ME-02 Dose and potency: the problem every herbalist faces

HEALING after the FALL, research library, ME-02

Researched 10 October 2026 by Claude Opus agent for THRIVING after the FALL, Book Four. Library document, unverified.

1. The size of the problem: how far potency actually swings

The library already holds one hard case. IN-09 concluded that "without an assay, the content of any given bark is unknown to within a factor of five, so bark dosing is dosing blind" (THRIVING library, IN-09). That is not a peculiarity of cinchona. It is the ordinary condition of every medicinal plant, and for several of the plants that matter most it is far worse.

The table collects content ranges I could trace to a named study or monograph, as a percentage of dry plant material unless stated. The "fold" column is my arithmetic on the quoted endpoints [VERIFY].

Plant, part	Active	Measured range	Fold	Source
Digitalis purpurea leaf, dried	cardenolides as digitoxin	not less than 0.3% monograph floor, 0.5 to 0.7% crude glycosides at two Colombian sites	about 1.4	Thai Ph., Rojas
D. purpurea leaf, fresh	cardenolides	0.020 to 0.040% m/m	2	French homeopathic monograph
Opium, air dry	morphine	8 to 19% in normal unadulterated opium, 9.20 to 20.86% across 98 germplasm lines, 16 to 20% from first lancings	about 2.3	UNODC 1953, *Nature* 1937
Artemisia annua dried leaf	artemisinin	0.01 to 0.5% across genotypes, 0.03 to 0.22% European stock, 1.1% a Chinese clone, 1.4% selected hybrids	about 100	Mueller 2000, Delabays

Plant, part	Active	Measured range	Fold	Source
Salix spp. bark	salicin	0.04 to 12.06% across 32 taxa, 3.04 to 10.96% total glycosides within 91 *S. purpurea* genotypes	over 100 across taxa, 3.6 within one	Jurkstiene 2009
Atropa belladonna leaf	tropanes as hyoscyamine	0.2 to 2.0% dry matter, average 0.3 to 0.5%, standardised powder 0.28 to 0.32%	10 wild, 1.14 standardised	EMEA CVMP
Datura stramonium	atropine, scopolamine	up to 20:1 between plants, 20 to 40 times lower outside the native range	20 to 40	Datura review
Aconitum napellus	aconitine group	0.3 to 2% fresh tuber, 0.2 to 1.2% fresh leaf, 1 to 2% seed	about 7	BC DPIC
Colchicum autumnale corm	colchicine	0.1 to 0.6% assumed in a fatal case reconstruction	6	Brvar 2004
Cinchona bark	quinine and allied alkaloids	about fivefold	5	IN-09
St John's wort products	hypericin	1.7 to 38.5% of the labelled amount across five products	about 22	Taiwanese market analysis

Read the table as one statement. For a plant bred and standardised by an industry, as belladonna powder has been, content sits inside a band of plus or minus 7 per cent. For a plant taken from a hedge the band is a factor of ten, and for willow or *Artemisia* taken without knowing the species it is a factor of a hundred. A dose written for the strong end is a non-dose at the weak end, and one written for the weak end is a poisoning at the strong end. For most plants that does not matter, because the margin between working and harmful is wide. For the ten or so plants where it is narrow, it is the whole safety problem of this book.

Willow is the worst case and the one a village will meet first. The Lithuanian survey found salicin from 0.04 to 12.06 per cent across 32 taxa, found the species most often sold as medicine, *Salix alba*, near the bottom at 0.5 to 1 per cent, and found two-year-old bark cut in autumn about 25 per cent richer than one-year-old bark cut in spring (Jurkstiene and others 2009). The European Pharmacopoeia sets a floor of 1.5 per cent salicin, which several common willows fail (EMA *Salix* monograph). Salvaged products are no better: ephedra supplements held 0 to 18.5 mg of ephedrine alkaloids per dose unit, with lot-to-lot variation inside one brand above 180 per cent (Gurley 2000, Schaneberg 2004).

2. The eight causes of variation

Species and genotype. The largest single cause, and the one a healer can control. *Artemisia annua* from European seed averaged 0.03 to 0.22 per cent artemisinin, while a Chinese clone reached 1.1 per cent in the same trial (Delabays and others, undated). Willow varies over a hundredfold between species. Identification must go to the species, and a

village that finds a good individual plant should propagate it rather than resow from mixed seed.

Plant part. Aconite is 0.3 to 2 per cent alkaloid in the fresh tuber and 1 to 2 per cent in seed (BC Drug and Poison Information Centre, undated). Opium poppy morphine is concentrated in the latex at 9 to 21 per cent, while capsule tissue runs 0.02 to 1.05 per cent and the peduncle 0.001 to 0.24 per cent (Pakistani study, undated). A recipe that says "the plant" is not a recipe.

Growth stage and season. Withering, who had no chemistry, saw this in 1785: the leaves "vary greatly in their efficacy at different seasons of the year, and, perhaps, at different stages of their growth" (Withering 1785). Belladonna shows maximal alkaloid yields at early night and early morning (EMEA CVMP, undated), and seasonal variation in total glycoside content has been measured in *D. lanata* (Rajukkannu and others 1981, abstract only). In *Datura*, the ratio of scopolamine to atropine is about 3:1 in young plants and reverses after flowering, so the same plant gives a different drug at a different time of year (Datura review, undated). Withering's harvest rule was to gather the leaves "after the flowering stem has shot up, and about the time that the blossoms are coming forth", discard the mid-rib and stalk, and dry quickly without scorching.

Drying. The digitalis monographs demand rapid drying at not more than 60 degrees C (Thai Pharmacopoeia, undated). For goldenseal, drying temperature left berberine and hydrastine unchanged but cut canadine by more than half (Penn State report, undated). In belladonna, total alkaloid was lowest in sun-dried leaf and highest in shade-dried (Iranian storage study, undated). Shade drying with moving air, finished fast, is the rule the record supports.

