Phytopharmaceutical approaches to herbal drug discovery and development: from traditional medicinal plants to modern allopathic drugs

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Abstract:

Most of our medicine today comes from previous healing practices and we are aware that we were introduced to these medicinal plants from a quite long time ago. In this review, I am going through phytopharmaceutical research if a drug is a standard extract or a drug made using one molecule. Identification of traditional use of drugs, division of active parts of plants, understanding of the structure of a compound, altering a compound to achieve a few effects; looking at how a drug operates differently and ensuring the medicine is reliable and reliable. This includes some of the plants in houses of India and specialized study, the most common of which are essential for worldwide medical treatments. In India the plant is most frequently used but its medicines don't have this. At each plant, you discuss what it traces, when and how it became scientifically studied, and what it's most common component in its active parts and what these changes into today's treatment. A typical example of these plants is popular and have medicinal properties such as aspirin, morphine, quinine, digoxin, and various other medicines. Other plants, especially for these kinds of things, tend to be considered supplements, skin treatments or research ideas, their own actual medical effects being explored, like curcumin, neem, allicin and gingerols. One such description, however, presents problems with standards. In being accepted, making it safe, and as ecofriendly materials. Key Words: phytopharmaceuticals; medicinal plants; natural products; drug discovery; ethnopharmacology; reverse pharmacology; bioactive compounds.

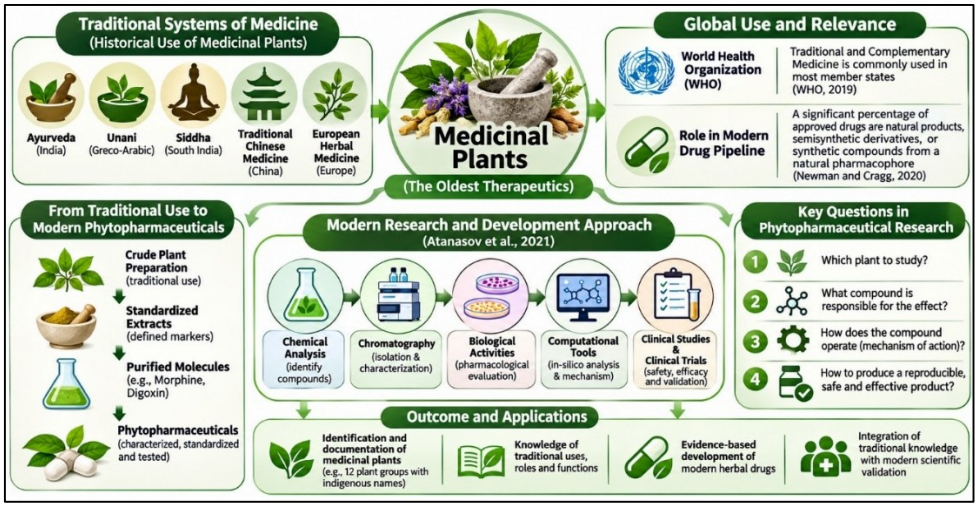
Keywords:

Phytopharmaceutical, Herbal drug, Drug discovery, Ethnopharmacology etc.

1. Introduction:

The oldest of Therapeutics is the Medicinal Plants. Ayurveda, Unani, Siddha, traditional Chinese medicine and European herbal medicine are the oldest practices that have had a historical role in their therapeutic practice, stating the study carried out in an article on traditional plants and found a large number of those still with their present application as the traditional herb (Fabricant and Farnsworth, 2001). The World Health Organization's report on the world, from April 2014, indicates that Traditional and Complementary Medicine is commonly used in most of its member states (WHO, 2019). The role of natural products and their derivatives remain an essential part of the modern drug pipeline: a significant percentage of approved small-molecule drugs are natural products, semisynthetic derivatives, or synthetic compounds which were formed by a natural pharmacophore (Newman and Cragg, 2020). Chemical analysis, chromatography and biological activities of the compound and using computational tools to further analyse their compounds and to determine that their

actions in clinical studies and clinical trials. (Atanasov et al., 2021). What the phytopharmaceutical is, derived from plant-derived medicinal products have been characterized, standardized, and tested beyond a crude conventional resurfacing preparation. This range includes standardized fractions with defined marker compounds, as recognized under Indian drug regulation, to purified single molecules such as morphine or digoxin. Moving around these lines means answering four questions: which plant to study, what compound is responsible for the effect, how that compound operates and how a reproducible, safe and effective product can be produced. This book shows one of the main methodologies that emerged during the use of a plant. Also, the 12 plant name groups were further identified as indigenous names. They serve as illustrations on how each plant was recognized and used, or their roles and their function.



