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Review

Natural bioactive products as promising therapeutics: A review of natural product-based drug development

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ABSTRACT

Since ancient times, natural medicines have had paramount importance in bolstering biotherapeutics to treat various diseases. The World Health Organization (WHO) revealed that more than 80% of the population of developing countries relies on traditional medicines, predominately herbal medicine, for their immediate medications. The drugs derived from medicinal plants have tremendous diversity with superfluous potency for managing communicable and non-communicable diseases, which diminishes the burden of modern pharmacopoeias in low and middle-developed countries. With the increasing importance and prevalence of herbal drugs, the appropriate evaluations are being implemented for their utilization. Most herbal medicines are prescribed by practical shreds of evidence and recommended in crude and semi-standardized forms. The inadequacy in pharmacological evaluation, preclinical and clinical examination of herbal drugs impedes their integration into contemporary medicinal practices. The preclinical investigation, prominently in-vivo and in-vitro studies, explores various attributes consisting of cell cytotoxicity, cell-cell interactions, intracellular activity, cell-environment interaction, gene expression studies, and metabolomics fingerprints of induced natural drugs. These pre-clinical evaluations and robust evidence consent to the safe and long-term utilization of herbal medicine to treat hideous diseases. Further, several modern practises are being considered for the precise and effective production of bioactive compounds at the commercial level. With this connection, this review illustrates the prominent sources of natural drugs, their pre-clinical assessments, the development of active drug molecules, and their commercialization in low-, middle-, and high-income countries.

1. Introduction

Natural products (NPs) have the utmost importance in developing therapeutics, particularly for chronic disorders and other therapeutic applications (Atanasov et al., 2021). In contrast to traditional synthetic drugs, NPs have unique properties, but their implementation into active drug molecules has challenging assignments (Harvey et al., 2015). NPs exhibit an enormous range of structural diversity compared to chemical compound libraries; they often have higher molar weight, significant carbon and oxygen atoms with more H-bond acceptors and donors, and greater molecular stiffness (Feher and Schmidt, 2003). These characteristics can be beneficial; for instance, the greater rigidity of NPs can be helpful in the drug development process. NPs have been structurally 'optimized' by evolution to perform specific biological roles, such as regulating intrinsic protective mechanisms and interacting (often competing) with other species, highlighting their importance in managing chronic and infectious diseases (Li and Vederas, 2009). Additionally, their usage in conventional medicine may reveal information about safety and effectiveness (Barnes et al., 2016).

Compared to traditional synthetic small-molecule libraries, the NPs are richer with 'bioactive' molecules that cover a larger area of synthetic chemistry (Clardy and Walsh, 2004). Drug development efforts based on NPs have been reduced by pharmaceutical corporations because of several limitations, despite the potential and numerous successful shreds of evidence. NPs screenings often employ a library of natural product extracts, which may be incompatible with conventional target-based assays (Atanasov et al., 2021). It can be complex to detect the bioactive molecules of relevance, and dereplication strategies must be used to prevent reconsideration of previously discovered compounds (Cragg et al., 1993). Isolating and characterization bioactive from biological samples can be complicated. In addition, obtaining Intellectual Property (IP) for (unmodified) NPs with significant bioactive components might be challenging because naturally revealed molecules in their original state could not

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be typically patented. At the same time, simple analogues can be secured by patent (Harrison, 2014).

Standardization and optimization of herbal resources for the primary healthcare systems in rural populations is often not considered necessary because of its remediable reliance. These natural medicines or plant-based products are being utilized as partially purified or extracted in water in low- and middle-income nations. Many studies are being conducted to discover and isolate the active chemicals involved in the treatment regimen (Dzobo, 2021). Extraction of plant components can result in a decline in curative ability and medicinal efficacy. In different situations, these preparations have different effects on biological systems, which makes it important to study how they work at the molecular level. Natural compounds and plant-based substances are difficult to study because they are combinations of metabolites and alter their activity once separated from their natural habitat (Li and Weng, 2017). When exploiting natural products for pharmaceutical development, a balanced approach is required to sustain the activity (Tollefson and Gilbert, 2012). However, when native communities or industries employ a pharmaceutical aspect, a scientific strategy is essential for ethnomedicine as it corresponds to contemporary medicines (Moffat et al., 2017). Considering the numerous chemical configurations found in natural substances, there is a possibility of discovering new molecules that can be transformed into medications. Several pharmaceutical industries like Merck, Johnson & Johnson, Pfizer, and Novartis explore natural products as drugs and commercialize them (Beutler, 2019).