Storage. The cause most often forgotten. Echinacea alkamides fell by over 80 per cent in 64 weeks at 24 degrees C, and lavender oil in dried flowers declined about 2.56 per cent a year over eight years. A village must assume a two-year-old jar is weaker than the batch it was dosed against, and must not assume it by a fixed percentage.

Fresh against dried. The herbal rule of 3:1 by volume comes from the kitchen, not from pharmacy. The same sources give 4:1 for some herbs and 6:1 for rosemary, so a healer who swaps fresh for dried at 3:1 on a narrow-margin plant is guessing at a factor that may be 2 or may be 6.

Extraction. Covered in section 3.

Adulteration and substitution. A Canadian study of 44 herbal products found one third contained no trace of the labelled plant (Newmaster and others 2013). [CORRECTION added by the compiler on 12 October 2026: that paper was retracted on 4 July 2024 after a University of Guelph investigation found evidence of data fabrication. Do not use its figures. See FO-03 and SY-02, which handle it correctly, and ME-13.] An analysis of nearly 6,000 products from 37 countries reported 27 per cent adulterated (trade press report, original not read), while a survey of 1,436 raw market samples in China found only 4.2 per cent adulterants, which suggests raw material is safer than processed product. After the Fall the problem returns as misidentification in the field.

3. The second lottery: from plant to cup

Knowing the content of the leaf does not tell you the dose, because the preparation decides how much of the active substance leaves the plant. The clearest measurement is for *Artemisia annua*. Van der Kooy and Verpoorte (2011) found over 90 per cent of the artemisinin can be extracted, but only at 9 g of dry leaf per litre for 5 minutes at 100 degrees C. Raise the loading to 40 g per litre and only 43 per cent of the extractable artemisinin appears in the tea. The reason is solubility: artemisinin dissolves in water at about 50 mg per litre, so a tea cannot carry much more however much leaf is used. WHO's 2012 statement put the consequence plainly: the highest artemisinin concentration released into one litre of tea was still under 20 per cent of a 500 mg pharmaceutical dose, and matching that dose would take up to 5 litres of tea a day for at least seven days (WHO 2012).

The same study found only 1.8 per cent of the casticin in the leaf reached the infusion and artemetin was undetectable. A water infusion is a selective extraction, not a dilution of the whole plant: water pulls out glycosides, tannins and salts, alcohol pulls out alkaloids and resins. This is why aconite tincture is so much more dangerous than aconite

decoction, and a Chinese review notes that tincture accounts for the great majority of aconite poisoning cases in China (Chinese aconite review, undated). Traditional Chinese processing goes the other way, soaking and boiling to hydrolyse the alkaloids into less toxic derivatives, and the recorded poisonings cluster on inadequate processing and overdose prescribing (Hong Kong series of 52 confirmed cases, 11.5 per cent severe, no deaths).

Two things follow. The ratio of plant to water matters more than the quantity of plant, because the solvent saturates, and a five-minute steep and a two-hour simmer of the same leaf are different medicines.

4. What standardisation was, and what the village keeps

Withering's *An Account of the Foxglove* (1785) is the founding document of dose control in Western medicine, because he solved the variability problem without chemistry, in four moves. He fixed the material: leaves gathered at flowering, mid-rib removed, dried fast, rubbed to a green powder. He fixed the quantity: "I give to adults, from one to three grains of this powder twice a day". He fixed the pace: allow sufficient time for the effects of each dose to take place. And he fixed the endpoint: continue until the urine flows, or sickness or purging take place, and stop "upon the first appearance of any one of these effects" (Withering 1785). His overdose signs were sickness, vomiting, purging, giddiness, confused vision, objects appearing green or yellow, and a pulse as slow as 35 in a minute.

What Withering could not do was compare one batch of leaf to another except through a patient. That is what biological standardisation was invented for. The frog method, a graded intravenous dose that stops the frog's heart, was the official United States method through the tenth revision of the Pharmacopoeia (Van Dyke and Li 1935). The cat method of Hatcher and Brody defined a cat unit as the amount of digitalis that stops a cat's heart given intravenously (quoted in a 1930s JAMA letter). That is the nearest I could get to the lead in the brief: I could not find the original paper or confirm Brody as a co-author [VERIFY]. The United States Public Health Service published an improved one-hour frog method in 1925, drawing on the International Conference on Biological Standards of January 1925 and a preliminary report by H. H. Dale (Smith and McClosky 1925). The international machinery began with a League of Nations conference in 1921, with further meetings at Edinburgh in 1923 and Geneva in 1925 (Sizaret 1988). J. H. Burn's *Biological Standardization* was published by Oxford University Press in 1937, not 1950 as the brief suggested [VERIFY]. The animal assays were themselves unreliable: a 1952 Japanese study found the Hatcher-Magnus cat method varied between laboratories with the cats' species, sex, weight and nutritional state. Even the best pre-chemical assay was a comparison, not a measurement.

So what can a village keep? Three things, none of them an assay in the chemical sense.

First, the comparison itself. You cannot measure the strength of a batch, but you can compare it to a batch of known behaviour. A village that keeps a sealed reference sample of a batch it has used successfully, and compares every new batch to it, has reinvented the method.

Second, the bitterness value, the one pharmacopoeial assay that needs no equipment, and a rare case of a written method surviving without a laboratory (THRIVING library, FO-03). The European Pharmacopoeia method (2.8.15, carried into the British Pharmacopoeia) defines bitterness as the reciprocal of the highest dilution that still tastes bitter, against quinine hydrochloride, whose value is fixed at 200,000. It takes 1.0 g of sample in 100 ml of boiling water, heated on a water bath for 30 minutes with stirring, filtered, then diluted in a series. A panel of at least six people, each with an individual correction factor, tastes the dilutions after rinsing, and anyone who cannot detect the quinine reference is excluded. It has been criticised as empirical and subjective, because different pharmacopoeias use different reference standards, but it is written down, and it is the only assay here a village of 300 can run. It cannot be used on narrow-margin plants, because tasting a dilution series of aconite or belladonna would poison the panel.