2. Phytopharmaceutical approaches and the discovery workflow:

Ethnopharmacology-led selection. Most plant drugs were first shown to start with traditional use, and are typically characterized by willow bark for fever, or foxglove for dropsy. Field observations and classical texts help researchers prioritize plants and signs rather than random screening (Fabricant and Farnsworth, 2001). Bioactivity guided fractionation. Crude extract undergoes a study in a related bioassay, and followed up step-by-step in various solvent partitioning steps (solvent chromatography, column chromatography, HPLC). Each fraction undergoes subsequent studies, with the complete active fraction being transported to arrive at a pure compound. NMR, mass spectrometry, and, where feasible, X-ray crystallography are used to obtain its structure. Some of the first examples of this logic are Sertürner's elimination of morphine, Pelletier's extinction of quinine, and Caventou's extinction of the quinine. Reverse pharmacology. The procedure proposed by Patwardhan and Vaidya (2010), using these steps reverses the shortest path from documented clinical experience or identified therapeutic effects to experimental validation, mechanism studies, and then exploratory clinical studies, then provides a shorter road to the clinical potential. A simple algorithm: Reverse pharmacognosy and in-silico screening. Instead of starting from the plant, this approach goes with a protein target where Docking or similarity searching is employed to see which synthetic compounds can bind it (Blondeau et al., 2010). Proposed hits are later confirmed in the laboratory. Semisynthesis and analogue design. Natural lead has also been used, to reduce potency, stability, tolerability, or supply. The generic aspirin from salicylic acid is common, and synthetic antimalarials from quinine are widely known. Standardization and quality control A plant's chemical composition vary with species, chemotype, climate, harvest time and processing resulting in herb-derived products that should be identified, fingerprinted by HPTLC, HPLC, GC-MS or spectroscopy in relation to the specified marker compounds and contamination constraints (Noviana et al., 2022).

The standardized development stage in which the organism is born is:

1. Plant species vs. animal for culture or history/literature, etc.
2. Authentication, extraction and preliminary bioassay
3. Foremant analysis of active constituents, reconstituted and structure derivation of active compositions
4. Mechanisms of action, drug-kinetics and toxicology studies
5. Standardization and formulation and/or where feasible semisynthetic optimization
6. Foremant tests and regulation based, then pharmacovigilance.
7.

Table. 1: Plants discussed in this review

Plant (local name)	Botanical source	Key active constituent(s)	Present role
Willow (vilow)	*Salix* spp.	Salicin, converted to salicylic acid	Led to aspirin: analgesic, antipyretic, antiplatelet
Opium poppy (afeem)	*Papaver somniferum*	Morphine, codeine	Opioid analgesics
Garlic (lahsun)	*Allium sativum*	Allicin (from alliin)	Supplement; antimicrobial lead
Aloe vera (alovera)	*Aloe vera* (*A. barbadensis*)	Acemannan, aloin	Topical gels; laxative anthraquinones
Turmeric (haldi)	*Curcuma longa*	Curcumin	Supplement; investigational
Neem	*Azadirachta indica*	Azadirachtin, nimbolide	Biopesticide; investigational
Ginger (adrak)	*Zingiber officinale*	Gingerols, shogaols	Antiemetic and digestive supplement
Mint (pudina)	*Mentha* × *piperita*, *M. arvensis*	Menthol	Enteric-coated oil for IBS; topical agent
Chamomile (komomile)	*Matricaria chamomilla*	Apigenin, α-bisabolol, chamazulene	Herbal tea; topical agent
Cinchona (sinkona)	*Cinchona* spp.	Quinine	Antimalarial
Ipecac (ipekak)	*Carapichea ipecacuanha*	Emetine, cephaeline	Historic emetic and amoebicide
Foxglove (digitalis)	*Digitalis purpurea*, *D. lanata*	Digoxin, digitoxin	Heart failure; atrial fibrillation

3. Medicinal plants: from traditional use to modern drug:

The following case studies follow a common format: source and traditional use, discovery, active constituents, and present-day use.

