1 Global Approach for Drug Discovery and Development from Indian Traditional Medicine

Shanti Bhushan Mishra, Alok Mukerjee, and Shradhanjali Singh

Abstract

Traditional medicine is the fusion of therapeutic experiences of generations of general physicians, tribal and rural peoples of indigenous systems of medication. Medicinal plants play a crucial role for the investigation of new entities (biologically active compounds in the current market). Drug discovery approaches based on natural products and traditional medicines are re-emerging as choices for new drugs to facilitate discovery process and also for the development of synergistic herbal formulations. Moreover, the integration of Ayurvedic knowledge and drug discovery brings the need for a revolution in the extraction process from sequential to parallel extraction. Bioassay-guided fractionation is a supportive measure through which standardized extract or isolated bioactive compound is obtained as the new drug. This integrated approach would result in saving of cost, time, and increased success rate in drug discovery. In this chapter we exemplified various approaches of drug discovery and application of Ayurvedic opinion in preference of plant for its therapeutic (e.g., antidiabetic) activity.

Keywords

Biological activity · Diabetes · Drug development · Screening · Traditional medicines

S. B. Mishra (✉) · A. Mukerjee
Department of Pharmacognosy, United Institute of Pharmacy, Allahabad, Uttar Pradesh, India
e-mail: shantipharma15@gmail.com

S. Singh
Department of Pharmaceutical Chemistry, United Institute of Pharmacy, Allahabad, Uttar Pradesh, India

© Springer Nature Singapore Pte Ltd. 2021

S. C. Mandal et al. (eds.), *Evidence Based Validation of Traditional Medicines*,
https://doi.org/10.1007/978-981-15-8127-4_1

Abbreviations

GMP Good Manufacturing Practice
GCP Good Clinical Practice
GLP Good Laboratory Practice
CMC Chemistry, Manufacturing and Controls

1.1 Introduction

Modern drug discovery and development endeavors typically come from the basic research and then gradually move on to definite sequential activities, which if successful ends in a new drug for the treatment of a human disease. The entire pathway is systematized by well-defined mileposts, which include identification of the lead compound, selection of the drug target, its modification to a compound suitable for toxicity testing in experimental animals, and choosing a drug molecule for clinical evaluation. Even before the beginning of human studies, a drug molecule suitable for clinical testing is assumed to satisfy specific and challenging safety criteria. It should bind selectively to the receptor on the target and prompt for the preferred functional response. There must be satisfactory bioavailability and distribution inside the body to reach the site of action, and this should produce the desired responses in in vivo models. Most importantly, a drug molecule suitable for testing in human being must pass toxicity evaluations to show that humans contributing in the phase 1 clinical trials are showing negligible risks only (Hefti 2008).

Presently traditional medicines are used in primary health-care systems in most countries equivalent to conventional medicine. Therefore, traditional medicine should be subjected to research for their efficacy and safety for greater health care. At present there is a requirement for evidence-based drug development with fluctuation of global economic scene. When developing novel drugs using traditional medicines, it is essential to consider novel standard parameters whenever possible (Zhang 2015). Quality control of traditional medicines is also prerequisite of standard clinical trials. It is essential to follow current standard quality controlling methods, viz., Good Manufacturing Practice (GMP); Chemistry, Manufacturing and Controls (CMC); Good Clinical Practice (GCP); and Good Laboratory Practice (GLP).

There are numerous examples of emergence of new drugs from the plant sources. Morphine was isolated from opium produced from latex of the poppy plant (*Papaver somniferum*) about 200 years ago. A number of drugs developed from natural/plant sources have certainly revolutionized medicine, like antibiotics (e.g., erythromycin, penicillin, tetracycline), anti-parasitics (e.g., avermectin), anti-malarials (e.g., quinine, artemisinin), hypolipidemics (e.g., lovastatin and analogs), immunosuppressants for organ transplants (e.g., rapamycins, cyclosporine), anticancer drugs (e.g., irinotecan, paclitaxel), and antidiabetic drugs (e.g., metformin) (Alamgir 2017).

There are about more than 100 plant-derived drugs and molecules/compounds that are in preclinical stage on which clinical trials are ongoing (Harvey 2008); undoubtedly, there are numerous species of plants in plant kingdom that contains the substance of medicinal value which will be discovered in the future; a lot of plants are continuously being screened for their possible pharmacological value (particularly for their hypotensive, anti-inflammatory, hypoglycemic, anti-fertility, antibiotic, anti-Parkinsonism, amebicidal, and cytotoxic properties) (Pan et al. 2013). The use of sole genuine compounds with synthetic drugs is also having lots of restrictions, and in the current years, there has been an immense resurgence of interest in the Ayurvedic and homeopathic systems of medicine, both of which rely profoundly on plant source (Kumar et al. 2017).

1.2 Drug Development from Natural Resources: Benefits and Drawbacks

Use of plant sources as preliminary point of the drug development program is related with few specific advantages:

- Typically, the assortment of a plant candidate species for research can be done on the basis of long-term use of folklore medicines by humans. This methodology is based on the finding that active compounds isolated from such plants are likely to be safer than those obtained from plant species without a history of human use. Subsequently, the synthesis of lead molecules could be reducing the pressure on natural resources. Drug development from *Cinchona officinalis*, *Rauwolfia serpentina*, *Digitalis purpurea*, etc. in the past fall under this category (Atanasov et al. 2015).
- The lead molecules isolated from natural source by using such methods can be of use with some limitations like low bioavailability, low toxicity, etc. Such type of limitations can be overcome through modification in the molecule like nanonization and by formulating their semisynthetic derivatives. For example, the bark of the willow tree (genus *Salix*) has been known from ancient times to have analgesic properties which is due to the presence of the natural product salicin and is hydrolyzed into salicylic acid (Jamshidi-Kia et al. 2018). A synthetic derivative acetylsalicylic acid (aspirin) is a widely used pain reliever. There are numerous examples of phyto-constituents which are obtained from natural sources and modified chemically, viz., morphine (*Papaver somniferum*), colchicine (*Colchicum autumnale*), penicillin G (*Penicillium citrinum*), paclitaxel (*Taxus brevifolia*), metformin (*Galega officinalis*), etc.

Although there is incredible growth in traditional system of health care globally, ITSM based on its different features of folklore medicines have also developed greatly. But there are several constrains in this development in a proper way which include:

- Rules and regulations imposed for traditional medicines are just similar to chemical-based drugs.
- Availability of raw material means dramatic depletion of wild populations of the plants; for example, the plants *Panax ginseng*, *Artemisia annua*, and *Taxus brevifolia* are now endangered due to the overexploitation.
- Once isolated from their source, compounds may work differently than expected. Moreover, the approach could be more time-consuming and more costly and may be less sustainable.

Already 29 plants and their worthy products have been banned by the government of India as they are considered as endangered species (Sen and Chakraborty 2016).

1.3 Colligative Properties of an Isolated Phyto-constituent

Not all lead molecules generated by the drug discovery persons are tested in complete regulatory packages. This is because the regulatory testing is very time-consuming and costly affair. A series of tests are initially conducted to help select certain candidate molecules within the desired pharmacological possibilities and safety profile for further regulatory testing. Drugs that do not meet the necessary requirements in these initial assays are less likely to be taken for testing in more expensive, time-consuming regulatory tests (Koehn and Carter 2005).

