rosary peas). These decorative seeds have long been used to make necklaces and bracelets. Although the seeds are quite hard, and therefore innocuous (because they are not degraded in the digestive tract), to be made into a necklace they must be *pierced*: then the toxin (abrin) can be absorbed if the necklace is inadvertently brought to the mouth. Of course, these are anecdotal cases; however, they do illustrate the dreadful efficacy of this type of molecule. The lectin (abrin) induces severe gastroenteritis (dehydration, hypotension), confusion, a coma, and convulsions. The sweet taste of jequirity root has led to its use as licorice root substitute (see abrusosides, p. 683).

• CASTOR, *Ricinus communis* L., Euphorbiaceae

Ricin interferes with protein synthesis by enzymatically inactivating the 28S ribosome subunit in eucaryotic cells and causing the hydrolysis of an adenyl residue. Ricin is responsible for the toxicity of the castor bean (see p. 144).

The minimal lethal dose is on the order of 0.4 µg/kg in the rat (by the parenteral route). The toxicity also manifests itself by the oral route: castor seed intoxications result in nausea, headaches, bloody diarrhea, dehydration, ECG modifications, liver necrosis, loss of consciousness, and more, with the autopsy revealing damage to most organs. Ricin is of interest because of its long known antitumor properties, and this interest has been emphasized by the introduction of monoclonal antibodies: by reversible coupling of an antibody with the A chain of ricin, an immunotoxin is created which is specifically targeted for a given antigen. Numerous experiments and a few preclinical trials have shown the potential of this approach in the search for antitumor agents; this may also be an interesting research avenue in the domain of viral infections and that of immunosuppressive agents. It is also an interesting tool in neurology (selective destruction of neurons).

• MISTLETOE, *Viscum album* L., Viscaceae

The Plant, The Drug. This is a semiparasite which grows affixed by roots modified into suckers, on various species of deciduous trees: poplars, apple trees, and other species, but also firs (Fagaceae mistletoe is *Loranthus europaeus* Jacq.). Morphologically, mistletoe is a dioecious subshrub that forms a more or less spherical tuft, with leaves placed symmetrically at the end of greenish-yellow stems ramified according to a false dichotomy. The flowers, male and female, are in groups of 2-6 at the insertion point of the leaves. The fruit is a spherical fleshy

berry, whitish and translucent at maturity, and monoseeded. The leaf was described in the 8th edition of the French Pharmacopoeia. It is yellowish, thick, coriaceous, and 3-6 clearly parallel ribs run along its surface. The blade, elliptic, appears articulated onto the branch and can be detached easily.

Chemical Composition. The leafy stems of the plant contain triterpenoids, sterols, amines (choline, histamine, tyramine) and phenolic compounds: phenolic acids (particularly in C6-C3), lignans (eleutheroside E, glycoside of syringaresinol), syringin and flavonoids (glycosides of the mono-, di-, and trimethyl ethers of quercetin, glycosides of flavanones and of methoxylated chalcones).

The specific proteins that have received attention are viscotoxins and lectins. Viscotoxins A_2, A_3, and B have a molecular weight near 5,000 daltons (they include 46 amino acids), and are resistant to heat and proteases. Lectins, ML I (or viscumin), ML II, and ML III are glycoproteins specific to D-galactose (ML I, MW 115,000), to *N*-acetylglucosamine (ML III) or to both (ML II). Viscumin, as ricin, consists of two (A and B) chains: its mode of penetration into cells is the same, as are its site and mode of action. Its toxicity is also considerable (100 µg/kg in the rat by the intraperitoneal route).

Pharmacological Activity. Tradition attributes to mistletoe hypotensive properties, but although these were demonstrated in the dog (by the IV route) at the beginning of the century, they have not been confirmed in clinical trials (*per os*). The substances responsible for the transient hypotension which is observed remain unidentified, and the activity varies depending on the host from which the plant has been collected.

The cytotoxic activity of mistletoe and of its preparations on various cell lines (HeLa, sarcoma 180) is due to the protein fractions. Lectins are particularly cytotoxic (inhibition of human leukemia cells at concentrations of 1-3 ng/mL); note also some immunogenic effects. Viscotoxins are also cytotoxic, but much less intensely; they have a cytolytic effect.