3.1. Willow (vilow): salicin and the birth of aspirin:

Source and traditional use. Willow bark and leaves, and other species of woodland (Salix Alba and other species), were used in ancient Mesopotamia, Egypt, and Greece for treating pain, fever, and inflammation (Desborough and Keeling, 2017; Montinari et al., 2019).

Discovery. In 1763 an English clergyman, Edward Stone, made an inquiry into the royal society in question to find out that willow bark had relief of fever. When it first came into use in the 19th century, chemists discovered glycoside salicin in the bark and eventually salicylic acid was obtained, which served a purpose but irritated the stomach. Acetylsalicylic acid (marketed as aspirin) made by Felix Hoffmann at Bayer in 1897 at Bayer was created (Desborough and Keeling, 2017; Montinari et al., 2019). Its mechanism was also revealed in 1971 in that Vane discovered that aspirin-like drugs inhibit prostaglandin synthesis (Vane, 1971).

Active parts. Salicin is the main active glycoside. The body has transformed it to salicylic acid, and aspirin is the synthetic acetylated derivative. The tannins and flavonoids in Willow bark may also contribute to its effectiveness, even in its form, to alleviate heart symptoms.

Use today. The first-line drugs aspirin is the agent of aspirin for use in analgesic, analgesic and antipyretic and for fighting on anti-inflammatory effects. It is a radical, and irreversible inhibitor of cyclooxygenase, in addition to having serious health implications: gastrointestinal bleeding (in children with viral illness, Reye's syndrome).

3.2. Opium poppy (Afeem): Morphine:

Source and traditional use. Opium — an unripe capsule of Papaver somniferum — is dried latex. Its purpose for pain, sleep, cough and diarrhoea was recognized by ancient civilizations, as well as in classical Indian and Arabic medicine (Duarte, 2005; Brook et al., 2017).

Discovery. Opium had several concentrations, and the dose was unpredictable. By the early 19th century the pharmacist Friedrich Sertürner isolated it from a plant and named it morphine (after Morpheus). It was the first crystalline organic compound synthesized from a plant and helped create the next step in alkaloid chemistry (Krishnamurti and Rao, 2016; Duarte, 2005). Later codeine, thebaine, papaverine and noscapine, were found

derived from the same latex.

Active components. Morphine (the chief analgesic alkaloid) accounts for the drying latex at ten percent. Codeine has a weaker analgesic and antitussive counterpart, papaverine is a smooth-muscle relaxant, and thebaine can be utilized as a precursor for semisynthetic opioids such as oxycodone and buprenorphine (Brook et al., 2017).

Use today. Morphine mostly involves -opioid receptors, a dominant active ingredient of lung pain and is a common treatment of severe and cancer pain and palliative care. Repressive depression, tolerance and dependence impair the use of this medicament, thereby maintaining an inflexible and tightlyregulated production and sales in India under the Narcotic Drugs and Psychotropic Substances Act.

3.3. Garlic (lahsun): allicin:

Source and traditional use. The bulb of *Allium sativum* has been eaten and used as medicine in Egyptian, Greek, Chinese and Ayurvedic traditions for infections, wounds, digestive complaints and heart and circulation problems (Rivlin, 2001).

Discovery. The antibacterial activity of garlic was recognized long before the responsible molecule was known. In 1944 Cavallito and Bailey isolated allicin, a thiosulfinate, as the antibacterial principle (Cavallito and Bailey, 1944). Allicin does not exist in intact garlic. When the clove is crushed, the enzyme alliinase converts the odourless precursor alliin (S-allyl-L-cysteine sulfoxide) into allicin, which is unstable and rapidly forms diallyl sulfides, ajoene and vinyldithiins (Borlinghaus et al., 2014).

Active components. Allicin and its transformation products are responsible for the pungent odour and most of the antimicrobial activity. They react with thiol groups of microbial enzymes. Other constituents include S-allylcysteine in aged garlic, saponins and fructans (Borlinghaus et al., 2014).

Use today. Garlic is used as a supplement and food for modest blood-pressure and lipid effects, although the evidence is mixed. No single garlic compound is a standard approved drug, but allicin remains a model lead for antimicrobial research. Because allicin is unstable, the content of commercial products depends strongly on preparation and storage.