Koehn and Carter have figured out the following some elite characteristics of the compounds isolated from natural sources. They are as follows.

1.3.1 Molecular Structure

The automatic screening technologies and wide range of chemical libraries and archives have made it reasonably easy to identify initial lead candidates for new drug targets. The chemists have developed specific rules that lead molecules must fulfill.

- Molecular weight should be less than 500.
- Not more than five hydrogen bond donors.
- Not more than ten hydrogen bond acceptors.

1.3.2 Octanol/Water Partition Coefficient

The lipid solubility of drugs is stated as octanol/water coefficients of the uncharged molecules or log P. When the log P value is higher, drugs will be highly lipid soluble and believably accumulated in the body (Bergström and Larsson 2018).

1.3.3 Structure-Activity Relationship (SAR)

SAR gives information about the possible toxicity of a chemical based on chemical structure, when no experimental data is available. It can make predictions about a wide variety of toxicological properties of compounds such as neurotoxicity, carcinogenicity, skin sensitization, thyroid toxicity, teratogenicity, respiratory, and mutagenicity.

1.3.4 Cytotoxicity

An essential part of the drug discovery/approval process is determining the toxic effects of potential drugs. Following a toxic attack, cells may react with changes in size or morphology depending on the type of cell and compound. Some toxins can affect the cell's functionality by changing the physiology of organs such as lysosomes and endosomes or by causing a rise in number of lysosomes seen in the case of phospholipidosis. There are several types of diagnostic kits that are available in the market that can be used to measure these types of parameters.

1.3.5 Parallel Artificial Membrane Permeability Assay (PAMPA)

The potential of a molecule is orally absorbed as one of the most important aspects in deciding whether a molecule is a probable lead candidate. Parallel artificial membrane permeability assay is a decent alternative to cellular models for the initial absorption, distribution, metabolism, and excretion (ADME) and primary investigations of the research compounds. This method is used to measure the effective permeability, P (e), as a function of pH from 4 to 10. This technique provides quick response, low-cost, and automation-friendly method to measure a chemical entity's passive permeability (Kansy et al. 2004).

1.3.6 Derived Solubility

The water solubility of a drug is a crucial physical property that affects both its ADME profile and screenability in high-output systems.

1.3.7 Aqueous/Plasma Stability

The stability of lead compounds in plasma is an important parameter that can strongly affect the in vivo efficacy of a test compound. Drugs that are exposed to enzymatic processes (proteinase, esterase) in plasma may undergo intra-molecular rearrangement or bind covalently to the proteins. Thus the determination of plasma

stability should be performed early in drug discovery phase. Measurement of plasma stability is performed at physiological pH level in plasma (Chung et al. 2015).

1.3.8 Protein Binding

In-depth understanding of plasma and tissue (brain, liver, etc.) protein binding is important for evaluating the distribution of drug molecules. The plasma or tissue homogenate is incubated with the test compound. The bound and unbound test compounds are separated using ultrafiltration or equilibrium dialysis, and the amount of test compound in both fractions is estimated using HPLC or LC/MS.

These unique characteristics of lead molecules of natural origin pose order of challenges for medicinal chemists as they start working upon development of analogs (Chung et al. 2015).

1.4 Benchmarks for Selecting the Plants for Research

It has been estimated that <10% of the approximately 300,000–500,000 species of plants worldwide have been studied for 1 or more bioactivities.

Success in identifying a new biologically active plant-based natural product can be influenced firstly by a clever choice of plant or secondly by how randomly the selection of plant extracts can be quickly and effectively screened. The following selection criteria are suggested for plant-related research (Dias et al. 2012). The sketch of possible approaches to the discovery of new drug leads has been mentioned in Fig. 1.1.

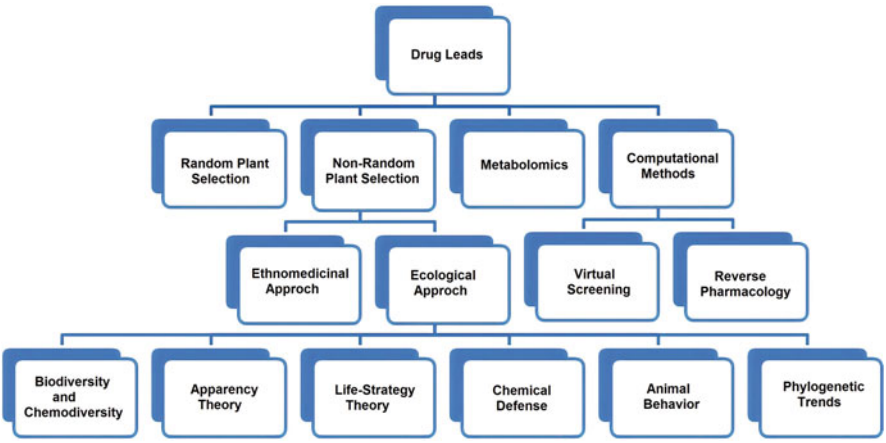

Fig. 1.1 Sketch of possible approaches to the discovery of new drug leads

1.4.1 Random Selection

In the random screening method, plant extracts, fractions, or isolated compounds are randomly selected on their convenience and availability. In the perception of plant-based drug discovery, this method can be highly beneficial when applied with samples originating from regions with high biodiversity and endemism. The random selection of test sample has the effectiveness in the identification of unpredicted biological activities that could not have been expected based on the existing information (Atanasov et al. 2015). Paclitaxel and camptothecin are the bio-actives which were isolated through this approach.

1.4.2 Selection Based on Traditional Use (Ethno-Medicinal Approach)

This is the widespread basis for selecting plants for investigation especially in societies and rural and ethnic communities where traditional medicine is whole sole part of human health care. If a traditional healer claims success in the treatment of a disease, the researcher can assume from the above selection criteria a chemical constituent with suitable pharmacological activity in the plant extract. The ethno-medicinal approach allows for better chance of finding an active compound as well as documenting and preserving local knowledge. This becomes of greater importance with the increased mobility among rural communities and the subsequent loss of local information of the use of native plant species (Lewis 2003). Regarding the ethno-medicinal approach for the selection of the plant, two important issues require attention. Firstly, the rights of the country of origin related to any drugs discovered need to be protected, as mentioned in the United Nations Convention on Biological Diversity (UNCBD) (Baker et al. 1995). Secondly, the prominence of any ethno-pharmacological field studies should be carried out before the plant selection which indicates an impact on the success of the research.

The ethno-medicinal approach has successfully been used by the researchers at Shaman Pharmaceuticals to verify the use of *Cryptolepis sanguinolenta* (Lindl.) as a treatment for type II diabetes as well as a source for the isolation of the active constituent, the alkaloid cryptolepine (Bierer et al. 1998; Luo et al. 1998). The dichloromethane and hot water extracts of the roots of *C. sanguinolenta* showed the ability to reduce the blood glucose in animal model. In vivo bioassay-guided fractionation using the same model results in the isolation of cryptolepine as an active constituent (Bierer et al. 1998; Luo et al. 1998).