To investigate a medicinal plant as a drug, researchers must explore the various elements, including cultivation, ethnopharmacology, its usage, the extraction and characterization of active ingredients, efficacy, safety, and pre-clinical and clinical evaluation (Stuart et al., 2020). Animal toxicological assessments are required to determine the possible negative consequences. A confluence of innovative drug formulation and cutting-edge technology, particularly artificial intelligence, should be employed to develop novel pharmaceuticals to fight existing and growing diseases concerning global health. Sophisticated computational and scientific approaches are required to identify molecules with targeted therapeutic effects are the new advances (Dzobo, 2021). Eventually, ethnomedicines must compete with modern medicines with surplus advantages (Ruth et al., 2014). In this review, the story of drug development from natural products has been revealed with existing challenges, current strategies, and techniques for the increasing value of natural products as a source of novel drug candidates in low and middle-income countries. It also focuses on all aspects of medicinal plant research, from plant material collection to safety and efficacy assessment through experimental investigations and phytoconstituents standardization.

2. Importance of phytomedicine in low and middle-income countries

Several factors influence the prevalence of traditional, complementary, and alternative medicine (TCAM) among less-developed nations, mainly historical and cultural aspects, legal frameworks, and TCAM's accessibility compared to modern treatment (World Health Organization, 2013). TCAM use is estimated to exceed 80% in low-income countries, according to WHO (Bodeker & Kronenberg, 2002). TCAM may be the principal choice for patients because of the limited availability of standard healthcare services or the cost of seeking conventional healthcare (World Health Organization, 2013). The continent of Africa, for example, has a traditional healer-to-population proportion of 1:500, compared with a professional doctor-to-population ratio of 1:40,000 (World Health Organization, 2013).

With the shreds of research evidence, traditional medicine (TM) is used by 60–80% of Asian and African people to address their healthcare needs. India is the highest traditional medicine using country among the other Asian countries, where 11.7% of people use them as a frequent source of health care. Despite the uniqueness and familiarity of Chinese traditional medicine, less than 3% population prefer natural medicines, whereas Chinese traditional medicine is a point of pride for the Chinese government (Goss et al., 2014). A similar thing happens in India, where the government and the community support and respect the use of certain traditional medicines through policies and funding.

Many African countries, like Ghana and South Africa, exploit less than 2% of traditional medicines. The principal cause responsible for the familiarity of conventional medicine is the lacunae of practitioners of modern medicine who do not meet the healthcare demands of the people in low- and middle-income countries, besides their cultural beliefs. Moreover, compared to modern or allopathic medicine, traditional medicine is considered cheap, affordable, and readily available in these countries (Organization, 2013). However, due to the advancements in modern medicine used for precision targets and therapies, the market for traditional medicine is declining. Moreover, the evidence suggests that traditional medicine usage is declining, and the reduction appears to be reasonably rapid.

3. Challenges in natural product-based drug development

There are 422,000 plant species documented worldwide, with 52,000 (or 12.5%) being used for medical reasons and 8% being classified as 'threatened' (U. Schippmann et al., 2002). Numerous plants haven't been studied for their pharmacological capabilities, and merely a few have been recognized and included in official pharmacopoeias like the Japanese and the Ayurvedic Pharmacopoeia. The 14th edition of the Japanese Pharmacopoeia specifies 165 herbal constituents, whereas the 16th edition specifies 276 crude pharmaceuticals, including herbal medicine and extracts, permitted for Kampo treatments (Pan et al., 2014). The Indian Ayurvedic Pharmacopoeia contains information on 976 component formulations and 540 plant monographs (Joshi et al., 2017). Plant phytoconstituents are responsible for pharmacological activities, and the content of phytoconstituents varies according to plant habits. The plant's habit has a significant influence, and this feature is crucial in determining the therapeutic value of any plant. Approximately 90% of the medicinal plants utilized in Indian Ayurveda are gathered from wild and natural resources. Inappropriate harvest (mature stage, irregular drying, and extended storage) is quickly diminishing the resource base, putting several species at risk (Lalitha, 2013). Several factors restrict the drug development process from natural products: Plant's habitat and their collection, proper cultivation of medicinal plants, environmental challenges for better productivity, identification of active ingredients from the medicinal plants, and scale-up strategies for the higher production.