3.4. Aloe vera (alovera): acemannan and aloin:

Source and traditional use. *Aloe vera* (also called *A. barbadensis*) is a succulent of the Asphodelaceae. Its leaf gel is applied to burns, wounds and skin conditions, and the dried bitter latex was taken as a purgative in Greek, Egyptian and Indian practice, where it is known as *kumari* or *ghritkumari* (Surjushe et al., 2008).

Discovery. Scientific work distinguished two different products from the leaf: the clear winner gel and the yellow latex beneath the rind. Chemical studies showed that the latex is rich in anthraquinone glycosides such as aloin, whereas the gel contains water, polysaccharides, glycoproteins, vitamins and minerals (Surjushe et al., 2008; Sánchez et al., 2020).

Active components. Acemannan, an acetylated glucomannan, is the best-studied gel polysaccharide and is linked to wound healing, immune modulation and moisturizing effects. Aloin (barbaloin) and aloe-emodin from the latex are stimulant laxatives. Anti-inflammatory, antioxidant and antimicrobial activity has also been reported for the gel (Sánchez et al., 2020).

Use today. The gel is widely used topically for burns, wound care and cosmetic products, with the most consistent evidence for superficial skin injuries. Oral anthraquinone laxatives are used less today because of safety concerns with long-term use (Sánchez et al., 2020). Because gel and latex differ chemically, products should state which part of the plant they contain.

3.5. Turmeric (haldi): curcumin:

Source and traditional use. The rhizome of *Curcuma longa* is a kitchen spice, dye and ritual material in India. In Ayurveda it (*haridra*) is used for wounds, inflammation, skin disease and digestive complaints, often with black pepper or milk (Gupta et al., 2013).

Discovery. A yellow pigment was first obtained from turmeric in the early 19th century, and the compound was named curcumin. Its structure was established in the early 20th century and it was later synthesized (Nelson et al., 2017). Turmeric contains a family of curcuminoids: curcumin, demethoxycurcumin and bisdemethoxycurcumin.

Active components. Curcumin is a diarylheptanoid that makes up a few percent of the rhizome. Laboratory studies show antioxidant and anti-inflammatory effects, including modulation of NF-κB signalling, and many clinical trials in inflammatory, metabolic and neoplastic conditions have been reported (Gupta et al., 2013).

Challenges. Curcumin is poorly absorbed, rapidly metabolized and chemically unstable, and it behaves as a promiscuous "frequent hitter" in many assays, so some biological reports are hard to interpret (Nelson et al.,

2017). Co-administration with piperine from black pepper increased the bioavailability of curcumin in human volunteers in one study (Shoba et al., 1998), which supports the traditional pairing.
Use today. Turmeric and curcumin are used as supplements and foods. Curcumin has no established indication as an approved drug, and better formulations and analogues are under investigation.

3.6. Neem: azadirachtin and nimbolide:

Source and traditional use. *Azadirachta indica* (Meliaceae), known as *nimba* or neem, is called the "village pharmacy" of India. Leaves, bark, seeds, oil and twigs are used for skin disease, fever, dental hygiene, wound care and as a natural insecticide (Alzohairy, 2016).
Discovery. Observations that locusts avoided neem trees led to the study of its seeds, from which the insect antifeedant azadirachtin was isolated in the 1960s. Its complex structure took years to resolve (Morgan, 2009). Many other limonoids, including nimbin, nimbidin, nimbolide and gedunin, were then identified from different parts of the tree (Alzohairy, 2016).
Active components. Azadirachtin is a tetranortriterpenoid limonoid that disrupts insect feeding and growth. Nimbolide and other limonoids, together with flavonoids and polysaccharides, show antimicrobial, anti-inflammatory and antiproliferative activity in laboratory models, including effects on NF-κB and related signalling pathways (Alzohairy, 2016).
Use today. Azadirachtin is mainly used in biopesticides (Morgan, 2009). In human medicine, neem is used in traditional preparations, toothpastes and skin products, while its extracts and nimbolide are research leads without an established approved indication. Neem oil should not be given to infants, since poisoning has been reported.

