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THERAPEUTIC SOURCE: PLANTS

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Abstract: Plants are used to cure many diseases due to their therapeutic properties. The history of phytotherapeutic applications using plants for treatment goes back thousands of years. The reason plants have been used for treatment for so long is that they have produced secondary compounds with thousands of different structures that have therapeutic properties. Many of the secondary metabolites produced by plants have been converted into drugs through rational phytotherapeutic applications. The demand for herbal medicines is increasing day by day all over the world because the synthetic drugs used for treatment have serious side effects, are not sufficiently effective and there are diseases for which there is no cure yet. In our country there are almost 13 thousand plant taxa, and very few of these plants are used for medicinal purposes. In fact, thousands of plants and tens of thousands of secondary compounds that can be used for treatment are waiting to be discovered. The discovery of new, effective and safe herbal medicines is a remarkable field of research today, and the discovery of effective and safe alternative medicines will bring great benefits to human health.

Keywords: Phytotherapy, Secondary compounds, Drug discovery

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1. Introduction

Plants have been used to treat many diseases for thousands of years (Samuelsson, 2004). The first records of treatment with herbs were found on clay tablets in the Mesopotamian civilization in 2600 BC. Hittite inscriptions, Egyptian papyrus and ancient books give local names of plants with healing properties and information about their use (Gurib-Fakim, 2006). The use of plants to treat and/or prevent various diseases was first defined as phytotherapy by the French physician Henri Leclerc (1870-1955) (Schulz and Tyler, 1998; Sarker and Nahar, 2018).

Phytotherapeutic applications were used in traditional ways until the 19th century.

Plants with therapeutic properties; consumed by society for centuries either directly nutrients (cranberry, Echinacea, hot herbs, garlic, Ginkgo biloba, etc.) or the lowland mix people in Mexico *Hyptis verticillata* (Lamiaceae) as used plant ground and made into an ointment with alcohol skin infections and was used to treat wounds or consumed as a tea to cure gastrointestinal disorders (Heinrich, 2001). This use of plants for therapeutic purposes is known as traditional phytotherapy, and traditional phytotherapy is a medical practice favored by people both today and in the past. Especially in developing countries, 80% of the population benefits from herbal products for therapeutic purposes. In some countries in regions such as Asia, Africa and the Middle East, this percentage is as high as 95%. The World Health Organization predicts that treatment with herbs will increase worldwide in the coming years (Ozçelik and Toprak, 2015; Heinrich et al., 2017).

In addition to the traditional use of plants for treatment, the discovery of drugs from plants is also an important area of research today. Obtaining new drugs from medicinal plants is one of the most important goals of rational phytotherapy. Rational (rational) phytotherapy applies an evidence-based approach that includes a set of scientific criteria for treatment efficacy and safety, in contrast to traditional phytotherapy, which is based on long-standing experiences and traditions (Fürst and Zündorf, 2015; Colalto, 2018). Rational phytotherapy could be applied with the development of distillation technology in the 19th century, and many drug discoveries were made with rational phytotherapy applications in the 19th century. The chemical structure of some of the discovered drugs is shown in Figure 1.

One of the first drugs identified in this century is the morphine alkaloid, discovered in 1804 by the German pharmacist FW SertuWrner in the poppy plant (*Papaver somniferum*, Papaveraceae) and used today as a very potent analgesic (Heinrich et al., 2017). Another drug discovered in the 19th century is the substance quinine, which was extracted from the bark of the tree (*Cinchona succirubra*, Rubiacea) in 1820 by French scientists Pierre Joseph Pelletier and Joseph Bienaime Caventou (Sappington, 1844). Quinine is the active ingredient in anti-malarial drugs such as quinacrine and chloroquine, which are currently used to treat malaria (Permin et al., 2016).