Third, the logbook. Standardisation is a record-keeping practice as much as a laboratory one. UK poisons law made the point in a form worth copying: the seller of a scheduled poison entered the purchase in a book with the purchaser's signature, and where a doctor's signed order stood in its place, entered the words "signed order" with the date and kept

the order for two years (UK poisons amendment 1923). That is the model: one book, one page per narrow-margin plant, one line per dose dispensed.

5. Therapeutic index and the narrow-margin list

The therapeutic index is the ratio of the dose that harms to the dose that helps, usually TD50 divided by ED50. The National Cancer Institute thesaurus defines a narrow index as less than a twofold difference between the median lethal and median effective dose, or between the minimum toxic and minimum effective blood concentrations. The honest figures for the plants that matter:

Drug or plant	Working dose	Harm appears at	Practical margin
Digitalis, digoxin	therapeutic serum 0.9 to 2.0 ng/ml, ESC recommending 0.6 to 1.2	toxicity at 2 to 3 times therapeutic, and within the therapeutic range where potassium is abnormal or the kidney injured	about 2, less in the sick
Colchicine	about 0.5 mg two or three times daily for gout	gut symptoms below 0.5 mg/kg, 0.8 mg/kg presumed fatal, UK paediatric deaths from 0.21 mg/kg	about 10, far less in children and in liver or kidney disease
Quinine	10 mg of salt per kg three times daily, 1.8 to 2 g a day for an adult	cinchonism at therapeutic doses, minimum toxic dose 3 to 4 g, fatalities from 1.5 g, average fatal dose about 8 g	under 2 at the low end
Atropine, belladonna	0.4 to 1 mg for an adult	delirium and coma at 10 mg and above, 65 mg may be fatal, and in a child 10 mg may kill	about 10 in adults, less in a child by weight
Opium, morphine	5 mg oral morphine four-hourly in a naive adult, 2.5 mg in the old or renally impaired	oversedation then respiratory depression, no fixed number because tolerance moves the curve	wide in the tolerant, very narrow in the naive, the old and the infant
Aconite	no safe lay dose	estimated lethal dose of aconitine in an adult 1 to 4 mg	effectively none

Digitalis is the hardest case because its toxicity overlaps its therapy: a 2025 case describes severe toxicity at 1.4 ng per ml in a 76-year-old after gastrointestinal bleeding and kidney injury. I could not find support for the sometimes quoted figure of 20 per cent mortality among hospitalised digitalis-toxic patients in the 1970s [VERIFY]. Quinine is where variation and narrow margin meet: bark content is unknown within a factor of five (THRIVING library, IN-09), and the fatal dose may be as low as 1.5 g against a daily therapeutic dose near 2 g. That combination should frighten a village healer more than any single plant.

The rule the book needs follows from the table, and it is about people rather than chemistry. **The one-in-a-village rule: for any plant in the narrow-margin list, one named person prepares every batch, from one identified**

source, by one written method, and dispenses every dose from a logbook. Nobody else prepares it, and nobody takes it from the common store. The named plants are foxglove (*Digitalis purpurea*, *D. lanata*), opium poppy (*Papaver somniferum*), cinchona (*Cinchona* spp.), belladonna (*Atropa belladonna*), henbane (*Hyoscyamus niger*), thorn apple (*Datura stramonium*), autumn crocus (*Colchicum autumnale*), monkshood (*Aconitum napellus*), and any salvaged pharmaceutical with a narrow index. Aconite and autumn crocus should not be prepared below a district infirmary, and arguably not there.

6. The measures and their error

The grain. One grain is exactly 64.79891 mg, fixed by the 1959 international yard and pound agreement and shared by the troy, avoirdupois and apothecaries' systems. One gram is about 15.43 grains. Twenty grains make a scruple, 3 scruples a dram, 8 drams an ounce, so 480 grains to the ounce. Withering's one to three grains twice daily is 65 to 194 mg twice a day. The grain survives in old texts and on salvaged labels, and a healer who cannot convert it will make a hundredfold error.

The drop. The pharmacist's convention rounds a drop to exactly 0.05 ml, that is 20 drops to the millilitre. The 20 to 60 range in the brief most likely comes from intravenous giving sets, where the drop factor is a property of the tubing, and I could not find a controlled study of drops per millilitre against viscosity for medicine droppers. General sources put the real spread between about 15 and 40 drops per ml, with thicker liquids giving fewer, larger drops. Treat the drop as having an error of about plus or minus 50 per cent unless the dropper and the liquid have been counted against a measured volume, which means dripping into a known volume several times and taking the mean.

The teaspoon. The best measured error in this report. Falagas and colleagues collected 71 teaspoons and 49 tablespoons from 25 households in Attica and found teaspoon volume from about 2.5 to 7.3 ml, mean and median 4.4, and tablespoons from 6.7 to 13.4 ml (Falagas and others 2010, read through the publisher's press release). A parent using the biggest household teaspoon gives 192 per cent more than one using the smallest, and a 2025 Sri Lankan survey found the same spread. Madlon-Kay and Mosch (2000) tested 130 volunteers at three Minnesota clinics: 73 per cent used a household teaspoon, 70 per cent of errors were measuring a teaspoon instead of a tablespoon, and 92 per cent measured correctly with an oral dosing syringe. Wansink and van Ittersum (2010) showed the spoon itself biases the pour, 8.4 per cent under into a medium tablespoon and 11.6 per cent over into a larger one.

The teaspoon of powder. Worse, because volume to mass depends on packing, particle size and moisture. Powders are weighed, not spooned, whenever the margin is narrow.