3.7. Ginger (adrak): gingerols and shogaols:

Source and traditional use. The rhizome of *Zingiber officinale* is eaten fresh (*adrak*) or dried (*sonth*). Ayurvedic and Chinese medicine use it for nausea, colds, indigestion, joint pain and as a warming carrier in many formulas (Mao et al., 2019).
Discovery. Chemical studies traced the pungency and activity of ginger to phenolic compounds in the oleoresin. The gingerols are the main pungent constituents of fresh rhizome, and on drying or heating they dehydrate to shogaols, which are generally more pungent and often more potent in assays (Mao et al., 2019).
Active components. [6]-Gingerol is the most abundant gingerol, and [6]-shogaol, zingerone and paradols are related compounds. The volatile oil adds terpenes such as zingiberene. Reported actions include anti-inflammatory effects through inhibition of arachidonic acid metabolism, antioxidant activity and effects on gastrointestinal motility and nausea pathways (Mao et al., 2019).
Use today. Ginger is used as a supplement and food for nausea, including motion sickness, chemotherapy-related and pregnancy-related nausea. A systematic review and meta-analysis found that ginger improved pregnancy-associated nausea and vomiting, with no clear increase in adverse pregnancy outcomes (Viljoen et al., 2014). Mild heartburn is the commonest side effect, and large doses may add to the effect of anticoagulants.

3.8. Mint (pudina): menthol:

Source and traditional use. Peppermint (*Mentha* × *piperita*, a hybrid of water mint and spearmint) and corn mint (*M. arvensis*, the main source of natural menthol in India) are used as digestive aids and for colic, headache, cold and itching. Leaves are taken as tea or applied as oil (McKay and Blumberg, 2006a).
Discovery. Steam distillation of the leaves yields an essential oil from which crystalline menthol can be separated by cooling, and menthol has been known as a chemical entity since the 18th century. Understanding of its action advanced in 2002, when McKemy et al. showed that menthol activates TRPM8, the sensory ion channel that detects cool temperatures, which explains the cooling sensation (McKemy et al., 2002).
Active components. Peppermint oil is rich in menthol, with menthone, menthyl acetate and 1,8-cineole. The leaf also contains flavonoids and phenolic acids such as rosmarinic acid that contribute antioxidant activity in tea (McKay and Blumberg, 2006a). In the gut, menthol relaxes smooth muscle, probably by blocking calcium channels, which underlies its antispasmodic effect (Chumpitazi et al., 2018).
Use today. Enteric-coated peppermint oil capsules are used for symptoms of irritable bowel syndrome, with the evidence reviewed by Chumpitazi et al. (2018). Menthol is also used in topical analgesic rubs, inhalations, lozenges and as a flavouring. Non-enteric-coated oil may cause heartburn, and menthol should be kept away from the faces of small children.

3.9. Chamomile (komomile): apigenin, α-bisabolol and chamazulene:

Source and traditional use. German chamomile (*Matricaria chamomilla*, syn. *M. recutita*, Asteraceae) flower

heads are used as a tea or extract for digestive upset, anxiety and sleep problems, mouth and skin inflammation and infant colic (McKay and Blumberg, 2006b; Srivastava et al., 2010).

Discovery. Steam distillation of the flowers gives a deep blue essential oil. The colour comes from chamazulene, which is not present in the fresh flower but forms from the precursor matricin during distillation. Other constituents were characterized as the sesquiterpene α-bisabolol and its oxides and the flavonoids apigenin, luteolin and quercetin (Srivastava et al., 2010).

Active components. The flavonoid apigenin is associated with anxiolytic and sedative activity and has been reported to bind benzodiazepine receptors, while α-bisabolol and chamazulene contribute anti-inflammatory and antispasmodic effects (McKay and Blumberg, 2006b; Srivastava et al., 2010). Coumarins and mucilage add to the profile of the flower.

Use today. Chamomile is consumed as a tea and used in mouthwashes and topical creams. Evidence for its use is mainly from small studies and pharmacological work, and large confirmatory trials are limited (Srivastava et al., 2010). People allergic to other Asteraceae (ragweed, daisies) may react to it.

3.10. Cinchona (sinkona): quinine:

Source and traditional use. The bark of *Cinchona* trees, native to the Andes, was used by indigenous South Americans, and Jesuit missionaries brought it to Europe in the 17th century as a remedy for intermittent fevers, later recognized as malaria (Kaufman and Rúveda, 2005; Achan et al., 2011).