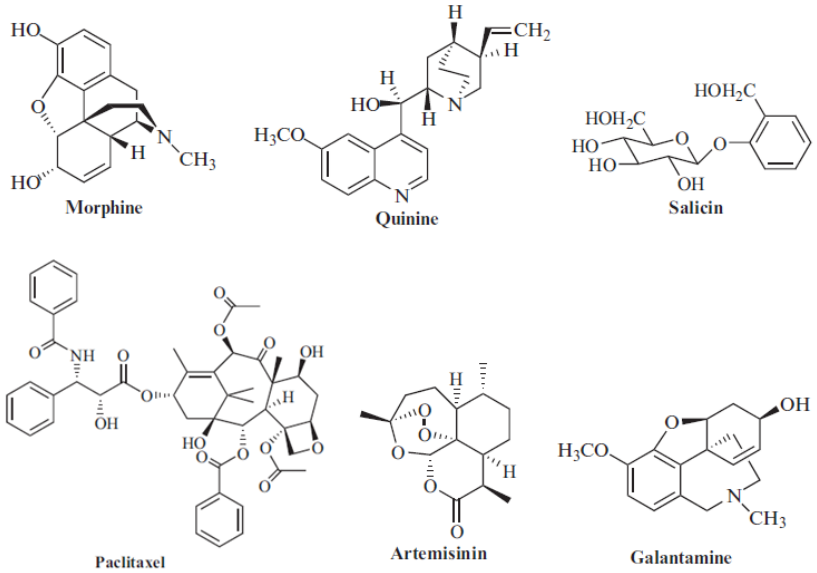

Figure1. Examples of drugs derived from therapeutic plants.

Salicin, a type of phenolic glycoside extracted from the bark of the willow tree (*Salix* spp., Salicaceae) by Johannes Buchner in Germany, was also discovered as a result of rational studies on phytotherapy. Also in 1899, the metabolite of salicin was used to make aspirin (Maclagan, 1876). Rational phytotherapeutic practices continued throughout the 20th century, and many drugs were discovered. The anticancer agent paclitaxel, the antimalarial agent artemisinin, and the antidementive galanthamine are just a few (Heinrich and Teoh, 2004; Cragg and Newman, 2005; Heinrich, 2010).

The reason plants are used in both drug discovery and traditional treatment is because of the secondary metabolites they produce. When plants are exposed to stressors such as pest attack, drought, and salt stress, they produce hundreds of thousands of different types of secondary metabolites to protect themselves. Secondary metabolites are a very important source for the production of drugs because of their therapeutic properties. Numerous drugs used in the treatment of many diseases such as cancer, neurodegenerative diseases, diabetes, heart diseases, muscle, and bone diseases have been produced from plant secondary metabolites (Heinrich et al., 2017). This review introduces researchers to the therapeutic potential of plants and also shows how important plants are for drug discovery.

2. What Do Plants Owe Their Therapeutic Properties?

For centuries, people have used plants not only to meet their food needs, but also for religious and cultural rituals, for hunting, for warfare, and to treat disease. The vast majority of plant chemicals used for purposes other than nutrition are secondary metabolites, which are biosynthetically produced from plant primary metabolites (e.g., carbohydrates, amino acids, and lipids) and are not directly involved in plant growth, development, or reproduction.

Secondary metabolites are active biomolecules that protect the plant from abiotic (drought, radiation, salinity, etc.) and biotic stresses (such as bacterial, viral, and fungal infections, and attacks by nematodes, mammals, and other animals) and regulate the mechanisms of flowering, oil production, pollination, and pigment production in the plant. These bioactive molecules can be classified into 4 groups according to their chemical structure: phenolic compounds, terpenes, alkaloids, and glycosides.

2.1. Phenolic Compounds

These compounds consist of at least one aromatic ring linked by one or more hydroxyl groups (Nicholson and Hammerschmidt, 1992). Phenolic compounds found in plants include secondary metabolites such as phenolic acids, coumarins, lignins, lignans, condensed and hydrolyzable tannins, phenylpropenes, and flavonoids (Soto-Vaca et al., 2012). The source of many drugs are phenolic compounds produced by plants.