1.4.3 Ecological Approach

In the ecological approach, the selection of plant candidate is dependent upon the observation of interactions between organisms and their surroundings from which bioactive natural compounds can be produced. The basic fundamental hypothesis of this approach is that secondary metabolites which possess ecological functions also

exerts pharmacological activity. Different investigators have considered different phases of the ecological argument, including the relationship between biodiversity and chemodiversity (Ramesha et al. 2011), the apparency theory (de Almeida et al. 2011), the life-strategy theory (Coley et al. 2003), chemical defenses and herbivory (Albuquerque et al. 2012), animal behavior (Obbo et al. 2013), and phylogenetic trends (Zhu et al. 2012).

Another approach which is simultaneously linked with ecological approach is the zoopharmacognosy approach. In this approach, the activity of plant is sometimes evaluated through observation of animal behavior. *Khaya* species are common to Madagascar and Africa, and people use their bitter bark and seeds for treating fevers, microbial infections, and worm infestations. Baboons and chimpanzees in Western Uganda have been observed to eat the bark and seeds that are bitter in taste and have no nutritional value (Obbo et al. 2013). The petroleum extract of *Khaya anthotheca* evidenced for good activity against *Plasmodium falciparum* K1 ($IC_{50} = 0.955$ μg/mL) and *Trypanosoma brucei rhodesiense* STIB 900 ($IC_{50} = 5.72$ μg/mL). It appears that chimpanzees and baboons were using seeds and bark for self-medicating, in addition to evidence of the effectiveness of these plants used by traditional healers (Obbo et al. 2013).

1.4.4 Computational Approach: Virtual Screening and Reverse Pharmacognosy

Computational methods are supplementary knowledge-based approach that assists to select plant material with a high probability for pharmacological activity. These methods can also aid with the validation of biological activity of natural compounds and selection of test samples dependent on in silico bioactivity predictions for constituents of plant species. Virtual screening (VS) uses the availability of large compound libraries generated by combinatorial and high-throughput chemistry to select low number of potential candidates for experimental testing (López-Vallejo et al. 2011). Virtual screening can follow two general strategies: ligand-based virtual screening and structure-based virtual screening. In this method, molecular docking is broadly used to explain the mechanism of action and defend the SAR of natural products. The purpose of docking is to accurately predict the position of a ligand within the protein binding site and the ability of binding with a docking score (López-Vallejo et al. 2011).

Reverse pharmacognosy intends to find out new biological targets for natural products by either virtual screening or real screening and then to connect these findings to original or different plant sources (Do et al. 2005).

1.5 Biological Activity-Guided Fractionation for Compound Isolation

Isolation strategies for natural products are constantly evolving. Originally, all compounds that could be purified were isolated from a plant that was used traditionally to treat diseases without concern if the specific compound was responsible for

activity. This ensures that the isolation of several inactive compounds and offered a way to bioassay-directed isolation, leading the disease to the responsible compound (Altemimi et al. 2017). Bioassay-guided isolations are currently the most common technique to purify the responsible compound for a certain bioactivity. Bioassay-guided fractionation starts with a crude extract from the dried plant material using either aqueous ethanol or aqueous methanol. The crude extract is then taken through a liquid-liquid extraction using solvents of increasing polarity, from hexanes to water, to produce five fractions (1–5) as shown in Fig. 1.2. Bioassay-guided fractionation of plant extracts can be achieved through chromatographic separation techniques which can lead to isolation of biological active molecules. If one of the fractions is bioactive, that fraction is further purified with either gravity column chromatography or flash column chromatography, depending on the complexity of the crude sample. The column fractions are then again screened with the bioassay to confirm the activity. This process is continued until a final pure compound is isolated responsible for the bioactivity. Final purification often requires high-performance liquid chromatography (HPLC) in order to obtain clean nuclear magnetic resonance (NMR) spectra and high-resolution mass spectrometric (HRMS) data for compound characterization. Even a small amount of an impurity can lead to mis-assignment of peaks in the spectrum. Advances in isolation and structural elucidation technologies provide a more comprehensive image of the entire plant extract.

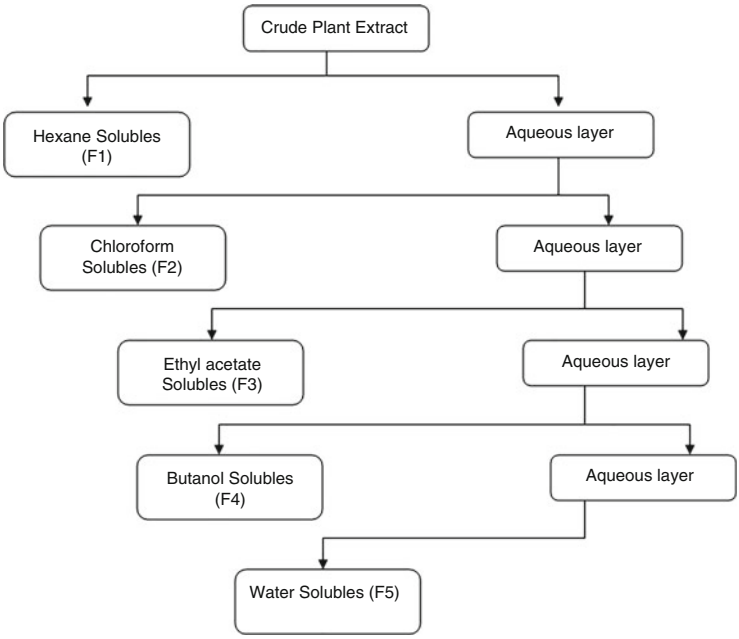

Fig. 1.2 Flow diagram of preliminary liquid-liquid extraction based on polarity

1.6 Ayurvedic Perception in Selection of Plant Candidate for its Therapeutic (e.g., Antidiabetic) Activity

On the basis of the above-said approaches of screening of medicinal plants, it is possible to apply the traditional knowledge on a variety of herbs to identify the improved lead compounds or phyto-chemicals for research and development to find out better treatment of diabetes. In Ayurvedic literature, prameha is characterized with undue urination (in both quantity and frequency) and turbidity. The nature of the turbidity may differ depending upon the body reaction with the tridoshas. Understanding of prameha is not merely related only to the patho-physiology and clinical picture of diabetes mellitus as depicted in Fig. 1.3. From the pathological and etiological state of complications, prameha is almost common in obesity and metabolic syndrome (Sharma and Chandola 2011).

The herbs from the authentic classical text *Charak Samhita*, *Sushruta Samhita*, and *Astanga Hrdaya* (Jadavaji 1992; Sharma 2001; Srikantha Murty 2000) are traditionally employed in the treatment of diabetes mentioned in Table 1.1 and scientifically explored by various investigators to evaluate the same in terms of *Rasa*, *Veerya*, *Vipaka*, *Guna*, and *Karma*. On the basis of the traditional elements for the herbs having *pramehahara/tridoshhara* effects, it can be assumed that these herbs have particular pharmacological traits in general. Going by the dominance investigation of these attributes, the following scenario appears.

