

2.1 History of herbs as sources of drugs and drug discovery

The history this unit teaches is the record of a method being invented. Traditional medical systems, Ayurveda, traditional Chinese medicine, Unani and the European herbal tradition among them, accumulated over centuries a working knowledge of which plants act on the body, but bound inside crude drugs whose strength varied with season and source. The turning point came when chemistry learned to isolate the active principle. Morphine was isolated from opium in the first years of the nineteenth century, the first pure alkaloid and the proof that a plant's action could be carried by one definable substance. Quinine followed from cinchona bark, and a procession of isolations, atropine, caffeine, cocaine, digitoxin and many others, converted the herbal materia medica into the beginnings of the modern pharmacopoeia. Two lessons from that period still govern the field. The pure compound can be dosed, standardised and studied as the crude drug never could. And again and again the plant compound proved to be a lead rather than a finished drug, a starting structure chemistry then improved, as the salicylates led to aspirin.

The twentieth century added the other half of the method. Microbial natural products, penicillin first among them, showed that screening organisms systematically could find drugs no tradition had recorded. Synthesis and semisynthesis solved supply, plant cell culture and fermentation moved production off the field, and spectroscopic structure determination replaced degradation chemistry. Herbs remain a major source of leads because evolution has already screened their chemistry against living targets: a plant defence compound is, by design, a molecule that binds a protein in another organism. The two worked examples of this unit show the two characteristic modern stories: a traditional remedy decoded into a world medicine, artemisinin, and a traditional drug's major constituent developed as a standardised lead, the andrographolides.

2.2 The lead structure selection process

A lead compound is a compound with the desired activity in a form that can be developed: active enough to optimise, selective enough to be worth optimising, and chemically tractable enough that analogues can be made. The selection process runs in a settled order. The starting choice is the source, by one of three strategies: the ethnobotanical strategy, following documented traditional use, which begins with a human use signal attached; the ecological and chemotaxonomic strategy, choosing plants by family relationship to known producers or by predicted defensive chemistry; and the broad screening strategy, testing large extract libraries without a prior use claim. Each has found real drugs, and answers should present them as complements.

From the chosen source the process is activity led. The crude extract is tested in the bioassay; if active, it is fractionated and every fraction retested, the bioassay guided fractionation of Unit 1, until the activity is concentrated into one pure compound. Dereplication runs alongside: the extract is checked early against databases of known compounds, so a known compound is recognised at once and effort is spent only on new chemistry. The pure active is then assessed as a candidate lead: potency, selectivity against counter screens, solubility, stability, toxicity flags and structural novelty, with its structure fully proved. Selection is a comparison: several actives usually emerge, and the lead chosen is the one whose whole profile offers the best starting point for development. The flow below shows the selection funnel.

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Source chosen: traditional use, family relationship or library screen
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Extract prepared and tested in the bioassay
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Active extract: dereplication against known compounds
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Bioassay guided fractionation to the pure active compound
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Structure proved; potency, selectivity, solubility assessed
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Lead selected: the best whole profile, not merely the most potent

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2.3 Structure development: selection and optimization of lead compounds

Once selected, a lead is developed by the cycle called lead optimization; the syllabus pairs selection and optimization because they are one continuous judgement. Optimization works on structure activity relationships: analogues are made, by semisynthesis from the natural product where it is plentiful, by modifying one functional group at a time, or by simplifying the skeleton to the part carrying the activity, and each is tested so the contribution of every part is mapped. The properties optimised together are potency, selectivity, solubility and permeability, metabolic stability and safety, and the standing difficulty is that improving one usually costs another. Natural product leads add two special problems: complexity, since many are large, stereochemically dense molecules, so semisynthesis is often the practical analogue route; and supply, since optimization is meaningless if the compound cannot be made at scale, so cultivation, cell culture, fermentation or total synthesis is part of structure development. The development flow below shows the cycle.

Lead development: the optimization cycle



Each turn of the cycle trades one property against another

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Figure: The lead development cycle. Each turn of the loop trades potency, selectivity, solubility, stability and safety against each other until one compound carries the best balance.

Optimization ends at a development candidate: one compound, or a defined standardised preparation in the phytopharmaceutical case. In the single compound route the candidate is one optimised molecule. In the phytopharmaceutical route the product is a standardised extract carried by a characterised group of constituents, and development means fixing the source, the extraction and the marker based specification so the preparation tested is the preparation sold. The two examples below divide between the routes.