Discovery. In 1820 the French chemists Pelletier and Caventou isolated quinine and cinchonine from the bark, allowing standardized dosing (Kaufman and Rúveda, 2005). Quinine was the main antimalarial for more than a century, and the pressure to secure supply drove the development of synthetic antimalarials such as chloroquine. A similar bioactivity-guided path later led to artemisinin from *Artemisia annua*, a plant used in Chinese texts for fevers, which Tu Youyou isolated in the 1970s, work recognized by the 2015 Nobel Prize in Physiology or Medicine (Tu, 2011).

Active components. The bark contains quinoline alkaloids, mainly quinine, quinidine, cinchonine and cinchonidine. Quinine acts against the blood stages of *Plasmodium* parasites, and quinidine, its stereoisomer, is used as an antiarrhythmic (Achan et al., 2011).

Use today. Quinine is still used for severe or drug-resistant *falciparum* malaria, mostly with other agents, although artemisinin-based combinations are now first-line (Achan et al., 2011). Overdose or prolonged use causes cinchonism (tinnitus, headache, visual disturbance, nausea) and may cause arrhythmia and hypoglycaemia.

3.11. Ipecac (ipekak): emetine:

Source and traditional use. Ipecac is the dried root of *Carapichea ipecacuanha* (syn. *Cephaelis ipecacuanha*, Rubiaceae), a forest plant of Brazil and neighbouring countries. Indigenous peoples used it to induce vomiting and to treat dysentery, and it reached Europe in the 17th century (Lee, 2008).

Discovery. European physicians used the root as a remedy for dysentery from the 17th century. In the early 19th century the French chemists Pelletier and Magendie isolated the alkaloid emetine from it, replacing a variable root powder with a defined compound (Lee, 2008).

Active components. The principal alkaloids are emetine and cephaeline. Emetine inhibits protein synthesis in eukaryotic cells, which explains both its action against the amoeba *Entamoeba histolytica* and its toxicity to the heart and muscle (Bleasel and Peterson, 2020). The emetic effect comes from irritation of the stomach and stimulation of the vomiting centre.

Use today. Syrup of ipecac was used for decades to induce vomiting after poisoning, but it is no longer recommended for routine use because of lack of benefit and risk of harm. Emetine was used to treat amoebiasis but has been replaced by safer drugs such as metronidazole because of cardiotoxicity. Recent laboratory studies have examined emetine and related analogues as antiviral candidates, which remain experimental (Bleasel and Peterson, 2020).

3.12. Foxglove (digitalis): digoxin:

Source and traditional use. Purple foxglove (*Digitalis purpurea*) and woolly foxglove (*D. lanata*) are European plants. Their leaves were used in folk medicine for "dropsy", the swelling that we now recognize as fluid retention in heart failure (Withering, 1785).

Discovery. In 1785 the English physician William Withering published an account of ten years of clinical observation of foxglove. He had been led to the plant by a family herbal remedy for dropsy, identified foxglove as the active herb, and described dosing and toxicity (Withering, 1785). Later chemists isolated cardiac glycosides from the leaf, and digoxin, obtained from *D. lanata*, entered clinical use in the 20th century (Ziff

and Kotecha, 2016).

Active components. Digoxin and digitoxin are cardiac glycosides, steroid nuclei with a lactone ring and sugar units. They inhibit the Na^+/K^+-ATPase of heart muscle cells, which raises intracellular sodium and then calcium, strengthening contraction, and they slow conduction through the atrioventricular node (Ziff and Kotecha, 2016).

Use today. Digoxin is used for symptomatic heart failure and for rate control in atrial fibrillation. Its therapeutic window is narrow, and toxicity causes nausea, visual disturbance and arrhythmias, so blood levels and kidney function are monitored (Ziff and Kotecha, 2016). Commercial digoxin is still obtained from *D. lanata*, which illustrates that some plant drugs are better extracted than synthesized.

4. Challenges in herbal drug development:

Variability and quality. Species identity, chemotype, soil, climate, harvest time, drying and storage all change chemical content. Garlic products illustrate the problem, since allicin is unstable and its yield depends on how the clove is processed (Borlinghaus et al., 2014). Authentication, chromatographic fingerprints and marker-compound limits are therefore essential for reproducibility (Noviana et al., 2022).

Bioavailability and assay artefacts. A compound that is active in a test tube may never reach its target in the body. Curcumin is the standard example: poor absorption, rapid metabolism and promiscuous behaviour in assays make much of its literature hard to translate (Nelson et al., 2017). Formulation strategies, such as co-administration with piperine, partly address this (Shoba et al., 1998).