4. Sources and classification of natural product

Natural products (NPs) and their derivatives have been recognized for many years as a source of therapeutic agents. NPs are biologically active substances originating from natural sources such as plant species, animals, and microbes (Baker et al., 2007). Fig. 1 illustrates that they are segmented into four categories depending on respective biosynthetic sources. For instance, plant NPs are often described as secondary metabolites, which are products of gene expression that are usually not required for reproduction, growth, and development but are formed as a consequence of environmental adaptation or as a potential protective strategy towards predators; in both circumstances, these metabolites are synthesized to support and strengthen the plant's existence (Dewick 2009). The diverse variety of natural substances is related to various factors, most notably the enormous biodiversity of aquatic and terrestrial species that synthesize a variety of molecular structures with a wide range of biological activities (Dias et al., 2012). Furthermore, biochemical variation is the

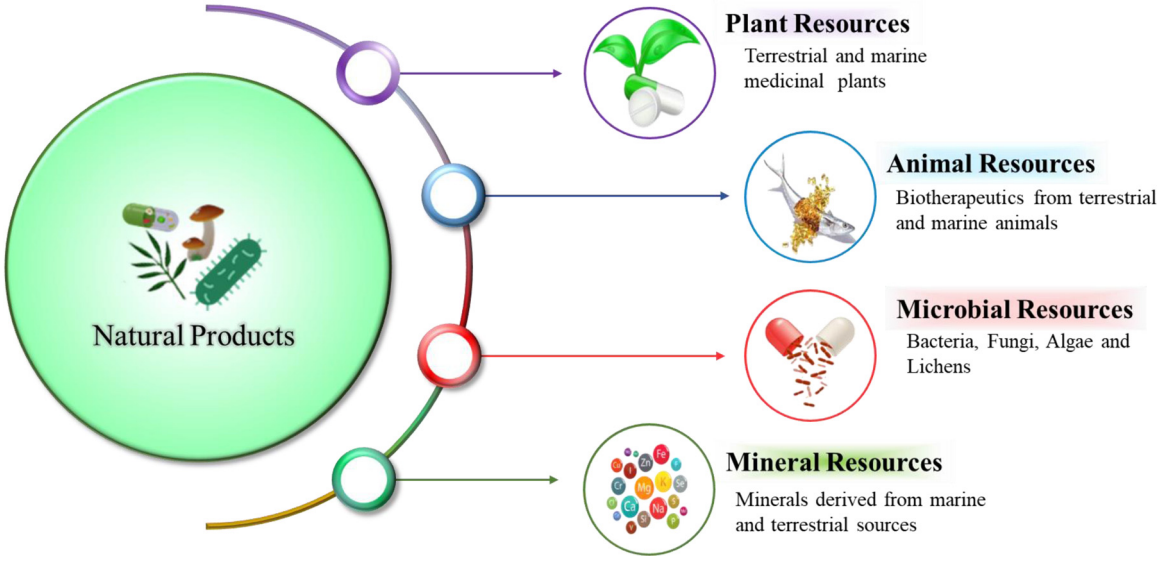

Fig. 1. Sources of natural products as a pharmaceutical.

consequence of evolutionary processes which have altered biosynthesis pathways that lead to diverse physical and biological pressures induced by natural (environmental changes) or artificial events (e.g., chemicals or radiations) (Sarker et al., 2006). For these reasons, NPs are an important, trustworthy source of the effective medication derived from Earth's enriched biodiversity (David et al., 2015).

Many people have relied on the findings of hundreds of years of experimentation utilizing plant products as conventional medicines and treatments without even any awareness of the bioactive components in the plants themselves (Kinghorn et al., 2011; Hicks, 2014). Indian tribes in Southern California used the herb *Salvia* in childbirth to treat newborn babies with hot ashes of *Salvia* genus species to stimulate their growth and protect them from any form of respiratory complications for the rest of their lives (Hicks 2014). Ayurvedic practitioners have recorded and stated that the plant *Alhagi maurorum* Medik. (Fabaceae) produces a delicious gummy compound primarily composed of sugar called melezitose and has significant efficacy in treating constipation, anorexia, dermatosis, fever, epistaxis, obesity, and leprosy (Duke et al., 2007). Furthermore, *A. maurorum* Medik. (Fabaceae) was used by various communities; for example, a boiled extract of the roots was used to treat bloody diarrhea, while Konkani people smoked it to treat asthma (Duke et al., 2007). *Ligusticum scoticum* L. (Apiaceae), a common herb of Eastern America and Northern Europe, is used to treat flatulence and is also considered an aphrodisiac and sedative (Beith 1995).