The compound podophyllotoxin, used as a precursor for anticancer drugs and extracted from the roots of *Pelarganium peltatum* (Geraniaceae), is one of the phenolic compounds that inhibit tubulin polymerase, the enzyme required for the synthesis of tubulin, an important component of cell division (mitosis). Because of this property, the podophyllotoxin compound has been modified and transformed into two anticancer drugs, teniposide and etoposide (Heinrich et al., 2017). The phenolic compound aesculetin, isolated from the plant *Aesculus hippocastanum* (Sapindaceae), is used to treat capillary fragility (Coruh and Ozdogan, 2014; Heinrich et al., 2017). Scopoletin synthesized by *Solanum tuberosum* (Solanaceae) has antimicrobial properties and is used in the treatment of fungal infections (Gnonlonfin et al., 2012). The plant *Hieracium pilosella* (Asteraceae), also known as mouse ear, produces the compound

umbelliferone, which is used in veterinary medicine to treat brucellosis and has antibacterial activity (Mazimba, 2017). Khellin is a product of *Ammi visnaga* (Apiaceae) and has spasmolytic and vasodilator activity (Travaini et al., 2016). The phenolic compound dicoumarol from the species *Melilotus officinalis* (Fabaceae) is used alone or in combination with heparin as an anticoagulant for prophylaxis and treatment of blood clots and prevention of gangrene after frostbite (Hroboňová et al., 2018). Figure 2 shows the chemical structure of some phenolic compounds used as drugs.

2.2. Terpenes (Terpenoids)

Terpenes are the most structurally diverse class of secondary metabolites and include more than 40,000 compounds (Bohlmann and Keeling, 2008). In plants, terpenoids occur as photosynthetic pigment (phytol and carotenoids), electron transmitter (ubiquinone, plastoquinone), hormone (gibberellins, abscisic acid), and structural component of cell membranes (sterols). It also contributes to the formation of aromas in the plant (Heinrich et al., 2017).

Secondary metabolites belonging to many terpene classes have been used as raw materials for drugs. The compound gaminobutyric acid (GABA) derived from the valerian plant (*Valeriana officinalis*, Valerianaceae) is converted to gabapentin and used for its sedative effects in the treatment of epilepsy and neuropathic pain (Heinrich et al., 2017). One of the most important examples of pharmaceutical terpenes is the antimalarial drug artemisinin from sweet jelly (*Artemisia annua*, Asteraceae). The drug artemether, the ether of dihydroartemisinin, is used for the treatment of Plasmodium falciparum (Zhang et al., 2020).

Paclitaxel, an ancient antitumor agent, is an important component of this natural product class. Paclitaxel is found in the bark of the Pacific yew (*Taxus brevifolia*, Taxaceae), a slow-growing tree in the forests of northwestern Canada and the United States. Paclitaxel (trade name Taxol®), which has antitumor activity, was introduced into the U.S. drug market in 1993 for the treatment of ovarian cancer (Rana et al., 2017). Diosgenin is another terpene compound used in the pharmaceutical industry, which is extracted from weeds (*Dioscorea* sp.). It enables the formation of many important hormones such as testosterone (a male sex hormone) and estradiol (a female sex hormone) through a chemical process known as diosgenin marker degradation. The diosgenin compound converts to progesterone through the loss of a methyl group (CH_3) (Nazir et al., 2021). Figure 3 shows the conversion of the diosgenin compound to progesterone.

2.3 Alkaloids

Alkaloids; nitrogenous compounds derived from amino acids such as tyrosine, lysine, tryptophan, and aspartic acid (Loomis and Croteau, 1980). A large number of biologically active alkaloids have been isolated from plants. At the cellular level, the actions of alkaloids vary widely. Some act on the nervous system, others on protein synthesis, and still others on membrane transport and enzyme activities (Yao et al., 2004). About 12000 alkaloids are used as narcotics, drugs, and poisons because of their different biological activities (Hesse, 2002).