Safety and narrow margins. Natural does not mean safe. Digoxin has a narrow therapeutic window (Ziff and Kotecha, 2016), emetine is cardiotoxic (Bleasel and Peterson, 2020), aloe latex anthraquinones raise concerns on long-term use (Sánchez et al., 2020), and morphine causes dependence (Duarte, 2005). Herbal products may also interact with prescribed drugs.

Whole extract versus single molecule. Some traditions argue that the whole plant works through several constituents acting together, whereas drug regulation favours defined single compounds. Standardized multi-component fractions, as in the phytopharmaceutical category, are one compromise (Patwardhan and Vaidya, 2010).

Evidence, supply and ethics. For many herbs, such as chamomile and garlic, large, well-controlled trials are lacking (Srivastava et al., 2010). Wild-harvested species can be over-exploited, and use of traditional knowledge raises questions of benefit-sharing and intellectual property, which international and national frameworks try to address. Approaches that combine authentication, modern analytics and reverse pharmacology offer a route to address these gaps (Atanasov et al., 2021).

5. Future perspective:

Future progress will depend on rigorous authentication and standardization, better formulations to improve bioavailability, mechanism-based and in-silico screening of traditional knowledge, and well-designed clinical trials. Combining these tools with reverse pharmacology and sustainable sourcing should allow phytopharmaceuticals to deliver safe, effective and reproducible medicines.

Conclusion and future perspectives:

The twelve plants reviewed here show the main routes by which traditional medicines become modern drugs. Willow (salicin to aspirin), opium poppy (morphine), cinchona (quinine) and foxglove (digoxin) followed the classic path of ethnomedical use, isolation of an active compound and, in some cases, chemical modification. Garlic, *Aloe vera*, turmeric, neem, ginger, mint and chamomile are used mostly as standardized extracts, topical agents or supplements, and their active compounds (allicin, acemannan, curcumin, azadirachtin and nimbolide, gingerols, menthol, apigenin and bisabolol) continue to serve as leads. Ipecac shows that even a long-established plant drug can be superseded when safer alternatives appear.

6. References:

(1) Fabricant DS, Farnsworth NR. The value of plants used in traditional medicine for drug discovery. Environ Health Perspect. 2001;109(Suppl 1):69-75.
(2) World Health Organization. WHO global report on traditional and complementary medicine 2019. Geneva: World Health Organization; 2019.
(3) Newman DJ, Cragg GM. Natural products as sources of new drugs over the nearly four decades from 01/1981 to 09/2019. J Nat Prod. 2020;83(3):770-803.
(4) Atanasov AG, Zotchev SB, Dirsch VM, Supuran CT. Natural products in drug discovery: advances and opportunities. Nat Rev Drug Discov. 2021;20(3):200-16.