Rasa: Kashaya, Tikta, and Katu
Guna: Laghu and Ruksha
Vipaka: Katu

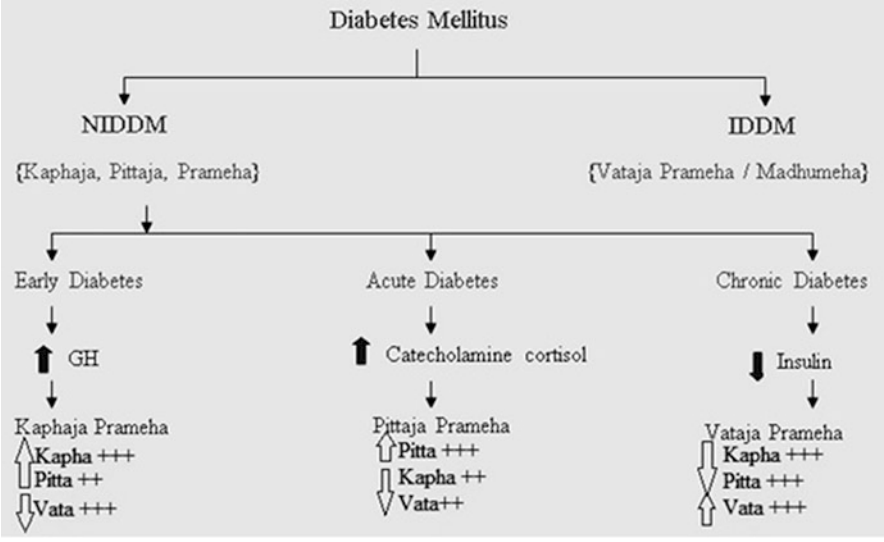

Fig. 1.3 Correlation of different types/stages of prameha with diabetes mellitus

Table 1.1 Pramehahara and madhumehahara (antidiabetic) drugs in Ayurveda

S. no.	Ayurvedic name	Botanical name	6.1.1.1.1.1.1. *Charak Samhita*	6.1.1.1.1.1.2. *Sushruta Samhita*	6.1.1.1.1.1.3. *Astanga Hrdaya*
1	Daruharidra	*Berberis aristata*	+	+	+
2	Devadaru	*Cedrus deodara*	+	+	+
3	Haritaki	*Terminalia chebula*	+	+	+
4	Vibhitaki	*Terminalia bellirica*	+	+	+
5	Amalaki	*Emblica officinalis*	+	+	+
6	Musta	*Cyperus rotundus*	+	+	+
7	Haridra	*Curcuma longa*	+	+	+
8	Katphala	*Myrica esculenta*	+	+	+
9	Lodhra	*Symplocos racemosa*	+	+	+
10	Patha	*Cyclea peltata*	+	+	+
11	Vidanga	*Embelia ribes*	+	+	+
12	Arjuna	*Terminalia arjuna*	+	+	+
13	Dhanvana	*Grewia tiliaefolia*	+	+	−
14	Tagara	*Valeriana wallichii*	+	+	+
15	Kadamba	*Anthocephalus indicus*	+	−	−
16	Shalasara	*Shorea robusta*	+	+	+
17	Yavani	*Trachyspermum ammi*	+	+	+
18	Khadira	*Acacia catechu*	+	+	+
19	Dhava	*Anogeissus latifolia*	+	+	+
20	Kustha	*Saussurea lappa*	+	+	+
21	Aguru	*Aquilaria agallocha*	+	+	−
22	Chandana	*Santalum album*	+	+	+
23	Agnimantha	*Premna integrifolia*	+	+	+
24	Murva	*Marsdenia tenacissima*	+	+	+
25	Gokshura	*Tribulus terrestris*	+	−	−

(continued)

Table 1.1 (continued)

S. no.	Ayurvedic name	Botanical name	6.1.1.1.1.1.1. *Charak Samhita*	6.1.1.1.1.1.2. *Sushruta Samhita*	6.1.1.1.1.1.3. *Astanga Hrdaya*
26	Ushira	*Vetiveria zizanioides*	+	+	+
27	Guduchi	*Tinospora cordifolia*	+	+	+
28	Chavya	*Piper retrofractum*	+	−	−
29	Chitraka	*Plumbago zeylanica*	+	+	+
30	Saptaparna	*Alstonia scholaris*	+	+	+
31	Patola	*Trichosanthes dioica*	+	+	+
32	Nimba	*Azadirachta indica*	+	+	+
33	Padmaka	*Prunus cerasoides*	+	+	−
34	Kutaja	*Holarrhena antidysenterica*	+	+	+
35	Dhataki	*Woodfordia fruticosa*	+	+	+
36	Utpala	*Nymphaea stellata*	+	+	+
37	Shirisha	*Albizia lebbeck*	+	+	+
38	Sarja	*Vateria indica*	+	+	+
39	Nagakesara	*Mesua ferrea*	+	+	+
40	Priyangu	*Callicarpa macrophylla*	+	+	+
41	Palasa	*Butea monosperma*	+	+	+
42	Aswatha	*Ficus religiosa*	+	+	+
43	Asana	*Pterocarpus marsupium*	+	+	+
44	Vetasa	*Salix caprea*	+	+	+
45	Kampillaka	*Mallotus philippinensis*	+	+	−
46	Rohitaka	*Tecoma undulata*	+	+	−
47	Kapitha	*Feronia elephantum*	+	−	−
48	Asmantaka	*Ficus rumphii*	+	−	−
49	Soma	*Ephedra gerardiana*	+	+	+

50	Ativisha	*Aconitum heterophyllum*	+	+	+
51	Vacha	*Acorus calamus*	+	−	+
52	Manjistha	*Rubia cordifolia*	+	+	+
53	Sati	*Hedychium spicatum*	+	+	+
54	Pushkaramula	*Inula racemosa*	+	+	+
55	Kramuka	*Areca catechu*	+	+	+
56	Kiratatikta	*Swertia chirayita*	+	+	+
57	Katurohini	*Picrorhiza kurroa*	+	+	+
58	Bharangi	*Clerodendrum serratum*	+	+	+
59	Pippali	*Piper longum*	+	+	+
60	Indravaruni	*Citrullus colocynthis*	+	+	+
61	Vyaghranakha	*Capparis horrida*	+	−	−
62	Tejapatra	*Cinnamomum tamala*	+	+	+
63	Maricha	*Piper nigrum*	+	+	+
64	Danti	*Baliospermum montanum*	+	+	+
65	Bhallataka	*Semecarpus anacardium*	+	+	+
66	Aragvadha	*Cassia fistula*	−	+	+
67	Madanaphala	*Randia spinosa*	−	+	+
68	Vikankata	*Flacourtia ramontchi*	−	+	+
69	Patala	*Stereospermum suaveolens*	−	+	+
70	Kuruntaka	*Barleria prionitis*	−	+	+
71	Gunja	*Abrus precatorius*	−	+	+
72	Kakajangha	*Peristrophe bicalyculata*	−	+	−
73	Karanja	*Pongamia pinnata*	−	+	+
74	Chirabilva	*Holoptelea integrifolia*	−	+	+
75	Karavellaka	*Momordica charantia*	−	+	+
76	Kadara	*Acacia suma*	−	+	+