For example, plant alkaloids widely used in medicine include vincristine and vinblastine, which are derived from the plant *Catharanthus roseus* (Apocynaceae) and used as anticancer agents. Colchicine, derived from the autumn crocus (*Colchicum autumnale*, Colchicaceae) and used as a gout remedy, and morphine, used as an analgesic and isolated from the opium fluid in immature poppy capsules (*Papaver somniferum*, Papaveraceae), are other alkaloid drugs (Crozier et al., 2008). Papaverine, which occurs with morphine in opium fluid, is an antispasmodic agent and is also used to treat male impotence, and the drug verapamil was developed from papaverine (Siddiqui et al., 2014).

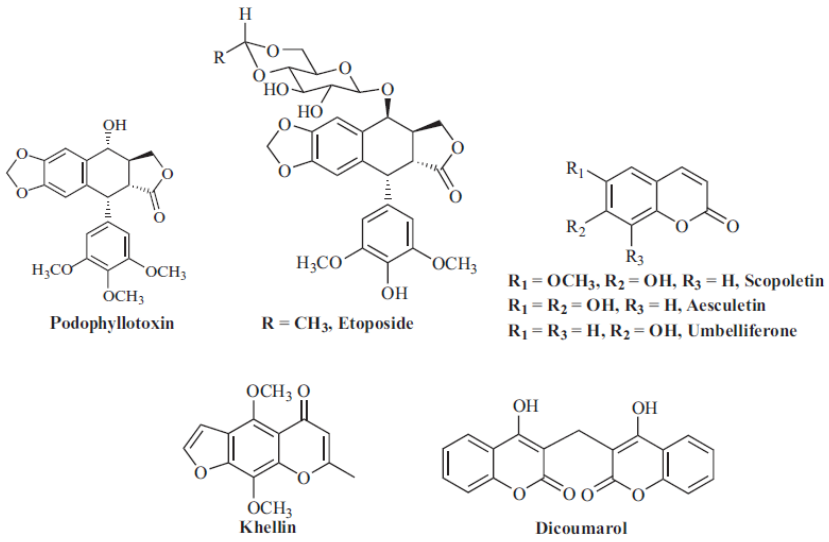

Figure 2. Chemical structure of some phenolic compounds used as drugs.

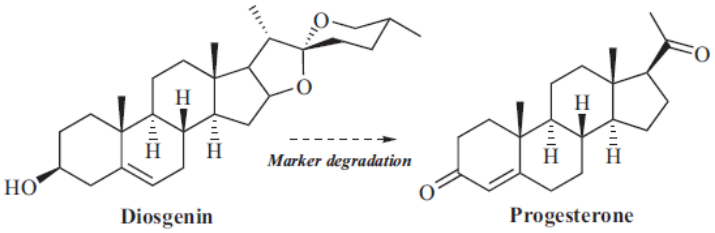

Figure 3. Conversion of the diosgenin compound to the hormone progesterone by the marker degradation.

Calabar bean (*Physostigma venenosum*, Fabaceae) is a plant that contains toxic alkaloids used to kill criminals. The toxic component of this species is physostigmine, an inhibitor of acetylcholinesterase that causes an increase in the activity of acetylcholine. This compound is of interest for the treatment of Alzheimer's disease, in which low concentrations of acetylcholine are observed in the brain (Batiha et al., 2020). Neostigmine and pyridostigmine, synthetic compounds prepared from physostigmine, are used to treat myasthenia gravis, a rare disease characterized by severe muscle weakness (Rumack, 1973). Pilocarpine, isolated from the jaborandi (*Pilocarpus jaborandi*, Rutaceae), a tree common in South America, is a cholinergic agent and is used to stimulate the muscarinic receptors of the eye in the treatment of glaucoma. In the eye, this compound and its derivatives (salts such as hydrochloride and nitrate) lower ocular pressure by providing pupillary constriction (miosis) and improved ocular outflow (Avancini et al., 2003). Figure 4 shows the chemical structure of some alkaloids used as drugs.