In addition to plants, various resources have produced significant amounts of NPs that have been exploited as a medication in the traditional systems. For instance, *Piptoporus betulinus*, a fungal species, was used to generate charcoal that showed antibacterial and disinfecting properties (Swanton 1915) and was used in dressing to heal wounds. Filed mushroom *Agaricus campestris* L. ex Fries (Agaricaceae) grew in Northern and Southern temperate zones and the Caribbean. This mushroom is being used to help people with throat cancer feel better after surgery (Hatfield 2002). At the same time, limited research evidence reported the medical application of lichens since lichens are widely employed in folkloristic applications (Muller 2001). *Usnea dillenius* ex Adanson, which is intended to manage scalp problems and also to be a constituent of shampoos (anti-dandruff); in addition, *Parmelia omphalodes* L. Acharius (Parmeliaceae) which is common in the British Empire and is dusted on socks before commencing a long journey to alleviate foot inflammation, as well as in Ireland, it is being used to treat bad sore Purvis (Allen and Hatfield 2004).

The marine ecosystems also contribute to producing various therapeutic medicines, but their exploration is impoverished. An algal beverage made from *Chondrus crispus* Stackhouse (Gigartinaceae) and *Mastocarpus stellatus* Stackhouse (Phyllophoraceae) was employed to treat colds and chest infections such as tuberculosis, renal problems, and burns (Vickery 1995). In the Aran Islands, the red algae *Porphyra umbilicalis* (Linnaeus) Kutzing was used to treat indigestion and breast cancer (Borlase 1758). Folkloristic information about the medicinal properties of natural compounds has served as a framework for the research going into the pharmaceutical companies for drug manufacturing. Following advances in dereplication strategies at the beginning of the 19th century, plant preparations with therapeutic benefits were thoroughly researched. By the mid-twentieth century, crude medicinal preparations were substituted with partially purified natural medicines (Mishra and Tiwari 2011). Following that, a timeline of natural compounds is exploited as a pharmaceutical to better comprehend significant drug development in modern medicine.

4.1. Plant-based natural products

4.1.1. Sources of phytomedicines: Its collection and challenges

The collection of medicinal plants from their wild habitat is challenging for plant material collection with intrinsic characteristics (Lange, 1998). The industry's exponential demand for the plant species leads to more collection and production, impacting their overexploitation. Most plant species are commonly available and can be easily collected from wide geographical locations (Lange, 1998). The prodigious harvesting of plant species restricted to a specific area and endemic to nature can lead to permanent deterioration. The medicinal plant species, including *Chlorophytum borivilianum* Santapau & R. R. Fern. (Asparagaceae), *Gentiana kurroo* Royle, *Gymnocladus assamicus* P. C. Kanjilal (Leguminosae), *Lilium abchasicum* Baker, *Curcuma caesia* Roxb. (Zingiberaceae), and *Rauvolfia serpentina* (L.) Benth (Apocynaceae), etc., are categorized as the critically endangered species due to their overexploitation (IUCN, 1994). Their cultivation can conserve these endangered plant species in the reserve biosphere, restricting their harvesting and vegetative propagation. The requirement of plant species to the industries can be fulfilled by medicinal plant farming and *in-vitro* micropropagation; these could create multifarious employment in rural areas.