(5) Patwardhan B, Vaidya ADB. Natural products drug discovery: accelerating the clinical candidate development using reverse pharmacology approaches. Indian J Exp Biol. 2010;48(3):220-7.
(6) Blondeau S, Do Q-T, Scior T, Bernard P, Morin-Allory L. Reverse pharmacognosy: another way to harness the generosity of nature. Curr Pharm Des. 2010;16(15):1682-96.
(7) Noviana E, Indrayanto G, Rohman A. Advances in fingerprint analysis for standardization and quality control of herbal medicines. Front Pharmacol. 2022;13:853023.
(8) Desborough MJR, Keeling DM. The aspirin story – from willow to wonder drug. Br J Haematol. 2017;177(5):674-83.
(9) Montinari MR, Minelli S, De Caterina R. The first 3500 years of aspirin history from its roots – a concise summary. Vascul Pharmacol. 2019;113:1-8.
(10) Vane JR. Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. Nat New Biol. 1971;231(25):232-5.
(11) Duarte DF. Opium and opioids: a brief history. Rev Bras Anestesiol. 2005;55(1):135-46.
(12) Krishnamurti C, Rao SC. The isolation of morphine by Serturner. Indian J Anaesth. 2016;60(11):861-2.
(13) Brook K, Bennett J, Desai SP. The chemical history of morphine: an 8000-year journey, from resin of opium to address of pain. J Anesth Hist. 2017;3(2):50-5.
(14) Rivlin RS. Historical perspective on the use of garlic. J Nutr. 2001;131(3 Suppl):951S-4S.
(15) Cavallito CJ, Bailey JH. Allicin, the antibacterial principle of Allium sativum. I. Isolation, physical properties and antibacterial action. J Am Chem Soc. 1944;66(11):1950-1.
(16) Borlinghaus J, Albrecht F, Gruhlke MCH, Nwachukwu ID, Slusarenko AJ. Allicin: chemistry and biological properties. Molecules. 2014;19(8):12591-618.
(17) Surjushe A, Vasani R, Saple DG. Aloe vera: a short review. Indian J Dermatol. 2008;53(4):163-6.
(18) Sánchez M, González-Burgos E, Iglesias I, Gómez-Serranillos MP. Pharmacological update properties of Aloe vera and its major active constituents. Molecules. 2020;25(6):1324.
(19) Gupta SC, Patchva S, Aggarwal BB. Therapeutic roles of curcumin: lessons learned from clinical trials. AAPS J. 2013;15(1):195-218.
(20) Nelson KM, Dahlin JL, Bisson J, Graham J, Pauli GF, Walters MA. The essential medicinal chemistry of curcumin. J Med Chem. 2017;60(5):1620-37.
(21) Shoba G, Joy D, Joseph T, Majeed M, Rajendran R, Srinivas PS. Influence of piperine on the pharmacokinetics of curcumin in animals and human volunteers. Planta Med. 1998;64(4):353-6.
(22) Alzohairy MA. Therapeutics role of Azadirachta indica (neem) and their active constituents in diseases prevention and treatment. Evid Based Complement Alternat Med. 2016;2016:7382506.
(23) Morgan ED. Azadirachtin, a scientifically gripping beast. Bioorg Med Chem. 2009;17(12):4096-105.
(24) Mao QQ, Xu XY, Cao SY, Gan RY, Corke H, Beta T, et al. Bioactive compounds and bioactivities of ginger (Zingiber officinale Roscoe). Foods. 2019;8(6):185.
(25) Viljoen E, Visser J, Koen N, Musekiwa A. A systematic review and meta-analysis of the effect and safety of ginger in the treatment of pregnancy-associated nausea and vomiting. Nutr J. 2014;13:20.
(26) McKay DL, Blumberg JB. A review of the bioactivity and potential health benefits of peppermint tea (Mentha piperita L.). Phytother Res. 2006;20(8):619-33. (cited as 2006a)
(27) McKemy DD, Neuhausser WM, Julius D. Identification of a cold receptor reveals a general role for TRP channels in thermosensation. Nature. 2002;416(6876):52-8.
(28) Chumpitazi BP, Kearns GL, Shulman RJ. Review article: the physiological effects and safety of peppermint oil and its efficacy in irritable bowel syndrome and other functional disorders. Aliment Pharmacol Ther. 2018;47(6):738-52.
(29) McKay DL, Blumberg JB. A review of the bioactivity and potential health benefits of chamomile tea (Matricaria recutita L.). Phytother Res. 2006;20(7):519-30. (cited as 2006b)
(30) Srivastava JK, Shankar E, Gupta S. Chamomile: a herbal medicine of the past with bright future. Mol Med Rep. 2010;3(6):895-901.
(31) Kaufman TS, Rúveda EA. The quest for quinine: those who won the battles and those who won the war. Angew Chem Int Ed Engl. 2005;44(6):854-85.
(32) Achan J, Talisuna AO, Erhart A, Yeka A, Tibenderana JK, Baliraine FN, et al. Quinine, an old anti-malarial drug in a modern world: role in the treatment of malaria. Malar J. 2011;10:144.
(33) Tu Y. The discovery of artemisinin (qinghaosu) and gifts from Chinese medicine. Nat Med. 2011;17(10):1217-20.
(34) Lee MR. Ipecacuanha: the South American vomiting root. J R Coll Physicians Edinb. 2008;38(4):355-60.

(35) Bleasel MD, Peterson GM. Emetine, ipecac, ipecac alkaloids and analogues as potential antiviral agents for coronaviruses. Pharmaceuticals (Basel). 2020;13(3):51.
(36) Withering W. An account of the foxglove, and some of its medical uses: with practical remarks on dropsy, and other diseases. Birmingham: M. Swinney; 1785.
(37) Ziff OJ, Kotecha D. Digoxin: the good and the bad. Trends Cardiovasc Med. 2016;26(7):585-95.