2.4. Glycosides

The term glycoside is a general term for a natural product that is chemically bound to a sugar. Many herbs contain cardioactive or cardiac glycosides that have a profound effect on heart rhythm. These glycosides are generally found in the genera *Convallaria*, *Nerium*, *Helleborus*, and *Digitalis*. *Digitalis purpurea*, a member of the plant family Scrophulariaceae, was widely used to treat heart disease until the 18th century because it contains the cardiac glycosides digoxin and digitoxin (Heinrich et al., 2017). Digoxin is the most commonly used cardiac glycoside in congestive heart failure (Figure 5) and is currently extracted from the related species *Digitalis lanata* (Withering, 2009).

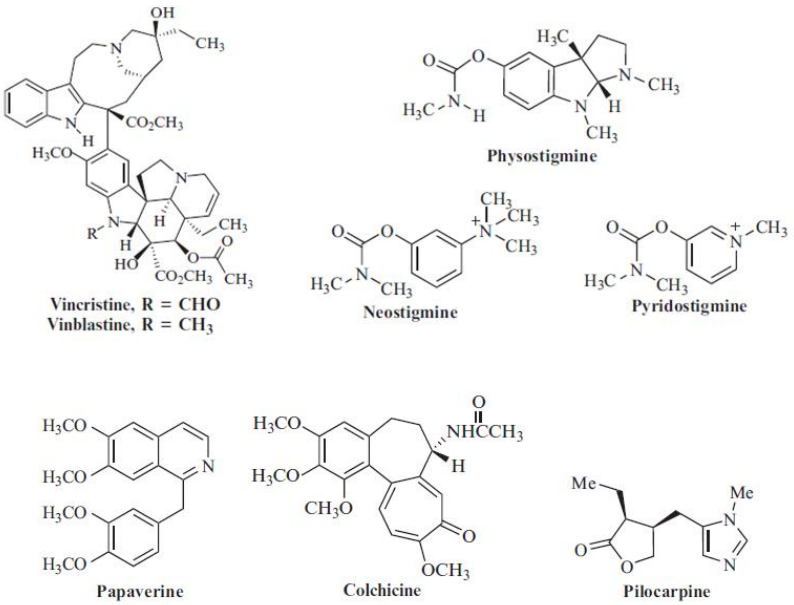

Figure 4. Chemical structure of some of the alkaloids converted into drugs.

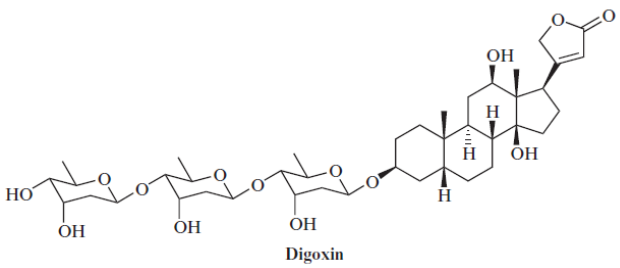

Figure 5. Chemical structure of digoxin glycoside.

The leaves of the senna plant, which is commonly used for constipation because of its laxative properties, contain the glycosides sennokote A and B. Senokot is a commercial product marketed as an anticonvulsant and contains these glycosides (Heinrich et al., 2017).

3. Role of Medicinal Plants in Drug Discovery

Although many drugs are used in modern medicine today, the discovery of new drugs is an important issue for life because existing drugs cannot effectively treat all known human ailments, many drugs have side effects, and there are still diseases today that are not treated with drugs (Hamburger and Hostettmann, 1991; Dar et al., 2017). Considering that antibiotic resistance is a major problem in the world and the incidence of many diseases such as cancer, heart disease, and neurodegenerative diseases that seriously affect people's lives is increasing every year, the need for effective, safe, and more economical medicines is important (McCord, 2000; Cars and Nordberg, 2005).