(continued)

Table 1.1 (continued)

S. no.	Ayurvedic name	Botanical name	6.1.1.1.1.1.1. *Charak Samhita*	6.1.1.1.1.1.2. *Sushruta Samhita*	6.1.1.1.1.1.3. *Astanga Hrdaya*
77	Bhurja	*Betula utilis*	−	+	+
78	Shyonaka	*Oroxylum indicum*	−	+	+
79	Meshashringi	*Gymnema sylvestre*	−	+	+
80	Tinisa	*Ougeinia oojeinensis*	−	+	+
81	Raktachandana	*Pterocarpus santalinus*	−	+	+
82	Shinshapa	*Dalbergia sissoo*	−	+	+
83	Talamuli	*Curculigo orchioides*	−	+	+
84	Shaka	*Tectona grandis*	−	+	+
85	Aswakarna	*Dipterocarpus turbinatus*	−	−	+
86	Mushkaka	*Schrebera swietenioides*	−	+	+
87	Snuhi	*Euphorbia neriifolia*	−	+	+
88	Sunthi	*Zingiber officinale*	−	+	+
89	Paribhadra	*Erythrina variegata*	−	+	+
90	Sheivalam	*Ceratophyllum demersum*	−	+	+

Veerya: Ushna and Sheet
Dosha Karma: Kapha-Pitta-Vata Shamana (Tridoshahara)

1.7 Effects of Medicinal Plant Extract on Type II Diabetes Mellitus

Botanical agents show promise for the development of new compounds to treat type II diabetes mellitus. Till now, over 400 traditional and folklore plant treatments for diabetes have been reported, although only few of these have established a scientific and medical evaluation to assess their effectiveness. The anti-hyperglycemic effect of a number of plant extracts has been confirmed in individuals and animal models of type II diabetes (Modak et al. 2007). The WHO Expert Committee on Diabetes Mellitus has also recommended that traditional medicinal herbs should be further investigated. Several phyto-constituents including glycosides, flavonoids, alkaloids, saponins, glycolipids, dietary fibers, peptidoglycans, polysaccharides, carbohydrates, amino acids, and others obtained from various plant sources have been reported as antidiabetic agents with different mechanisms of action which are mentioned in Table 1.2, and scientifically explored plants as antidiabetics are mentioned in Table 1.3 (Mishra et al. 2010; Alam et al. 2019).

Table 1.2 Mechanism of action of phyto-chemicals of different chemical categories involved in diabetic pathway

S. no.	Constituents	Mode of activity
1	Alkaloids	Inhibit alpha-glucosidase and reduce glucose transport through the intestinal epithelium
2	Imidazoline compounds	Stimulates insulin secretion in a glucose-dependent manner
3	Polysaccharides	Increased the levels of insulin, decrease the blood glucose levels, and improve tolerance of glucose
4	Flavonoids	Suppressed the glucose level, decrease plasma triglycerides and cholesterol significantly, and increased their hepatic glucokinase activity possibly by improving the insulin release from pancreatic islets
5	Dietary fibers	Effectively adsorbed glucose, delay glucose diffusion, and reduce the alpha-amylase activity and possibly responsible for decreasing the rate of glucose absorption and concentration of postprandial serum glucose
6	Saponin, (triterpenoid +steroidal glycosides)	Stimulates the secretion of insulin and blocks the formation of glucose in the bloodstream
7	Ferulic acid	Stimulatory effects on insulin secretion (secretagogue)

Reproduced with permission from Mishra et al. 2010

Table 1.3 Scientifically explored plants investigated for their antidiabetic activity (Mishra et al. 2010; Alam et al. 2019)

S. no.	Botanical name/ family	Common name	Parts used	Chemical constituents	Antidiabetic mechanism in relation to chemical constituents
1	*Abies pindrow* (Pinaceae)	Silver fir	Entire plant	D-Pinitol, myrcene, limonene	Exert an insulin-like effect to improve glycemic control
2	*Abroma augusta* (Sterculiaceae)	Devil's cotton, Ulatkambal	Roots and leaves	Abromin, friedelin, abromasterol, taroxerylacetate, taraxeral	Reduces the absorption of glucose, thus assisting in glucose tolerance
3	*Acacia arabica* (Leguminosae)	Babool	Seed	Epicatechin, strictinin, Arabin	Inhibited the α-amylase and α-glucosidase enzymes
4	*Achyranthes aspera* (Amaranthaceae)	Apamarga	Entire plant	Oleanolic acid, betaine, triterpenoid saponins	Provide some necessary nutrients like zinc, calcium, manganese, magnesium, and copper to the β-cells and inhibit oxidative stress
5	*Agrimonia eupatoria* (Rosaceae)	Church steeples	Leaves	Essential oils, quercetin, luteolin, and tannins	Inhibited the formation of advanced glycation end products
6	*Allium sativum* (Liliaceae)	Garlic	Roots, leaves	Allin, allicin, essential oils, saponin steroids	Inhibited aldose reductase and alpha-glucosidase
7	*Allium cepa* (Liliaceae)	Onion	Bulb, leaves	Flavonoids and organo-sulfur compounds and allyl propyl disulfide	Decrease plasma glucose levels in alloxan-induced diabetic rats; alter enzyme activity of hexokinases and glucose-6-phosphate
8	*Aloe barbadensis* (Liliaceae)	Aloe	Leaves	Barbaloin, isobarbaloin, resin, pseudo-prototinosaponin, and prototinosaponins	Stimulate synthesis and release of insulin from pancreatic β-cells in vivo
9	*Anacardium occidentale* (Anacardiaceae)	Cashew, Kaju	Entire plant	Terpenoid, flavonols, coumarin, phenolic compound, essential oil	Enhance glucose metabolism and inhibited alpha-glucosidase
10	*Andrographis paniculata* (Acanthaceae)	Kalmegh	Entire plant	Diterpenoid lactone andrographolide	Delayed absorption of glucose