2.4 The product discovery process and drug registration

From candidate to marketed product the process is regulated, in the same outline for a natural product derived drug as for any drug. Preclinical development completes the pharmacology and runs the toxicology programme, together with a stable, manufacturable dosage form and the analytical methods that will control it. Clinical development (Section 2.7) then tests the product in humans under an approved protocol and trial authorisation. Registration closes development: the sponsor submits the full dossier of quality, preclinical and clinical evidence to the regulatory authority, in India the Central Drugs Standard Control Organisation under the Drugs and Cosmetics Act framework for a new drug, internationally in Common Technical Document format, and the authority grants or refuses marketing authorisation on that evidence. For herbal products the registration category must be stated accurately: a standardised herbal product may be regulated as a drug, as a traditional medicine under the AYUSH framework in India, or as a food supplement, and the evidence demanded follows the category and the claims. A product claiming to treat disease is held to drug standards whatever its origin: natural origin is not an evidence exemption.

2.5 Worked example: artemisinin

Artemisinin is the unit's complete drug discovery story. The source was traditional: qinghao, *Artemisia annua*, recorded in Chinese medical literature for fever and selected in a systematic screening programme of traditional remedies. The decisive insight was extraction method: the traditional preparation suggested heat destroyed the activity, and a low temperature ether extraction preserved it, giving a strongly antimalarial extract from which artemisinin was isolated. Its structure carried a feature no antimalarial had shown: a sesquiterpene lactone skeleton, built from farnesyl diphosphate through amorpha-4,11-diene and artemisinic acid, bearing an endoperoxide bridge, and that bridge is the pharmacophore, reacting in the parasite to generate the damaging species that kill it. Structure development followed the optimization pattern: artemisinin has poor solubility and a short duration, so semisynthetic derivatives were made, dihydroartemisinin, the oil soluble artemether and arteether, and the water soluble artesunate, each fixing a pharmaceutical defect while keeping the peroxide intact. Supply was developed in parallel, by cultivation, improved extraction and engineered yeast fermentation of artemisinic acid with chemical conversion. The artemisinin based combination therapies became the world standard for falciparum malaria, and the discovery was recognised by the Nobel Prize in 2015.

2.6 Worked example: the andrographolides

Andrographolide, from *Andrographis paniculata*, kalmegh, shows the phytopharmaceutical face of the same process. The plant is a major Ayurvedic drug for fever, liver complaints and infections, and its bitter diterpene lactones, andrographolide chief among them, are its characteristic constituents, built by the diterpene route from geranylgeranyl diphosphate. Lead selection here identified the major standardisable constituent group of an already used drug, and development proceeded on both tracks of Section 2.3. On the standardised extract track, andrographis products are defined by their andrographolide content, assayed chromatographically, with source and extraction fixed so the tested and sold preparations match. On the analogue track, andrographolide has been widely modified in research, at its hydroxyl groups and lactone system, seeking better solubility and potency. The contrast with artemisinin is the point: artemisinin became a family of single compound drugs, while andrographolide remains chiefly a standardised phytopharmaceutical lead and marker. Both are correct outcomes of the same process.