Although pharmaceutical companies are now interested in molecular modeling, combinatorial chemistry, and other synthetic chemistry techniques to produce new drugs, natural products and especially medicinal plants remain an important resource for new drugs and new drug precursors (Raskin et al., 2002; Kumar et al., 2015). Compared to chemical synthesis, the World Health Organization (WHO) advocates the inclusion of medicines from natural sources in national health programs because natural sources are much safer and more affordable than synthetic medicines (Ghosh et al., 2008; Dar et al., 2017). Plants, in particular, have long attracted the interest of researchers as they provide valuable raw material for drug discovery from natural sources (Samuelsson, 2004; Gurib-Fakim, 2006). About 270000 plant species have evolved over billions of years of evolution, and it is known that there are about 35,000 plant species used for the treatment of diseases, with only about 15% of the world's cultivated plant species being studied for their medicinal uses. Despite this low rate, 25% of the drugs used in modern medicine are of plant origin (Süntar, 2020).

One of these drugs is arteether (trade name Artemotil®), a potent antimalarial derived from artemisinin, a sesquiterpene lactone isolated from *Artemisia annua* (Asteraceae), a plant used in traditional Chinese medicine (van Agtmael et al., 1999; Balunas and Kinghorn, 2005). Nitisinone (trade name Orfadin®) is a medicinal plant-derived drug that is active against the rare hereditary disease tyrosinemia (Frantz and Smith, 2003). Nitisinone was synthesized by modification of the herbicide mesotrione, which is produced from the compound leptospermone, a natural product of *Callistemon citrinus* (Myrtaceae) (Hall et al., 2001; Mitchell et al., 2001). Tiotropium (trade name Spiriva®) has recently been marketed in the United States for the treatment of chronic obstructive pulmonary disease (COPD) (Mundy and Kirkpatrick, 2004). Tiotropium is an inhaled anticholinergic bronchodilator based on ipratropium, an atropine derivative isolated from *Atropa belladonna* (Solanaceae) and other members of the Solanaceae family (Mundy and Kirkpatrick, 2004; Balunas and Kinghorn, 2005). Tiotropium has shown greater efficacy and longer-lasting effects compared with other available COPD medications (Mundy and Kirkpatrick, 2004).

Metformin, a derivative of natural products, is the main drug used in the treatment of type 2 diabetes mellitus (T2DM) and is prepared from the alkaloid aegiline, which is derived from the plant *Galega officinalis* (Fabaceae) (Bailey and Day, 2004). The structure of aegiline was confirmed by Barger and White in 1923. However, studies on diabetes in animals and humans have limited the use of aegiline due to the variety of therapeutic effects and short duration of action. As a result of the studies, the aegiline compound was modified and diguanidine compound was obtained by chemical synthesis. This compound prepared from aegiline was found to have significant blood glucose-lowering effect (Zhang et al., 2020). As a result of long-term, multicenter, large-scale randomized controlled clinical trials, diguanidine (trade name Metformin®) has become the drug of choice for the treatment of T2DM. Nearly eighty years after the discovery of aegiline, metformin was finally approved by the FDA for the treatment of T2DM in 1994. During the course of metformin's clinical use, other effects were discovered, including cardiovascular protection, antitumor activity, and blood glucose-lowering activity.