11	*Annona squamosa* (Annonaceae)	Sugar apple	Leaves	Isosquamosin, acetogenins-squamosin B, reticulatain-2, squamosamide	Stimulate and enhance glucose uptake
12	*Artemisia pallens* (Compositae)	Davana	Aerial parts	Davanone, artabsin, umbelliferone	Increase consumption of glucose via glucose transporter type 4
13	*Azadirachta indica* (Meliaceae)	Neem	Leaves	Nimbidin, nimbin, nimbidol, nimbosterol	Inhibited intestinal glucosidases
14	*Beta vulgaris* (Chenopodiaceae)	Chukandar	Leaves	Betaines, indicaxanthin, anthoxanthin	Reduce the level of skeletal hexokinases
15	*Bidens pilosa* (Compositae)	Spanish needle	Aerial parts	Polyyne, (2-β-D- glucopyranosyloxy-1-hydroxytrideca-5,7,9,11-tetrayne)	Protects β-cells of the pancreas and rejuvenates them
16	*Bixa orellana* (Bixaceae)	Annatto plant	Entire plant	Geranylgeranyl octadecanoate	Improving glucose uptake by adipose tissue and muscle
17	*Boerhaavia diffusa* (Nyctaginaceae)	Punarnava	Leaves and entire plant	Punarnavine and punarnavoside	Retard the intestinal absorption of glucose
18	*Brassica juncea* (Cruciferae)	Rai	Leaves and seed	Isothiocyanate glycosides sinigrin, protein, and fixed oil	Reduces plasma glucose and postprandial hyperglycemia
19	*Caesalpinia bonducella* (Leguminosae)	Kathkaranj	Seed kernels	Bonducin, caesalpin, voucapane diterpenoids, α-, β-, and γ-caesalpins	Insulin secretagogue property
20	*Camellia sinensis* (Theaceae)	Green tea	Leaves	Polyphenolic constituents (EGCG)	Enhance insulin secretion in vivo and affect gene expression
21	*Capparis decidua* (Capparidaceae)	Kair	Powder	Cappariloside A, stachydrin, capparines A and B, apigenin, kaempferol	Carbohydrate absorption and exert its postprandial hypoglycemic effect
22	*Capsicum frutescens* (Solanaceae)	Red chili	Entire plant	Capsaicin, capsicidin	Inhibited the alpha-glucosidase and alpha-amylase in vitro
23	*Carum carvi* (Umbelliferae)	Zeera, caraway	Fruits	Limonene, carvacrol, carvone, α-pinene, linalool, p-cymene	Lowers serum glucose level and inhibited the aldose reductase A

(continued)

Table 1.3 (continued)

S. no.	Botanical name/ family	Common name	Parts used	Chemical constituents	Antidiabetic mechanism in relation to chemical constituents
24	*Cassia auriculata* (Caesalpiniaceae)	Senna	Flower, roots	Goratensidine, flavonoids, and glycosides Sennosides, sennidin, gluco-aloe-emodin, auriculacacidin	Enhances the activity of hepatic hexokinase and phosphofructokinase and suppresses fructose l,6-bisphosphatase and glucose 6-phosphatase
25	*Catharanthus roseus* (Apocynaceae)	Sadabahar	Leaves, twig, and flower	Vincristine, vinblastine, serpentine, ajmalicine, tetrahydroalstonine, yohimbine	Increase glucose metabolism and inhibited the protein tyrosine phosphatase 1B
26	*Cinnamomum zeylanicum* (Lauraceae)	Dalchini	Bark	Essential oils, flavonoids, coumarins, phlobatannins, glycosides, terpenoids, and anthraquinones	Enhance the glycogen synthase activity and activate the insulin receptor by diverse mechanisms
27	*Clausena anisata* (Rutaceae)	Maggot killer plant	Roots	Scopoletin, pimpenellin, methyl chavicol, myrcene, umbelliferone, xanthotoxin, bergapten; clausanitine	Stimulate the pancreatic beta-cells and subsequent secretion of insulin
28	*Coriandrum sativum* (Umbelliferae)	Dhania	Seed, leaves, fruits	Coriandrol, D-mannitol, β-sitosterol, flavonoid glycoside, coumarins, phthalides	Enhance glucose uptake and glucose oxidation in vivo and function as secretagogue in vitro
29	*Coscinium fenestratum* (Menispermaceae)	Yellow wine	Stem	Berberine, glycoside, and saponin	Inhibited the intestinal glucose
30	*Cryptolepis sanguinolenta* (Asclepiadaceae)	Senegal	Entire plant	Neocryptolepine, cryptolepine, quindoline	Enhance glucose uptake by 3T3-L1 cells
31	*Eclipta alba* (Compositae)	False daisy	Leaves	Ecliptin alkaloid, wedelolactone Resins	Decrease activity of fructose 1,6-bisphosphatase and glucose 6-phosphatase
32	*Enicostemma littorale* (Gentianaceae)	Chhota chirayata	Entire plant	Enicoflavin, gentiocrucine, betulin, apigenin, genkwanin, isovitexin, swertisin, saponarin	Increase antioxidant enzymes and reduce the blood glucose level

33	*Eugenia jambolana* (Myrtaceae)	Jamun	Seed, fruits leaves, kernel	Anthocyanins, raffinose, gallic acid, and cyanidin diglycoside	Decrease plasma glucose level in vivo by changing glucose metabolism
34	*Eucalyptus globulus* (Myrtaceae)	Eucalyptus	Leaves	Essential oil and cineole	Increase insulin secretion from clonal pancreatic beta line BRIN-BD 11
35	*Euphrasia officinale* (Scrophulariaceae)	Eyebright	Leaves	Iridoids, flavonoids, phenolic acids, and etheric oils	Insulin mimetic property
36	*Ficus religiosa* (Moraceae)	Pipal	Entire plant	Bergapten, bergaptol, lanosterol, β-sitosterol, stigmasterol	Modulated the enzymes of antioxidant defense system to combat oxidative stress
37	*Ficus benghalensis* (Moraceae)	Bargad	Bark	Tannin, leucocynidin, 3-*O*-beta-D-galactosyl cellobioside, leucopelargonidin	Acts as insulin secretagogue
38	*Ficus carica* (Moraceae)	Fig, Anjeer	Leaves	Quercetin-3-*O*-glucoside, ferulic acid, triterpenoids, and sesquiterpenes	Causes glucose-lowering effect in vivo by stimulating insulin secretion
39	*Gymnema sylvestre* (Asclepiadaceae)	Gurmar	Leaves	Gymnemic acid, gymnemosides, and quercetin	Stimulate secretion of insulin from existing β-cells of islets and significant enhancement in the level of insulin
40	*Gentiana olivieri* (Gentianaceae)	Asbarg	Flowers, roots	β-Myrcene, isoorientin, α-pinene, limonene, and C-glycoside	Reduces blood glucose in vivo
41	*Glycyrrhiza glabra* (Leguminosae)	Mulethi	Root/ rhizome	Triterpenoid, saponin, and glycyrrhizin	Lowers blood glucose in vivo by inducing hepatic enzymes
42	*Gynura procumbens* (Compositae)	Sambung Nyawa	Leaves	Rutin, kaempferol, quercetin, and astragalin	Promoting glucose uptake by muscles
43	*Hibiscus rosa-sinensis* (Malvaceae)	Gudhal, China rose	Entire plant	Rutin, quercetin, kaempferol, myricetin	Regulating the activities of glycogen-metabolizing enzymes

(continued)

Table 1.3 (continued)