The pinch and the handful. I found no study quantifying either. They are tradition's units and they are not measures. Thomson's *Botanic Family Physician* dosed powdered lobelia "from half a teaspoon to a full teaspoon", a twofold range on top of a threefold spoon range, before the plant's own variation is counted.

The balance. An equal-arm balance is the village's best instrument and its errors are known. NIST guidance treats unknown and standard as balanced when they agree within one scale division. Arm-length inequality biases every comparison, and the classical remedy is weighing by transposition: weigh, swap the pans, weigh again, take the mean.

The decimal errors. A five-year review of one paediatric hospital's reports identified 252 tenfold errors out of 6,643 medication reports, 22 of them causing harm, with dose calculation, decimal points and confusion with zeroes as frequent causes and morphine the commonest drug. The traps are the trailing zero, where 15.0 mg read without the point becomes 150 mg, and the missing space, where "propranolol10mg" becomes 110 mg. The salvaged-pharmacy version is the laudanum and paregoric confusion: opium tincture holds 10 mg of morphine per ml and paregoric 0.4 mg per ml, a 25-fold difference between products whose synonyms overlap. The FDA received eight reports of errors between them since 1997, three fatal and three more needing treatment, and in one near miss a 13-day-old would have had about 42 mg a day instead of 1.68 mg. The safeguard is a rule of form: opium tincture is dosed in drops, paregoric in teaspoons, so any opium tincture order written in teaspoonfuls is wrong.

7. Who is not a standard adult

Children. Clark's rule takes the child's weight in pounds, divides by 150 and multiplies by the adult dose. It is better than nothing and worse than mg per kg. Elias and others (2005) tested the old rules against mg per kg standards for six drugs in children aged 1 to 12 and found antibiotics and diclofenac acceptable, dipyrone likely to be ineffective, and paracetamol by Penna's rule and the body-surface-area formula uncomfortably close to the hepatotoxic dose at ages 1 to 5. Clark's rule assumes a 150-pound adult and ignores developmental changes in handling, so it is least reliable in neonates and infants, where the margin is smallest.

Three sets of deaths explain why children are not small adults. Chloramphenicol produces grey baby syndrome in neonates whose liver conjugation is immature: abdominal distension, progressive pallid cyanosis, vasomotor collapse and death within hours of onset, after three to four days of dosing, with reported mortality of 35.3 per cent in a review of 17 cases. In one study of 64 neonates, nine of the ten who showed toxicity had received the prescribed dose. The dose was right and the child was wrong. Second, aspirin and Reye's syndrome: case-control studies in Ohio, Michigan and Arizona found about 95 per cent of Reye's patients had taken salicylates against 48 to 70 per cent of controls with similar illnesses, odds ratios reaching 40.5, and United States cases fell from a peak of 555 in 1980 to no more than 36 a year after 1987, following the 1980 CDC caution and the 1986 FDA label. A UK study found cases in the highest-certainty category fell by 79 per cent against about 50 per cent in lower ones, which argues against the fall being an artefact of diagnosis. Third, codeine: people with duplicated CYP2D6 convert it to morphine unusually fast. The FDA reviewed 13 deaths and four overdoses in children in reports from 1999 to 2012, and in August 2007 the death of a healthy breastfed 13-day-old whose mother, on a low dose for episiotomy pain, was an ultra-rapid metaboliser. The phenotype runs about 1 to 10 per cent in Europeans and higher in some groups. The EMA contraindicated codeine in breastfeeding women, in known ultra-rapid metabolisers of any age and in children having tonsillectomy for sleep apnoea, noting its effect in children is no better than paracetamol.

Dosing by weight needs a weight, and estimates without a scale are poor: the Broselow tape puts only about half of children within 10 per cent of true weight, and age-based formulas do worse, with bias running opposite ways in well-fed and malnourished populations (Nepalese, New Zealand, South African and Peruvian comparisons). Bias runs opposite ways in different populations, the tape underestimating in well-fed children and overestimating where malnutrition is common, and one review reported errors over 20 per cent in up to half of drug calculations made from it.

The old. Clearance falls with age through reduced renal and hepatic blood flow while receptor sensitivity rises, so the correction is to reduce the dosing rate. The dangerous part is that serum creatinine stays normal while filtration falls: the worked example in the literature is an 82-year-old woman of 50 kg with a creatinine of 1.0 mg per dl whose Cockcroft-Gault estimate is about 34 ml per minute. Without a laboratory the usable rule is age and frailty themselves: halve the starting dose above about 70, and halve again in anyone visibly wasted.

The pregnant. Pregnancy raises plasma volume, total body water and fat, lowers albumin, raises the unbound fraction, and raises renal blood flow and filtration, so renally cleared drugs leave faster. The changes peak in the second or third trimester and normalise within one to two weeks of delivery, and the net effect is not predictable from first principles. The practical rule for a village is not a dose adjustment but a prohibition list, because the plants most often reached for in pregnancy are abortifacients that kill the mother. Pennyroyal is the standard case. A review of 18 case reports found moderate to severe toxicity at 10 ml or more of the oil and fatalities one to two hours after 15 ml. Pulegone runs 80 to 90 per cent in European oil and 16 to 30 per cent in American, a fivefold difference between two bottles with the same name. The liver injury resembles paracetamol overdose, and the abortifacient effect requires lethal doses to occur at all.

The dehydrated. Dehydration removes the kidney's margin. The documented mechanism is the "triple whammy", where volume depletion lowers afferent pressure, a renin-angiotensin blocker removes efferent constriction and an NSAID blunts afferent dilation. One study estimated a 31 per cent increased risk of acute kidney injury when an

NSAID is added to a diuretic and RAS inhibitor, and an Australian commentary reported that such events made up about half of national reports of drug-induced acute renal failure. Look for tachycardia, postural hypotension and dry mucous membranes. The rule that matters is that willow bark is an NSAID, and the fever and diarrhoea for which a village reaches for willow are exactly the states in which it damages kidneys.