Medicinal plant farming could provide the optimum plant material to the industries and minimize the burden on wild plant

harvesting. *In-vitro* micropropagation of medicinal plants could generate enormous plant communities with a higher metabolomics yield through various biotechnological aspects such as metabolomic engineering and genetic manipulation (Suryawanshi et al., 2022). Although the *in-vitro* cultivation of non-indigenous plants is challenging, the advancement in cultivation techniques could minimize these challenges. The non-indigenous plant cultivation at the particular cultivation site requires matching all the existing environmental challenges such as soil parameters, temperature, water level, humidity, and nutrient requirements for the precise bioactive compound production (Aware et al., 2017). The biotechnological approach can be enabled to overcome environmental challenges for the production of desired metabolites from non-indigenous plants. For instance, *Mucuna macrocarpa* Wall. (Leguminosae), one of the higher anti-Parkinson's drugs, L-DOPA (L-3,4-dihydroxyphenylalanine) containing species from the genus *Mucuna* (Aware et al., 2019), found in the North-Eastern region of India, cannot be grown and cultivated in the distinct geographical area. In such a context, *in-vitro* micropropagation with metabolomics engineering could overcome the climatic challenges (Aware et al., 2019a).

4.2. Screening of plants and their active part

The selection and collection of desired plant material should be carried out according to international and national taxonomical guidelines (Waldchen et al., 2018). The taxonomist and subject experts should identify the newly potent plant species and be documented them in the regional and national herbarium centers for authentication. Species with slightly different morphological characteristics can be correctly identified by genetic barcoding or biochemical fingerprinting (Patil et al., 2016).

The selection of the desired medicinal plant depends on the ethnobotanical survey of that particular region (Mohamed et al., 2012). The selection process can be done by focusing on a particular disease to identify a specific plant with an ethnomedical approach. In the ethnobotanical survey, the regional plants having competency for the disease treatment are identified with the help of the local rural community, regional medical practitioner, or botanist for the appropriate identification and their collection (Khan, 2015). The local rural community and regional medical practitioners have traditional knowledge of indigenous plants to combat the particular ailments which are essential in plant collection (Mohamed et al., 2012).

4.3. Collection of plants and harvesting of plant material

Prior to the collection site, it is a prerequisite to have a comprehensive botanical identity of the plant species for the correct verification (Mander et al., 2007). The botanical identity includes the plant family, genus, species, subspecies and variety, and geographical information such as the distribution of the species, physiochemical factors, and vegetation (U. Schippmann et al., 2002). The indigenous name of the species at the different collection sites should be obtained to avoid erroneous interpretation. It is imperative to consider the abundance of the species and whether it is endemic, threatened, or endangered to the ecosystem (U. Schippmann et al., 2002). The voucher specimen of collected plant species should be deposited in the respective herbarium for further research consultation.

The harvesting of plant material should be carried out at a specific season to avoid the distinct peculiarity in harvested and finalized products (Cunningham, 1997). The harvesting of plant material at different seasons can change the bioactive composition, which ultimately changes the biological activity (Cunningham, 1997). For example, seeds of *Mucuna pruriens* (L.) DC. (Leguminosae) collected in February-March showed a higher L-DOPA level.

In contrast, seeds collected in other seasons explored a lower level of L-DOPA content (Patil et al., 2019). This seasonal variation in bioactive constituents occurs due to different environmental conditions and geographical distribution (Cunningham, 1997). In this concern, the collection and harvesting of plant material should be carried out at a defined season to avoid the variation in bioactive constituents (Aware et al., 2017). The different parts of plant material such as flowers, seeds, leaves, stems, and roots should be harvested at a particular season as per their bioactive competency.

The various precautionary steps should be considered while collecting and harvesting plant material. The collection method and practice of plant material harvesting should be safe, harmless, and non-destructive to the plant system (Cunningham, 1997). A specific plant's stem and root collection should be conducted without disturbing the main stem and root system. The plants belonging to the industrial area, road site, or nearby drainage should not be preferred for the collection to avoid chemical toxicants, microbial contaminants, and other toxicants (Wyk et al., 2013). After collecting plant material, proper cutting, washing, and further storage should be carried out thoroughly under expert observations to avoid further complications.

4.4. Processing and preparation of plant material

After collecting plant material, its immediate process and desired plant extract preparation is a preliminary process. While processing, the collected plant material should be washed thoroughly to remove the dirt and soil particles (Wyk et al., 2013). The plant material should be protected from deterioration and environmental challenges such as rain, temperature, humidity, etc. The freshly harvested material is sometimes used immediately after the collection, so such material should be delivered as early as possible (Cunningham, 1997). Before processing, the collected material needs to be dried to avoid microbial contamination and further deterioration. In the drying process, the plant material is kept in the shade drying with constant drying conditions such as temperature and humidity (Sharma et al., 2021). The proper circumspection is taken while drying the plant material, which is essential in maintaining the integrity and essential ingredients from the leaves, flowers, stem, roots, and seed.