S. no.	Botanical name/ family	Common name	Parts used	Chemical constituents	Antidiabetic mechanism in relation to chemical constituents
44	*Helicteres isora* (Sterculiaceae)	Indian screw tree	Root	Fibers, phytosterols, carotenoids, antioxidants, proteins, saponin, tannin, and lignins	Initiate insulin release and reduce plasma triglycerides
45	*Hordeum vulgare* (Gramineae)	Barley	Barley seed	Beta-glucan, vitamins, and proteins	The dietary supplement to control diabetes
46	*Hovenia dulcis* (Rhamnaceae)	Japanese raisin tree	Entire plant	Tocopherol, flavonoids, ascorbic acid, anthocyanins	Stimulate hepatic enzymes to lower plasma glucose levels
47	*Ipomoea batatas* (Convolvulaceae)	Sweet potato	Tubers	Batatinoside I, citrusin, caffeic acid, β-carotene, manganese, and vitamins	Decrease insulin resistance in vivo
48	*Juniperus* communis (Cupressaceae)	Common juniper	Fruits	Apigenin, essential oils, sitosterol, cupressuflavone	Increase peripheral glucose consumption and induce insulin secretion
49	*Luffa aegyptiaca* (Cucurbitaceae)	Sponge gourd	Seed, fruits	Elaterin 2-*O*-β-D-glucopyranoside, cucurbitacin S, gypsogenin, and sitosterol	Lowers blood glucose level
50	*Leucas lavandulifolia* (Labiatae)	Halkusha	Entire plant	Acacetin, chrysoeriol, rhamnoglucoside, lupeol, taraxerone	Lowers plasma glucose in vivo
51	*Lagerstroemia speciosa* (Lythraceae)	Crepe myrtle	Leaves	p-Coumaric acid, kaempferol, quercetin ellagitannins, corosolic acid, gallic acid, 4-hydroxybenzoic acid, 3-*O*-methyl protocatechuic acid, caffeic acid, and isoquercitrin	Stimulated glucose uptake and inhibited adipocyte differentiation that could be responsible for reducing the blood glucose level
52	*Mangifera indica* (Anacardiaceae)	Mango	Leaves, fruits	Mangiferin	Inhibited the alpha-glucosidase
53	*Musa sapientum* (Musaceae)	Banana	Flower	Vitamins, starch, and minerals	Lowers blood glucose and glycosylated hemoglobin

54	*Momordica charantia* (Cucurbitaceae)	Bitter gourd	Fruit	Momordicine alkaloid and ascorbic acid	Increase oral glucose tolerance
55	*Morus indica* (Moraceae)	Shehtoot, mulberry	Leaves, fruits	Polyphenols and flavonoids	Regulates glucose uptake and aldose reductase in vivo
56	*Murraya koenigii* (Rutaceae)	Curry leaf	Leaves	Essential oils	Increase glycogenesis and decrease glycogenolysis and gluconeogenesis
57	*Nelumbo nucifera* (Nymphaeaceae)	Lotus	Rhizome	Nuciferin and nornuciferin	Reduce sugar level in diabetic rats
58	*Ocimum sanctum* (Labiatae)	Tulsi	Leaves	Alkaloid, tannin, volatile oil, phenol, aldehyde, fixed oil, and ascorbic acid	Leaf extract showed hypoglycemic effect in vivo
59	*Olea europaea* (Oleaceae)	Olive	Leaves, fruits	Oleuropeoside	Potentiate glucose, induced insulin released, and increase peripheral uptake of glucose
60	*Punica granatum* (Punicaceae)	Pomegranate	Seed, fruits	Vit. C, protein, tannin, gallic acid, and pelletierine	Inhibition of alpha-amylase
61	*Phaseolus vulgaris* (Papilionaceae)	Red beans	Pod, seed, whole plant	Iridoid, flavonoids, lignins, and phenols	Hypolipidemic, hypoglycemic, inhibit alpha-amylase activity and antioxidant
62	*Salacia reticulata* (Celastraceae)	Marking nut tree	Stem and root	3-Oxofriedelane, 3β-hydroxyfriedelane, β-sitosterol, 28-hydroxy-3-oxofriedelane, and dulcitol	Anti-hyperglycemic
63	*Swertia chirayita* (Gentianaceae)	Chiretta	Entire plant	Amerogentin, ameroswerin, mangiferin, gentiopicrin, sweroside, swertiamarin, swerchirin	Insulin release from isolated beta-cells of the pancreas
64	*Trigonella foenum-graceum* (Leguminosae)	Methi	Seed	Protein, fat, volatile oil, fixed oil, and carbohydrate	Inhibition of alpha-amylase
65	*Tinospora cordifolia* (Menispermaceae)	Guduchi	Root, leaves	Isocolumbin, palmatine, tinosporin, tinocordiside, cordioside, and β-sitosterol	Stimulation of insulin release via modulation of β-cell and Ca^{2+} concentration

(continued)

Table 1.3 (continued)

S. no.	Botanical name/ family	Common name	Parts used	Chemical constituents	Antidiabetic mechanism in relation to chemical constituents
66	*Urtica dioica* (Urticaceae)	Nettle leaf	Leaves	Beta-sitosterol, trans-ferulic acid, dotriacontane, erucic acid, ursolic acid, scopoletin, rutin, quercetin, and p-hydroxylbenzalcohol	Decreasing blood glucose in both pancreatic and extra-pancreatic pathways and inhibitory effects on the α-amylase activity
67	*Viscum album* (Loranthaceae)	Mistletoe	Leaves, entire plant	Viscotoxins, mistletoe lectin, quercetin, naringenin, chlorogenic acid, ferulic acid, rosmarinic acid, vanillic acid, ursolic acid, betulinic acid	Stimulates insulin secretion from β-cells, attenuates lipid peroxidation, and lowers the production of free radical derivatives, therefore contributing to protection against oxidative stress
68	*Withania somnifera* (Solanaceae)	Ashwagandha	Root	Withanolides, withaferins, isopelletierine, anaferine, cuscohygrine, anahygrine	Increased serum level of insulin, decreased serum level of lipids
69	*Xanthium strumarium* (Compositae)	Common cocklebur	Fruits	Xanthinin, xanthatin, xanthinosin, caffeic acid, ferulic acid, caffeoylquinic acid, strumaroside	Stimulate insulin secretion from pancreatic beta-cells and/or sensitizing insulin receptors, inhibit amylolytic enzyme
70	*Zingiber officinale* (Zingiberaceae)	Ginger	Rhizome	Essential oils, sesquiterpene, and phenols	Stimulate insulin secretion in beta-cells

1.8 Conclusion

There is a reasonable need to renew scientific interest toward natural products for inclusion in the drug discovery program. One of the vital concerns related to plant products is the prediction of hit rate during several stages of drug development. Such a prediction is expected to be lower in case of random selection of plant species considering the overall complexity of botanical sources for new chemical entities. The best drug of the future will come from a combination of a natural product research and synthetic approaches.

Clinical experience with herbal medicine as classified in traditional medicine may simplify issues associated with deprived prognosis. New functional leads taken from traditional knowledge and experiential databases can help to reduce the time, money, and toxicity, which are the three specific barriers to drug development. Furthermore, the trend today, especially in an industrial setting, is to seek biologically active compounds from plants that will serve as lead compounds for synthetic or semisynthetic development to assure patent protection.