8. Titration: dosing an unknown batch

Titration is the only method that converts an unknown potency into a usable dose, and Withering wrote the protocol in 1785 without the word. Its structure: define an observable effect that appears before harm, start below the dose expected to produce it, wait long enough for the full effect of each dose, raise in fixed small steps, stop at the first sign, record everything.

The two hard parts are the endpoint and the interval. Withering used urine flow as the wanted effect and sickness, purging, giddiness, green or yellow vision and a slowing pulse as the stop signs, and abandoned vomiting as a target once he saw the diuresis did not depend on it. For cinchona bark the early sign is tinnitus, because mild cinchonism appears at standard therapeutic doses, which makes quinine one of the few plant drugs with a built-in dose indicator. For opium it is drowsiness and a falling respiratory rate. For belladonna it is dry mouth and blurred near vision. For aconite there is no early sign that reliably precedes collapse, which is the reason it is not a village medicine.

The interval must exceed the time to peak effect, and it is the part lay healers get wrong. Withering's instruction not to repeat too quickly exists because digitalis accumulates, and his own cases show what happens when it is ignored. In Case CVI the patient kept taking it after diuresis began, "his pulse sunk down to forty in a minute, every object appeared green to his eyes". In Case CXVII, "the medicine being still continued, his pulse became slow, and he apparently sunk under its sedative effects" (Withering 1785).

The step size should be a fixed fraction of the expected dose, not a doubling. A reasonable scheme, my inference from the structure of the historical practice rather than a quoted rule [VERIFY], is to start at one quarter of the expected dose, raise by one quarter at each interval, and never exceed twice the expected dose before concluding the batch is inactive.

Self-experiment by the healer is a pitfall, not a method. It tests one person's response, it risks the one trained person in the village, and for narrow-margin plants it is a poisoning. The bitterness panel is the defensible version: several tasters, dilutions, no swallowing, and only for bitter plants whose toxicity is not acute. Where a dangerous batch must be assessed, titrate in the patient who needs it, with the stop signs written down in advance and a second person watching.

Evidence grades

Practice	What tradition says	What the record shows	Grade
A marked syringe or a balance instead of a household spoon	tradition uses volume	teaspoons vary 2.5 to 7.3 ml, syringes gave the correct dose in 92 per cent	A for the syringe, B for weighing
Withering's titration to first effect	a rule of the art	survived 240 years, still the structure of digoxin loading	B
Stop signs as dose limits (tinnitus, slow pulse, green vision, dry mouth)	side effects	dose-related in Withering's cases and in quinine and atropine toxicology	B

Practice	What tradition says	What the record shows	Grade
Bitterness value as a batch comparison	tradition tastes the medicine	pharmacopoeial method with a defined panel and reference, criticised as subjective	C
One named preparer and a logbook	the apothecary's poisons book	UK poisons registers, ISMP safeguards after fatal opium tincture errors	B
Clark's rule for children	taught for a century	no study found validating it against outcomes, structurally poor in infants	D
mg per kg with a measured weight	modern	the standard against which the other rules are judged	A
"A handful", "a pinch", "a cup of the herb"	the common form of herbal dosing	no quantification found, sixfold compound error with spoon variation	D, X for narrow-margin plants
Self-experiment by the healer as assay	folk practice	no supporting record found, mechanism of harm obvious	D, X for narrow-margin plants
Tincture of a narrow-margin plant at village level	traditional in several systems	tincture accounts for the great majority of aconite poisonings in China	X
Artemisia annua tea as malaria monotherapy	widely promoted	under 20 per cent of a 500 mg dose per litre, 5 litres a day needed	X (WHO 2012, 2019), see IN-09

Means ledger

Rung	What it can do about dose and potency	What it changes in outcome
Hands and knowledge alone	Identify to species. Harvest at the right stage. Dry in shade. Reject the wrong part. Keep the stop signs in the head. Titrate from a quarter dose.	Removes misidentification deaths and the worst of the seasonal swing. Does nothing about absolute strength.
At the hearth	The above, plus a counted dropper, a measured medicine spoon, a labelled jar with the harvest date, and a written record of each dose and its effect.	Cuts the measuring error from about plus or minus 90 per cent to plus or minus 10 per cent for liquids. The largest single safety gain in this report.

Rung	What it can do about dose and potency	What it changes in outcome
Garden and still, with a scale	A lever balance and weights. Doses by mass, not volume. One cultivar propagated from a known good plant. Standardised drying and a sealed reference sample of each year's batch. A bitterness panel for bitter plants. Alcohol extraction, which also means the first real capacity to poison.	Brings narrow-margin plants within reach, and simultaneously creates the tincture hazard. The scale is the threshold between herbalism and pharmacy.
Village dispensary of 300	One named preparer per narrow-margin plant. A poisons book with a line per dose. A locked store. A microscope for powder identity against reference slides. Batch comparison against the sealed reference. A scale and weight-for-age charts for children.	Where the one-in-a-village rule becomes enforceable. Expect the failure to be social, not technical.
District infirmary of 3,000	A bench balance reading to 10 mg. A trained person who can run a bitterness panel and keep a herbarium. Pooling and blending of several harvests to average out variation. A district standard sample held for all villages to compare against.	Blending across sources is the one real approximation to standardisation available after the Fall. It narrows the range without measuring it.
Hospital before the Fall	HPLC assay of each batch, serum drug levels, standardised extracts guaranteed within a few per cent, unit-dose dispensing, computerised dose checking, an antidote cupboard.	Reduces the variability problem to near zero and replaces it with prescribing error.