The process of drying the plant material also depends on its medical application. The medical practitioner uses most of the traditional and well-reported drying methods concerning diseases. The dried plant material is then pulverized in the mill to obtain the uniform powder to prepare the appropriate plant extract (Sharma et al., 2021). The powdered plant material is further stored in a dry and clean container at freezing temperature to maintain the quality and prevent contamination. The various solvents and different mechanical treatments are used to prepare the effective plant extract (Aware et al., 2019a). The choice of the solvents and the solvent preparation technique depend on the targeted plant metabolites and respective diseases. The extraction of specific metabolites in the defined solvents depends on the polarity of the solvents and the metabolites. Most of the time, polar solvents such as water, methanol, and ethanol or a combination of these solvents with a fixed ratio are used to extract desired plant metabolites (Aware et al., 2019b). The complete extraction of plant bioactive compounds from the various parts of the plant is carried out by different extraction methods.

Plant metabolites can be extracted with physical or mechanical methods such as sonication, shaking, microwave, pressure, supercritical fluid extraction, etc. (Aware et al., 2019b). The selection of a specific solvent and the desired extraction method solely depends on the inquisitive metabolites. For example, ultrasound-assisted aqueous extraction methods have been used to extract phenolics and flavonoid compounds from the *M. macrocarpa* Wall. (Leguminosae) seed powder (Aware et al., 2019b). In contrast, heating-assisted aqueous extraction was carried out to extract the metabolites, especially alkaloids, from *Pancratium parvum* Dalzell (Amaryllidaceae) (Bulb powder) for acetylcholinesterase inhibition (Patil et al., 2020). Even

the same extraction method was employed to synthesize gold nanoparticles from *P. parvum* Dalzell (Amaryllidaceae) bulb to study the potential medicinal aspects (Patil et al., 2021). Also, *Tinospora cordifolia* (Willd.) Miers (Menispermaceae) was extracted in methanol and acetone (70:30) for alkaloid extraction by using the Soxhlet apparatus to study anti-cancerous activity (Ali and Dixit, 2013). Thus, the extraction of specific and most critical compounds requires precise extraction conditions such as supercritical fluid extraction or pressure drop process. The extraction of various bioactive compounds such as alkaloids, acids, tannins, steroids, essential oils, and saponins are being performed with appropriate solvents and techniques.

4.5. Storage of extracted plant samples

The storage of extracted plant samples requires appropriate storage conditions to maintain the biochemical and medical efficiency for the respective periods. The limited shelf life of most plant metabolites restricts their longer time storage (Fennel et al., 2004). Customized storage conditions are sometimes required to store the most exceptional and precious plant extract. Most medical practitioners use freshly prepared plant extract for superior activity, whereas some plant extract activity is enriched by aging. In general, storing plant material or extract requires a clean, airtight, and sterile storage container and invariable storage conditions such as temperature, light, humidity, etc. (Fennel et al., 2004).

4.6. Bioprospecting of plant material

Medicinal plants are a plethora of enormous bioactive compounds, strengthening the paramount importance in medical science for treating hideous diseases (Aware et al., 2017). The biological screening and validation of phytochemicals with various analytical tools confer their secure utilization for disease treatment (Suryawanshi et al., 2020a, Suryawanshi et al., 2020b). The biochemical investigation of extracted samples and their standardization can promote pre-clinical and clinical assessments to develop competent therapeutic products (Wyk et al., 2013). The biochemical examinations reveal the insights of potent bioactive constituents and discern their indispensable role in disease management.

Bioprospecting of any plant material depends on its phytochemical constituents. Chemical fingerprinting of the extracted sample can be done by colorimetric or spectrometric technique to estimate protein, sugar, fat, alkaloids, antioxidant compounds, and other molecules. Further, several analytical tools, such as HPTLC, GCMS, HPLC, LCMS, etc., can be employed for the qualitative and quantitative layout of desired phytochemicals (Patil et al., 2019). For example, extraction of L-DOPA from the *Mucuna* seeds can be carried out in slightly acidic polar solvents. Further quantification is performed by the RP-HPLC method to know the actual percentage of L-DOPA in a given sample (Aware et al., 2017). The optimized samples of known constituents could be used further for dose optimization and pre-clinical and clinical investigation. Each technique has its advantage over the other, considering improved accuracy and precision and better selectivity. Volatile compounds are detected mainly by the GC technique rather than other techniques. Whereas compounds available in traces are detected using LCMS-QTOF MS.