References

Alam F, Shafique Z, Amjad ST, BinAsad MHH (2019) Enzymes inhibitors from natural sources with anti-diabetic activity: a review. Phytother Res 33:41–54

Alamgir ANM (2017) Drugs: their natural, synthetic, and biosynthetic sources. In: Therapeutic use of medicinal plants and their extracts, volume 1. Progress in drug research, vol 73. Springer, Cham

Albuquerque UP, Ramos MA, Melo JG (2012) New strategies for drug discovery in tropical forests based on ethnobotanical and chemical ecological studies. J Ethnopharmacol 140:197–201

Altemimi A, Lakhssassi N, Baharlouei A, Watson DG, Lightfoot DA (2017) Phytochemicals: extraction, isolation, and identification of bioactive compounds from plant extracts. Plants (Basel, Switzerland) 6(4):42. https://doi.org/10.3390/plants6040042

Atanasov AG, Waltenberger B, Pferschy-Wenzig EM, Linder T, Wawrosch C, Uhrin P et al (2015) Discovery and resupply of pharmacologically active plant-derived natural products: a review. Biotechnol Adv 33(8):1582–1614. https://doi.org/10.1016/j.biotechadv.2015.08.001

Baker JT, Borris RP, Carte B, Cordell GA, Soejarto DD, Cragg GM et al (1995) Natural product drug discovery and development: new perspectives on international collaboration. J Nat Prod 58:1325–1357

Bergström C, Larsson P (2018) Computational prediction of drug solubility in water-based systems: qualitative and quantitative approaches used in the current drug discovery and development setting. Int J Pharm 540(1–2):185–193. https://doi.org/10.1016/j.ijpharm.2018.01.044

Bierer DE, Fort DM, Mendez CD, Luo J, Imbach PA, Dubenko LG et al (1998) Ethnobotanical -directed discovery of the anti-hyperglycemic properties of Cryptolepine: its isolation from *Cryptolepis sanguinolenta*, synthesis and its in vitro and in vivo activities. J Med Chem 41:894–901

Chung TDY, Terry DB, Smith LH (2015) In vitro and in vivo assessment of ADME and PK properties during lead selection and lead optimization—guidelines, benchmarks and rules of thumb. In: Sittampalam GS, Grossman A, Brimacombe K et al (eds) Assay guidance manual. Eli Lilly & Company and the National Center for Advancing Translational Sciences, Bethesda, MD. https://www.ncbi.nlm.nih.gov/books/NBK326710/

Coley PD, Heller MV, Aizprua R, Araúz B, Flores N, Correa M et al (2003) Using ecological criteria to design plant collection strategies for drug discovery. Front Ecol Environ 1:421–428

de Almeida CFCBR, de Amorim ELC, de Albuquerque UP (2011) Insights into search for new drugs from traditional knowledge: an ethnobotanical and chemical-ecological perspective. Pharm Biol 49:864–873

Dias DA, Urban S, Roessner U (2012) A historical overview of natural products in drug discovery. Metabolites 2(2):303–336. https://doi.org/10.3390/metabo2020303

Do QT, Renimel I, Andre P, Lugnier C, Muller CD, Bernard P (2005) Reverse pharmacognosy: application of Selnergy, a new tool for lead discovery. The example of ε-viniferin. Curr Drug Discov Technol 2:1–7

Harvey AL (2008) Natural products in drug discovery. Drug Discov Today 13:894–901

Hefti FF (2008) Requirements for a lead compound to become a clinical candidate. BMC Neurosci 9(Suppl 3):S7. https://doi.org/10.1186/1471-2202-9-S3-S7

Jadavaji T (ed) (1992) Charaka Samhita. Chaukhamba Surbharati Prakashan, Varanasi

Jamshidi-Kia F, Lorigooini Z, Amini-Khoei H (2018) Medicinal plants: past history and future perspective. J Herbmed Pharmacol 7(1):1–7. https://doi.org/10.15171/jhp.2018.01

Kansy M, Avdeef A, Fischer H (2004) Advances in screening for membrane permeability: high-resolution PAMPA for medicinal chemists. Drug Discov Today Technol 1(4):349–355. https://doi.org/10.1016/j.ddtec.2004.11.013

Koehn FE, Carter GT (2005) The evolving role of natural products in drug discovery. Nat Rev Drug Discov 4:206–220

Kumar S, Dobos GJ, Rampp T (2017) The significance of ayurvedic medicinal plants. J Evid Based Complement Alternat Med 22(3):494–501. https://doi.org/10.1177/2156587216671392

Lewis WH (2003) Pharmaceutical discoveries based on ethnomedicinal plants: 1985 to 2000 and beyond. Econ Bot 57:126–134

López-Vallejo F, Caulfield T, Martínez-Mayorga K, Giulianotti MA, Nefzi A, Houghten RA et al (2011) Integrating virtual screening and combinatorial chemistry for accelerated drug discovery. Comb Chem High Throughput Screen 14:475–487

Luo J, Fort DM, Carlson TJ, Noamesi BK, nii-Amon-Kotei D, King SR et al (1998) *Cryptolepis sanguinolenta*: an ethnobotanical approach to drug discovery and the isolation of a potentially useful new anti-hyperglycaemic agent. Diabet Med 15:367–374

Mishra SB, Rao CV, Ojha SK, Vijayakumar M, Verma A, Alok S (2010) An analytical review of plants for anti diabetic activity with their phyto-constituents & mechanism of action. Int J Pharm Sci Res 1(1):29–46

Modak M, Dixit P, Londhe J, Ghaskadbi S, Devasagayam TP (2007) Indian herbs and herbal drugs used for the treatment of diabetes. J Clin Biochem Nutr 40(3):163–173. https://doi.org/10.3164/jcbn.40.163

Obbo CJD, Makanga B, Mulholland DA, Coombes PH, Brun R (2013) Antiprotozoal activity of Khaya anthotheca (Welv.) C.D.C. a plant used by chimpanzees for self medication. J Ethnopharmacol 147:220–223

Pan SY, Zhou SF, Gao SH, Yu ZL, Zhang SF, Tang MK (2013) New perspectives on how to discover drugs from herbal medicines: CAM's outstanding contribution to modern therapeutics. Evid Based Complement Alternat Med 2013:627375. https://doi.org/10.1155/2013/627375

Ramesha BT, Gertsch J, Ravikanth G, Priti V, Ganeshaiah KN, Shaanker RU (2011) Biodiversity and chemodiversity: future perspectives in bioprospecting. Curr Drug Targets 12:1515–1530

Sen S, Chakraborty R (2016) Revival, modernization and integration of Indian traditional herbal medicine in clinical practice: importance, challenges and future. J Trad Complement Med 7 (2):234–244. https://doi.org/10.1016/j.jtcme.2016.05.006

Sharma PV (ed) (2001) Sushruta Samhita. Chaukhamba Vishwabharati, Varanasi

Sharma H, Chandola HM (2011) Prameha in ayurveda: correlation with obesity, metabolic syndrome, and diabetes mellitus. Part 1–etiology, classification, and pathogenesis. J Altern Complement Med 17(6):491–496. https://doi.org/10.1089/acm.2010.0396

Srikantha Murty KR (ed) (2000) Astanga Hridaya. Krishnadas Academy, Varanasi

Zhang Q (2015) Traditional and complementary medicine in primary health care. In: Medcalf A, Bhattacharya S, Momen H et al (eds) Health for all: the journey of universal health coverage. Orient Blackswan, Hyderabad. https://www.ncbi.nlm.nih.gov/books/NBK316267/

Zhu F, Ma XH, Qin C, Tao L, Liuy X, Shi Z et al (2012) Drug discovery prospect from untapped species: indicators from approved natural product drugs. PLoS One 7:e39782. https://doi.org/10.1371/journal.pone.0039782