Harm test

How dosing error kills or maims. By overdose, where the batch was stronger than the one the dose was written for, the measure larger than assumed, or the decimal moved. By underdose, the quieter harm, where a malaria or pneumonia treated at a third of the needed dose relapses and breeds resistance. By accumulation, which is how digitalis kills. By the wrong patient, where a correct adult dose reaches a neonate, a wasted elder or a dehydrated patient.

The errors that harm, with numbers. Tenfold from a misread decimal. Twenty-fivefold from confusing two opium preparations. Threefold from a household teaspoon. Twofold from the fresh to dried conversion. Fivefold to hundredfold from the plant itself. These multiply: a healer who takes willow bark of unknown species, converts fresh to dried by a guessed ratio and measures with a household spoon cannot know the dose within a factor of fifty.

Who must never receive what. Neonates: no chloramphenicol at adult-scaled doses, no codeine or opium in any form, no narrow-margin plant. Children under 12: no aspirin or willow bark during viral illness or chickenpox, no

codeine. Pregnant women: no pennyroyal, aconite, colchicum or any plant taken as an abortifacient, and no comfrey root. The dehydrated: no willow bark or other NSAID until rehydrated. The old and the wasted take half doses of everything and a quarter of anything on the narrow list.

Misidentification and contamination. The archetype is the autumn crocus: a 76-year-old Slovenian man with liver disease and renal insufficiency ate *Colchicum autumnale* mistaking it for wild garlic and died, his intake estimated at 0.14 to 0.82 mg per kg from plant mass and an assumed 0.1 to 0.6 per cent colchicine content (Brvar 2004). Aconite has been eaten after mistaking leaves for parsley and roots for horseradish. The industrial version is the Belgian slimming clinic, where the *Stephania tetrandra* in a formula changed in 1990 was in fact *Aristolochia fangchi*, and the result was renal failure in two women presenting in early 1992, seven more across Brussels dialysis units, and later urothelial cancer.

Signs that it is going wrong, and what to do. Slowing pulse, nausea, vomiting, colour change or halos in vision on foxglove: stop and keep the patient still. Tinnitus, deafness, blurring, sweating on bark or quinine: stop at tinnitus, reduce rather than abandon a malaria course, and fetch the most experienced person. Dry mouth, flushed dry skin, wide pupils, confusion and retention on belladonna or thorn apple (CDC 1995, Texas jimsonweed series): stop, cool, dark quiet room, protect from self-injury. Drowsiness with slow shallow breathing on opium: stop, rouse, position on the side, stay through the night. Vomiting and profuse diarrhoea hours after colchicum or aconite: a lethal course has begun and the village can only give fluids.

Historical cases of harm. Godfrey's Cordial, laudanum in sweet syrup, was sold unregulated at about a penny an ounce and given to infants to keep them quiet. One Manchester druggist admitted selling half a gallon of the cordial and five to six gallons of "quietness" a week. Historians judge that opium killed more infants through suppressed appetite and starvation than through acute overdose, and a bill to classify opium as a poison failed in 1857, restrictions coming only in 1908. Samuel Thomson was tried in Massachusetts in 1809 over Ezra Lovett's death after lobelia powders and acquitted, the facts still disputed. It shows what happens when a popular system dispenses a potent emetic by the teaspoon with no record of what was given.

Red flags

The signs that the dose has already done what the village cannot undo.

1. **A pulse below 40 with vomiting and coloured vision in a patient on foxglove.** Digitalis toxicity with bradycardia needs digoxin-specific antibody fragments, which do not exist here. Stop the drug, keep the patient flat and quiet, and expect either slow recovery over days as the drug clears or death from arrhythmia.
2. **Profuse vomiting and watery diarrhoea two to twelve hours after a colchicum or aconite exposure.** Treatment started more than two hours after ingestion is significantly impaired even in a hospital. The village can give oral fluids, keep the patient warm and stay with them. Honest comfort means saying that the next two days decide it.
3. **Slow, shallow or irregular breathing in a patient given opium, especially an infant or an opioid-naive adult.** Without naloxone there is nothing but stimulation, positioning and watching through the night.
4. **Falling urine output with dark urine in a patient on willow bark or any NSAID during a diarrhoeal or febrile illness.** Stop the drug and rehydrate. If output does not return within a day, the injury may not be recoverable.
5. **Jaundice, abdominal swelling and a tender liver weeks to months after comfrey root, pennyroyal or any bitter tea taken daily.** Pyrrolizidine injury and hepatic veno-occlusive disease progress to liver failure. Stop everything, and treat it as a dying patient's care problem.
6. **A neonate on day three or four of any drug with abdominal distension and grey-blue pallor.** The grey baby picture. Stop the drug. Most published cases died.
7. **Any convulsion, coma or collapse in a child after an adult-sized dose.** Assume overdose until proved otherwise, and tell the family the truth.

The case against

The strongest case against this chapter is that it demands a precision no village will keep, and that demanding it will push people towards doing nothing.

The critics of the herbal. WHO's position on *Artemisia* is the sharpest statement of the case. It does not support using *Artemisia* plant material in any form for malaria, because content varies substantially, is often insufficient to clear parasites, and widespread use could hasten artemisinin resistance (WHO 2019). That logic generalises to every plant whose active is also a modern drug, and IN-09 reached a similar verdict for cinchona bark. Against WHO, a 2004 commentary on the Mueller trial argued that the day-7 clearance endpoint was unnecessarily strict and that *A. annua* tea was better tolerated than oral quinine. The honest position is that the critics are right about the variability and the advocates are right that a variable medicine beats no medicine when nothing else exists.

The case that standardisation is overrated. The animal assays that replaced tradition were themselves unreliable between laboratories (Japanese 1952 study). The bitterness assay was criticised as empirical and subjective. The regulatory definition of a narrow therapeutic index has been called inadequate for researcher, clinician and regulator alike. And the clinical record contains the humbling fact that in one study of 64 neonates, nine of the ten who suffered chloramphenicol toxicity had received exactly the prescribed dose. Precision in measurement does not guarantee safety when the patient is the unknown.