Although there are enormous known medicinal plants and their bioactive constituents being used in medicaments, the challenges in identifying unknown compounds with known activity can be a laborious assignment to the biochemical investigation (Patil et al., 2019). The identified plant material is taken and further extracted in various solvents in such an instance. The plant sample extracted in various solvents is used for preliminary analysis to know their significant biomolecules, and the desired solvent is confirmed for further investigation. Further, the screened solvent is preferred in a single or gradient mode to obtain the various fractions by using chromatographic techniques, and fractions are further analytically characterized to know the biochemical directory of the compounds (Muhamad et al., 2017). In this connection, the novel compound is confirmed, purified, and isolated in high quantity/volume for pre-clinical assessments from these analytical and biochemical investigations.

The activity of crude extract and isolated compounds may vary due to their concentration. The isolated or purified compounds are concentrated and show superior activity to the crude plant extract (Muhamad et al., 2017). Whereas isolated or concentrated compounds sometimes show adverse side effects and restrict their further utilization. In the various pre-clinical and clinical studies, the simple crude extracts show tremendous potentiality and competency (Atanasov et al., 2021). The enormous compounds present in the crude extract act synergistically and counteract the potential side effects of individual compounds. For example, when L-DOPA is administered orally to Parkinson's induced rats, it shows several secondary complications. At the same time, the crude water extract of *Mucuna* seed powder showed superfluous activity in the Parkinson's disease model (Patil et al., 2019). This study shows that the various compounds present in the extract act synergistically and have a specific target in cellular metabolism.

4.7. An access and benefit-sharing (ABS) regulation for the medicinal plants under the Nagoya protocol (NP)

Traditional medicines, rooted in centuries to millennia of experience-based wisdom of indigenous tribal groups and communities, are currently supplemented by pharmacological investigation to reveal the chemical and cellular mechanisms of action (Efferth, 2019). Advances in biomedical research, particularly ethnomedicinal research, raise the question of who belongs to the information? If knowledge about the medicinal potential of natural resources is patented and financially exploited, one may find themselves in a predicament (Efferth, 2019). Bio-patenting debates have gained traction in the medical sciences and other fields such as botany, zoology, biotechnology, microbiology, gene technology, nutrition, agriculture, etc. Because this problem touches so many parts of daily life, it requires parallel multidisciplinary discussions from legal, ethical, and cultural viewpoints.

Research in natural product-based drug development is dependent on the availability of resources, particularly in biodiversity enriched countries. This field of study encompasses anything from fundamental research to studies focused on the commercial invention of novel products (Michael, 2000). It is presently governed by a series of international conventions, notably the Convention on Biological Diversity (CBD) and the Nagoya Protocol (NP). The NP specifically demands "the fair and equitable distribution of benefits emerging from the use of genetic resources" and its promotion and protection (Buck and Hamilton, 2011). Following the global acceptance and implementation of the CBD, relationships between countries/territories in connection to biodiversity use and sustainable development have taken on a new dimension. Grassroots activities were critical in these processes, which attempted to overcome centuries of oppressive relationships, frequently led by colonial forces. For example, Tobin (2008) and others have emphasized the relevance of customary law in preserving traditions. Following that, a range of international treaties and protocols were developed, including the NP in 2014 and the Aichi Biodiversity Targets for the 2011–2020 period. The nation's sovereign rights over genetic resources discovered within their national jurisdiction (Heinrich and Hesketh, 2019; M Ruiz Muller, 2018) which are crucial as indigenous peoples' and local communities' participation in the process of granting access based on traditional knowledge relating to such resources through agreements and Access and Benefit Sharing (ABS). The NP also acknowledges indigenous and local groups' traditional knowledge (Buck and Hamilton, 2011).