Today, metformin is also used to treat thyroid disorders, to treat polycystic ovary syndrome (PCOS), and to prevent bone fractures. The discovery of metformin is a good example of the discovery and development of drugs based on the therapeutic effect of natural products through structural modification and chemical synthesis (Zhang et al., 2020). Galantamine (trade name Reminyl®) is a natural product isolated from *Galanthus woronowii* (Amaryllidaceae) in Russia in the early 1950s (Heinrich and Teoh, 2004). Galantamine is an approved drug for the treatment of Alzheimer's disease because it slows the neurological degeneration process by inhibiting acetylcholinesterase (AChE) (Heinrich and Teoh, 2004). Vinflunine is a modification of vinblastine derived from the plant *Catharanthus roseus* (Apocynaceae) and is an anticancer agent with increased potency (Bonfil et al., 2002). Calanolide A is a natural dipyranocoumarin product isolated from *Calophyllum lanigerum var. austrocoriaceum* (Calophyllaceae) (Yu et al., 2003) and is an anti-HIV drug with a unique and specific mechanism of action as a non-nucleoside reverse transcriptase inhibitor (NNRTI) of type 1 HIV (Balunas and Kinghorn, 2005). All these examples and many more show how important plants are in drug discovery.

4. The Road to Medicine

Throughout history, herbal products have formed the basis of medicine, and even today most pharmaceutically and medically important compounds are derived from plant sources. There are a number of approaches that can be used to explore the potential for new medicines from plant sources, and all of these approaches are being used by large and small pharmaceutical companies to exploit the biological potential of plant products (Heinrich et al., 2017).

One of these approaches, the ethnobotanical approach, uses information about the use of a particular plant by an indigenous people to search for a drug precursor. In this case, observation of the use of a plant for a particular ailment, usually by a well-trained ethnobotanist, allows that plant to be collected and then tested for biological activity (Cox and Balick, 1994). In the chemotaxonomic approach, knowledge that a particular group of plants contains a particular class of natural products can be used to predict that taxonomically related plants might contain structurally similar compounds. This approach is particularly useful when the chemistry and biological activity of a compound are well defined and compounds with similar chemical structure are needed for further biological testing (Verpoorte, 1998). In the random approach, plants are collected regardless of knowledge of their chemical composition or biological activity. This approach is based on the availability of abundant plants in a given area. This approach is purely random, as random plant selection has a chance of providing access to extracts (and thus compounds) with biological activity (Katiyar et al., 2012). The knowledge-based approach uses a combination of ethnobotanical, chemotaxonomic, and random approaches, as well as a database containing all relevant information about a given plant species. The database is used to prioritize which plants to extract and screen for bioactivity. This approach is preferred by large organizations, such as pharmaceutical companies, interested in screening thousands or even hundreds of thousands of samples for bioactivity because avoiding repeated discovery of common or known drugs can reduce costs and save time (Patwardhan et al., 2004).

After determining the appropriate approach to search for plant drug sources, the first step is to collect the plant biomass. The collected biomass is then dried and extracted in a suitable organic solvent. The resulting extract is then analyzed to evaluate its biological activity (bioactivity). Screening or biological activity assessment is usually performed in two ways, depending on the number of extracts to be assessed (Katiyar et al., 2012; Heinrich et al., 2017). In low-throughput screening (LTS), a small number of extracts (from a single extract to hundreds of extracts) are analyzed in microplates or test tubes. This approach is widely used in academic laboratories where relatively few extracts are evaluated. High-throughput screening (HTS), on the other hand, typically involves thousands of extracts in multiwell microplates. This approach is preferred by the pharmaceutical industry.

This large-scale approach means that decisions about the status of an extract in the discovery process can be made quickly (Patwardhan et al., 2004; Katiyar et al., 2012; Heinrich et al., 2017). Extracts showing bioactivity as a result of analysis are fractionated using chromatographic techniques and biological activity is controlled at all stages until a pure active compound is obtained. The isolated bioactive product is subjected to a process known as cross-screening, and information is obtained on how selective the compound is, i.e., whether it is active in all assays or has specificity for a particular assay (Jachak and Saklani 2007; Heinrich et al., 2017). This is an important consideration because specificity is one of the criteria for selecting an agent for further development. In further biological evaluation, it will be necessary to determine the three-dimensional structure of the active molecule, as this will allow a search to determine whether the compound is novel, to which chemical class it belongs, and whether this type of compound has shown biological activity in the corresponding bioassay or another bioassay (Katiyar et al., 2012).