The case that the real danger is the opposite. The quiet harm in a village will not be overdose but underdose. Underdosed antimalarials and antibiotics fail, relapse and select resistance. A rule that frightens healers into giving a quarter of what is needed will kill more people than the occasional overdose, and invisibly. Any dosing discipline must therefore include a rule for raising the dose when the expected effect does not appear, which is why titration and not caution is the method of this chapter.

The romance on both sides. The herbal romance holds that plants are gentle because they are plants, which the pennyroyal, aconite, colchicum and comfrey records refute. The hospital romance holds that without assay nothing can be done, which Withering refutes. Neither is the position of this book.

10-line summary

1. Potency varies by a factor of two in a standardised powder, ten in a wild-gathered leaf, and a hundred across species sold under one common name.
2. The causes are species and genotype, part, growth stage, season, drying, storage, preparation and adulteration, in roughly that order of size.
3. Extraction is a second lottery: a water infusion of *A. annua* saturates near 50 mg per litre and delivers under 20 per cent of a pharmaceutical dose however much leaf is used.
4. The margin between a working and a harmful dose is about 2 for digitalis, under 2 at the worst reported figures for quinine, about 10 for atropine and colchicine, and effectively zero for aconite.
5. Withering solved the problem in 1785 without chemistry, by fixing the material, the quantity in grains, the interval, and a stop sign, and his method is still the method.
6. The measures a village will use have known errors: the grain is exact at 64.8 mg, the drop is plus or minus 50 per cent, the household teaspoon runs 2.5 to 7.3 ml, and a spoon of powder is worse.
7. Nine out of ten dosing disasters in the modern record are arithmetic, not pharmacology: a decimal point, a trailing zero, a confused synonym, a tenfold error.
8. Children are not small adults, and the proof is three sets of deaths at correct adult-scaled doses: grey baby, Reye's and codeine in ultra-rapid metabolisers.
9. For narrow-margin plants, the only control that works without a laboratory is social: one named preparer, one batch, one written method, one logbook.

10. Titration from a quarter dose with a pre-agreed stop sign is the only honest way to dose an unknown batch, and the only way to avoid the invisible harm of underdosing.

Open questions

- I could not find the original Hatcher and Brody 1910 paper, nor confirm Brody as a co-author of the 1910 publication. The only trace is a 1923 reference to the "Hatcher-Ouabain Method, as published in the American Journal of Pharmacy, 1910" [VERIFY].
- The brief cites Burn 1950 *Biological Standardization*. I found the Oxford University Press edition dated 1937 and no evidence of Burn's role in the 1925 digitalis standard [VERIFY].
- The brief's range of 3 to 20 per cent morphine in opium could not be confirmed as a single published range. Published figures are 8 to 19 per cent for commercial air-dry opium and 9.2 to 20.9 per cent across 98 germplasm lines [VERIFY].
- The brief's 0.01 to 1.4 per cent for artemisinin combines two sources. 0.01 to 0.5 per cent is from Hien and White 1993 as cited by Mueller 2000, and 1.4 per cent is an upper value for selected hybrids, not for the species.
- No controlled study was found measuring drops per millilitre against viscosity for medicine droppers, no study quantifying the pinch or the handful, and no per-year rate of alkaloid loss in storage for any medicinal alkaloid.
- Whether the 20 per cent mortality figure sometimes quoted for hospitalised digitalis toxicity in the 1970s exists in a real source is unresolved.
- Whether a lay-run bitterness panel gives usable batch-to-batch discrimination has, so far as I could find, never been tested.

Sources to read in full

1. Withering, W. (1785) *An Account of the Foxglove and Some of its Medical Uses*. Above all the "Effects, Rules and Cautions" section. It is the model for every dosing protocol in this series.
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3. Jurkstiene, V. and others (2009) "Salicylates amount variation in different species of Lithuanian willow", *Medicina (Kaunas)* 45(8):644-651. The widest documented potency range for a plant a village will use.
4. European Pharmacopoeia 2.8.15, "Bitterness value", as carried in the British Pharmacopoeia. The only assay in this report a village can run.
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9. THRIVING library, IN-09, for the cinchona case this report generalises.

At the bedside after the Fall

A household. The minimum is a medicine spoon whose volume has been measured once and written on its handle, a dropper whose drops per millilitre have been counted, a labelled jar for every dried plant giving species, part, place, month and year, and a notebook. The household rule is one sentence: use only plants whose wrong dose cannot kill, which means no foxglove, no poppy latex, no aconite, no colchicum, no belladonna, no thorn apple, and no bark from a tree nobody has identified to species. Needs to start: a measured spoon, a notebook, a pencil, and the

discipline to write before giving. First failure to expect: the notebook stops being kept within a month, and nobody then knows whether the last batch worked.

A village of 300. The minimum is a lever balance with weights, one named preparer per narrow-margin plant, a locked store, a poisons book with one line per dose and the preparer's mark against it, a sealed reference sample of every batch kept until the next harvest, and a pressed, labelled herbarium sheet of every medicinal plant used, so that identification does not depend on one person's memory. The village should propagate its best plants rather than resow from mixed seed, and a bitterness panel of six adults, run yearly on each bitter plant, gives a crude but written strength comparison. Needs to start: a balance and weights, paper, a lockable box, pressed specimens, and one person trained for a season. First failure to expect: the named preparer dies or leaves with nobody trained behind them, so the logbook becomes unreadable within a year. Train two from the beginning.