Uses. Despite claims that the drug has hypotensive properties, it is seldom used in France. It is not listed in Annex 1 of the French Explanatory Note of 1998. The viscotoxin and lectin toxicity requires extreme caution in the use of this drug whose benefit-to-risk ratio has not been clearly established.

In Germany, "anthroposophic" medicine believers think, on the basis of considerations that are anything but pharmacological, that mistletoe has antitumor properties, which is far from being clearly established by reliable clinical experiments. Taking into consideration cytostatic and immunostimulating properties that have been observed experimentally, various German pharmaceutical companies market mistletoe-based products that they promote as antitumor agents (fermentation products, extracts titrated for lectins). The German Commission E monograph mentions the cytostatic and immunostimulating properties observed in animals and lists the following uses: as palliative therapy for malignant tumors via non specific

product titrated for ML-1 might have stabilized the patients' quality of life, even though it didn't alter the tumor development at all. Other authors also observed this modest improvement in quality of life, and an increase in β-endorphin level.

Other Proteins. Other vegetable proteins have pharmacological potentials that probably deserve to be studied thoroughly, for example trichosanthin, a 234-amino acid protein isolated from the subterranean parts of a Chinese Cucurbitaceae, *Tian Hua Fen*, *Trichosanthes kirilowi* Maxim or *T. japonica* Regel. This drug from the traditional Chinese Pharmacopoeia is known and still used for its abortifacient properties due to trichosanthin, which acts directly on the placental villi: 1.2 mg of the protein (IM) induces abortion in 4 to 7 days in 98% of test subjects. Like the A chain of ricin, this protein inactivates protein synthesis at the ribosomal level. *In vitro*, it inhibits the replication of the HIV virus.

Trichosanthes is not the only Cucurbitaceae genus to contain biologically active proteins: in the genera *Momordica* and *Luffa*, several species are used by traditional Chinese medicine, and there are several glycoproteins of molecular weight near 30,000: momorcharins, momorcochin, luffaculin, luffins... (e.g., *M. cochinchinensis* [Lour.] Sreng [tubercles], *M. charantia* L. [= bitter-melon], *L. acutangula* [L.] Roxb., *L. cylindrinca* [L.] Roem [seeds]). Like trichosanthin, momorcharins have abortifacient and antitumor properties (on choriocarcinomas and melanomas), and inhibit protein synthesis. Similarly, they inhibit the replication of the HIV virus *in vitro*; their activity on the humoral and cellular immunity is complex: they are allergens, but can inhibit the reactions induced by other allergens.

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Enzymes

• PAPAYA TREE, *Carica papaya* L., Caricaceae

The fruit of this species, the papaya, is rich in sugars, vitamins, and volatile compounds. It is widely consumed in tropical countries. The 10th edition of the French Pharmacopoeia devotes a monograph to the "mixture of enzymes possessing proteolytic and esterase activities from the thickened latex obtained by incision of the fruits shortly before maturity", designated *suc de papayer* or "papaya latex". In therapeutics, a purified fraction, chymopapain, is often used for the treatment of sciatica due to a herniated lumbar disc.

The Plant, The Drug. The papaya tree belongs to a small family reduced to four genera. It is a tree reaching 3 to 10 m in height, with the habit of a palm: the fleshy stem, marked by scars where leaves have fallen off, is surmounted by a terminal panache of large leaves on long petioles and with 5-7 lobes. A dioecious species, the papaya tree bears ovoid berries of variable size: they can reach 20-30 cm in diameter and weigh 5 kg. When ripe, papayas are yellowish-green, their flesh juicy and orangy-yellow, and their central cavity is filled with black seeds surrounded by mucilage. Within the fruit pericarp and the leaf mesophyll runs a network of anastomosed laticiferous ducts.

The species is native to Central America, and is cultivated in virtually all of the intertropical regions (Brazil, Sri Lanka, Thailand, India, but also on the African continent: Tanzania, Uganda, Zaire).

The drug, that is the latex, is collected after incision of the unripe fruits; the