The precursor determined to have novel and potent biological activity is isolated in large quantities and it is decided whether the compound can be synthesized de novo or whether the chemical modification is required to improve biological activity. The precursor compound will undergo extensive in vivo studies for activity and toxicity research. First, preclinical experiments, known as animal experiments, are performed. A drug precursor will finally enter clinical trials after positive results from preclinical trials. This is the most comprehensive and most important evaluation stage of a drug candidate, as many drugs have failed at this stage due to toxicity or insufficient efficacy in humans. Successful completion of these trials usually results in the product being licensed, meaning that the compound is now a drug (Heinrich et al., 2017). Figure 6 schematics all processes to obtain the drug from therapeutic plants.

Given the complexity of the process described above, it is not surprising that many drugs of natural origin fail to enter the market. By some estimates, only 1 in 10,000 drugs are thought to actually enter the market. The process is very long and can take 12-15 years from the collection of the original biomass to the issuance of a new natural product-derived drug (Heinrich et al., 2017).

5. Conclusion

Plants have been used for centuries, both traditionally and commercially, as medicine to treat many diseases because they produce a variety of secondary metabolites with antibacterial, antiviral, antifungal, anticancer, antioxidant, antidiabetic, antimalarial, neuroprotective, and cardioprotective effects (Beppe et al., 2014; Afsheen et al., 2018; Governa et al., 2018; Reichling, 2018; Kamble and Gacche, 2019). The interest in exploring new drugs and compounds from plants is increasing day by day.

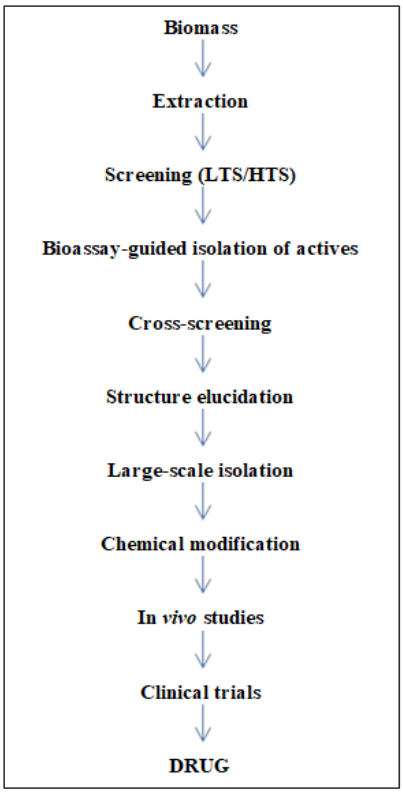

Figure 6. The process of obtaining drug from therapeutic plants.

Reasons for this include the fact that synthetic drugs used in the treatment of many diseases do not have the desired effect, cause serious side effects, some diseases cannot be treated until today, especially the negative effects of many chemotherapeutic drugs used in cancer on healthy cells and tissues, the positive attitude of Western countries towards natural medicines, and the increasing demand for herbal medicines (Klein et al., 2005).

There are 270000 tall stem plants in the world, and while humanity uses only about 70000 plants, the number of unused plants is 200000, and about 35000 of the used plants are used for therapeutic purposes. In our country, only 650 out of 13 thousand plant taxa have been defined as medicinal plants (Arslan, 2016). Considering both the world and our country, it would not be wrong to say that plants are a very rich source for discovering new medicines. If this wealth is properly utilised, safer and more effective drugs will take their place in the global pharmaceutical market.

Author Contributions

H.A. (100%) The idea of researching the article, obtaining the data, comments and writing of the article. E.Y. (100%) article edited. All authors reviewed and approved final version of the manuscript.

Conflict of Interest

The authors declare that there is no conflict of interest.

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