A district of 3,000. The minimum adds a bench balance reading to 10 mg, a district reference collection against which the villages compare, blending of several villages' harvests into one pooled batch to average out potency, a written formulary giving doses in grams of a stated batch rather than in spoons, a scale for children with a weight-for-age chart, and one person who can run the bitterness assay and keep the herbarium. The district should hold the narrow-margin plants centrally and dispense them against a written request. Needs to start: a balance, glassware, a locked store, a scribe, and a trained herbarium keeper. First failure to expect: the pooled batches drift year to year and the formulary's doses silently stop matching the medicine, because nobody is comparing this year's pool to last year's reference.

Protocols

Protocol 1. Preparing a leaf drug so the dose means something. 1. Identify the plant to species with a flowering specimen beside a pressed reference sheet. If identification is not certain, stop. 2. Harvest leaf after the flowering stem has risen and as the blossoms are coming out (Withering 1785). For bark, cut two-year-old wood in autumn. 3. Remove the mid-rib and leaf stalk. They dilute the dose. 4. Dry in shade with moving air, fast, never above 60 degrees C and never in direct sun. 5. Rub to a powder when the leaf snaps rather than bends, and sieve to one grade. 6. Label with species, part, place, month, year and a batch letter, and store in a sealed opaque jar away from heat. Keep a sealed 10 g reference sample of every batch. 7. Downgrade any batch over 12 months old. Assume it has lost strength by an unknown amount.

Protocol 2. Measuring a dose without a scale. 1. Measure your spoon once. Fill it with water, pour into a container of known volume, repeat ten times, divide. Write the result on the handle. Expect 2.5 to 7.3 ml. 2. Count your dropper once. Drip into a measured 5 ml, count, repeat three times, take the mean. Expect 15 to 40 drops per ml. 3. Never measure a powder by spoon for a narrow-margin plant. 4. Where a balance exists, weigh, and weigh by transposition under 1 g: weigh, swap the pans, weigh again, take the mean. 5. Accept nothing under 100 mg as weighable on a village balance. 6. Conversions: 1 grain is 64.8 mg, 20 grains a scruple, 60 grains a dram, 480 grains an ounce, 1 g is 15.4 grains.

Protocol 3. Titrating an unknown batch. 1. Write the expected dose, the stop sign and the interval on paper before giving anything. Two people read it. 2. Give one quarter of the expected dose. 3. Wait one full interval, which must exceed the time to peak effect: four to six hours for most oral plant drugs, 24 hours for anything that accumulates, such as digitalis. 4. Record pulse, breathing, urine, mental state and any stop sign at each interval. 5. If there is no effect and no stop sign, raise by one quarter of the expected dose. 6. Stop at the first appearance of any stop sign and do not give the next dose (Withering 1785). 7. If twice the expected dose produces no effect and no stop sign, conclude the batch is weak or inert and stop raising. 8. Write the final working dose on the batch label. That is the batch's dose, for that batch only.

Protocol 4. The one-in-a-village rule for narrow-margin plants. 1. The list: foxglove, opium poppy, cinchona, belladonna, henbane, thorn apple, autumn crocus, monkshood, and any salvaged narrow-index medicine. 2. One

named person prepares all of them, with a second trained from the start. 3. One source, one method, one batch at a time. Never blend an old batch into a new one. 4. Store locked and apart. Label with a mark that cannot be confused in dim light. 5. Dispense dose by dose, never by the jar. Enter each dose in the book: date, patient, plant, batch letter, quantity, who gave it, what happened. 6. Autumn crocus and monkshood are not prepared at village level at all. 7. Any order written in the wrong unit is refused and rewritten. Opium preparations are dosed in drops, never in spoons.

Protocol 5. Dosing a child. 1. Weigh the child. If there is no scale, measure length and use a chart, and accept that the estimate is within 10 per cent in only about half of children. 2. Dose by mg per kg from a written table. Use Clark's rule, weight in pounds divided by 150 times the adult dose, only when nothing else exists, and never for narrow-margin plants. 3. Never write a trailing zero. Write 15 mg, never 15.0 mg. Never abbreviate units. 4. Have a second person repeat the calculation aloud before the dose is given. 5. No aspirin or willow bark under 12 during fever, viral illness or chickenpox, and no codeine or opium of any kind under 12 or to a breastfeeding mother. 6. No narrow-margin plant to a child at all.

Protocol 6. Home-made oral rehydration solution, the one measure-by-spoon recipe that is safe. 1. Six level teaspoons of sugar and half a level teaspoon of salt to one litre of clean boiled and cooled water, stirred until dissolved (Rehydration Project). A second published formula gives eight level teaspoons of sugar and one of salt per litre (African home formulas review 1988, citing WHO). The safer error is the weaker solution. 2. Too much sugar worsens the diarrhoea. Too much salt is extremely harmful to a child. Too dilute is not harmful. 3. Taste it. It should be no saltier than tears. 4. Make fresh daily.

Numbers to carry

1. **64.8 mg.** One grain. The conversion that stands between a reader and every pre-1900 dose in an old book.
2. **2.5 to 7.3 ml.** The range of a household teaspoon. Nearly a threefold error before the medicine is considered.
3. **Factor of five.** The uncertainty in cinchona bark alkaloid content, a fair default for any wild-gathered bark or root (THRIVING library, IN-09).
4. **Factor of ten.** The uncertainty in a wild-gathered leaf drug, as belladonna's 0.2 to 2.0 per cent shows.
5. **2.** The therapeutic index of digitalis. Two doses of the working dose is the poisoning dose.
6. **1 to 4 mg.** The estimated lethal dose of aconitine in an adult. There is no village dose of monkshood.
7. **10 mg.** The dose of atropine at which a child may die, and the dose at which an adult enters delirium and coma.
8. **One quarter.** The fraction of the expected dose at which titration of an unknown batch begins.
9. **25.** How many times stronger opium tincture is than paregoric, and the shape of every synonym error.
10. **Half.** What you give an adult over about 70, or anyone visibly wasted, and then you go slowly.

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