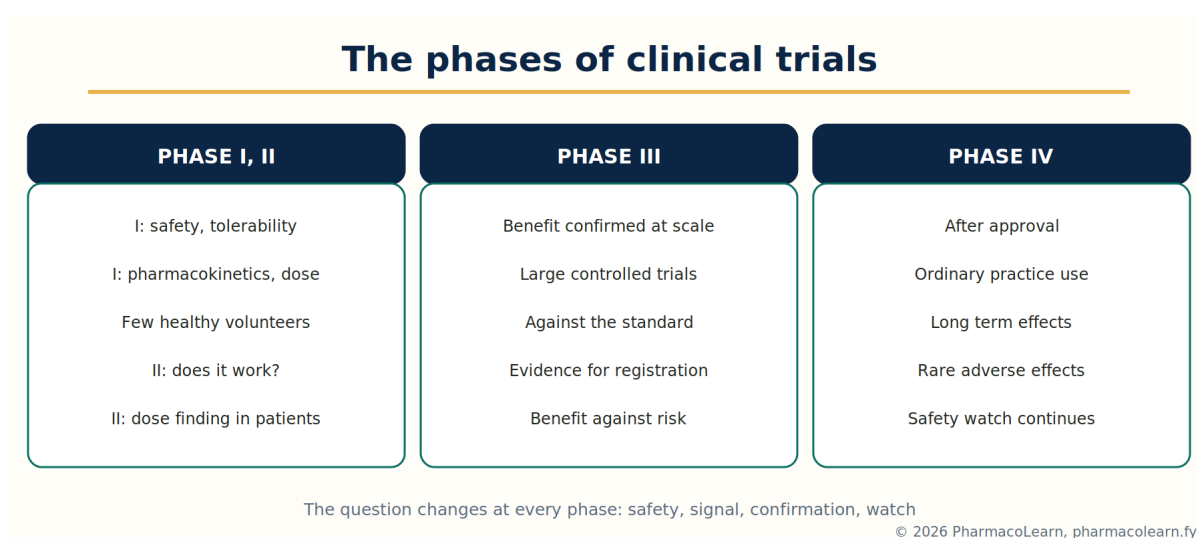
2.7 Clinical studies: the phases of clinical trials

Clinical studies are the controlled testing of a lead molecule or product in humans, and the syllabus asks for emphasis on the phases, because the phases are the structure every protocol obeys. The phases answer

different questions and must not be merged in an answer.

Phase	Main question	Who takes part	What is chiefly measured
Phase I	Is it safe and tolerable, and how does the body handle it?	Small numbers of healthy volunteers, or patients where the drug's nature requires	Safety, tolerability, pharmacokinetics, dose range
Phase II	Does it work in the target disease, and at what dose?	Patients with the condition, in controlled studies	Efficacy signals, dose response, further safety
Phase III	Is the benefit confirmed at scale against the standard?	Large patient groups, usually randomised and controlled	Confirmed efficacy, safety in broad use, benefit against risk
Phase IV	What emerges in ordinary practice after approval?	Patients in routine care after marketing	Long term and rare adverse effects, real world use

Phase I establishes the human safety and pharmacokinetic profile and the doses worth carrying forward. Phase II is the first test of the therapeutic idea in patients and the dose finding stage, where most weak leads end. Phase III provides the confirmatory evidence for registration. Phase IV continues the safety watch after marketing. For natural product leads two points are specific. The material tested must be the material defined in development, a pure compound of stated purity or an extract of stated standardisation, or the trial proves nothing transferable. And traditional use, however long, does not replace any phase for a new claim: it informs dose and safety expectations and may support a traditional use registration category, but a drug level therapeutic claim is proved in trials. The diagram below shows the phases.



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Figure: The phases of clinical trials. Numbers grow and the question changes at every phase: safety, then dose and signal, then confirmation, then real world watch.

2.8 Protocol design for lead molecules

A clinical trial protocol is the written plan that makes a trial ethical, lawful and interpretable; protocol design for a lead molecule writes that plan around the lead's profile. Its standard elements are these. The objectives and endpoints, with primary endpoints defined before the trial starts. The design: randomised, blinded and controlled wherever the question allows, the comparator chosen and justified. The population: inclusion and exclusion criteria selecting the patients the question is about and protecting those an early lead should not yet reach. The treatment plan: dose and regimen from preclinical and Phase I evidence, route, duration, and the rules for dose change and stopping. The assessments: efficacy measures, safety monitoring and pharmacokinetic sampling. The statistics: sample size and analysis plan, fixed in advance. And the ethical frame: ethics committee approval, informed consent, trial registration and good clinical practice. For a phytochemical lead the protocol carries three extra definitions examiners look for: the exact identity and standardisation of the test material, with marker assay and batch; control of background

exposure, since patients may already take the same herb as a food or supplement; and interaction vigilance, since a lead affecting drug metabolising enzymes, as piperine does, can distort the handling of other medicines.

2.9 Unit 2 in one view

Herbs gave pharmacy its first pure drugs, and the method built on those isolations is now formal: choose the source by tradition, relationship or screen; follow activity through bioassay guided fractionation with dereplication to a pure active; select the lead on its whole profile; optimize it by analogue work; complete preclinical development; prove the product in the four phases of clinical trials under a defined protocol; and register it in the category its claims demand. Artemisinin shows the single compound outcome; the andrographolides show the standardised phytopharmaceutical outcome.

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