Plant species offer tremendous economic promise; they offer huge biochemical diversity; these unexplored resources of novel molecular types lead to medicines and consumer product development. These international initiatives are crucial in the sector of natural product development (Heinrich and Prieto, 2008). Due to the difficulties in obtaining genetic resources, several corporations have diminished or abandoned their involvement in natural products (Amirkia and Heinrich, 2015). The objectives of the Convention and Protocol are frequently misunderstood and misaligned, putting fundamental research at risk as a result of the 'restrictions' enforced by the international treaties and agreements (Divakaran Prathapan et al., 2018). The ABS clauses of the CBD and NP operate on the principle that one nation offers accessibility to its genetic resources to another nation in exchange for sharing the benefits that result from its use. The first point is to understand the difference between 'benefits and utilization. Whereas benefits arising from the commercial and other usage of genetic resources are mentioned in CBD Art 15.7.

As a consequence, it is evident that business benefits are being considered. If an ABS framework is to succeed, it must encourage industry from countries with a strong research facilities, which is why comprehending commercial business perspectives is critical. Furthermore, Article 11 of the CBD mandates that governments develop policies that serve as incentives for protecting and sustainable use of biological diversity components. The NP defines the term 'utilization' as research and development. It is critical to understand that genetic resources and plant products are not being sold. That would be the trade of genetic resources as commodities unregulated by the NP and CBD.

On October 29th, 2010, the Conference of the Parties to the Convention on Biological Diversity accepted the NP at its 10th meeting in Nagoya, Japan. It became effective on October 12th, 2014. As of April 2020, the NP had 123 Parties, including the European Union, but excludes a number of states and territories with significant indigenous populations and biodiversity (Canada, Australia, Greenland, Brazil, Colombia, New Zealand, the Russian Federation, and the United States). Furthermore, the CBD's near-universal acceptance ensures that its more basic provisions for ABS for the sustainable use of biodiversity, including articles 1, 8, and 15, continue to apply to all non-Parties to the NP, with the exception of the United States and the Holy See. Aside from numerous national and regional initiatives, the CBD Secretariat has developed an ABS clearing house to assist users and providers in implementing ABS provisions (Singh, 2011).

5. Current strategies for drug development from natural products

Changing lifestyles, food choices, and environmental changes/pollution have enhanced the worldwide population's susceptibility to infection and disease acquisition. The WHO encourages the usage of traditional medicine to satisfy the healthcare demands of the worldwide population since it is economical, safe, and culturally suitable (Organization, 2013). The anticipated or estimated marketplace for pharmaceuticals and pharmaceutical materials in 2025 is $2.12 trillion, indicating increased global interest in pharmaceuticals. Traditional Chinese medicine provides for 40–50% of all healthcare provisions in China, and its utilization fulfills the demands of emerging countries (Karunamoorthi et al., 2012). Recently, many studies have been conducted to investigate and discover new medications or modify current drugs to improve people's living standards. Several new diseases that have evolved in the last few decades, such as acquired immune deficiency syndrome (AIDS) and Ebola, still lack a confirmed therapy. Tuberculosis has resurfaced as a new menace, resistant to modern chemotherapeutic treatments (Sohail, 2006).

On the other hand, synthetic chemists have been unable to overcome these obstacles so far. In the absence of this, the herbal drug domain could be another option for addressing these health issues, as herbal pharmaceuticals are less expensive, more commonly accepted, and less toxic than allopathic treatments. Plants are responsible for around 25 to 50 percent of all pharmaceutical medications. Herbal medications may appear to have novel clinical effects as a therapy option for disorders. The interdisciplinary research strategy yields new pharmacophores that may expedite the identification of new targets (Pathak- Gandhi and Vaidya, 2017). There is currently no standard process for determining the plant species utilized in herbal medicines, which could lead to unethical and fraudulent activities (Newmaster et al., 2013). To analyze the authenticity of herbal products and examine the existence of residual substances, WHO issued the "guidelines for evaluating the efficacy of herbal products with relation to impurities and residues" in 2007 (Organization, 2013).

5.1. Technologies for drug discovery from natural products

Natural product-based drug discovery (NPDD) includes various strategies such as high throughput screening, genomics, proteomics, metabolomics, computer-aided drug designing, and artificial intelligence. These strategies are being utilized in pharmaceutical drug discovery research and have significantly impacted NPDD, as depicted in Fig. 2. It involves the identification of appropriate molecules, their medicinal chemistry, and optimum dose to increase the affinity, selectivity, efficacy, metabolic stability, and bioavailability.

5.2. High-throughput screening

High-throughput screening (HTS) is a specially designed for natural product drug discovery technique to identify desired molecules through the database repository. HTS employs data processing and

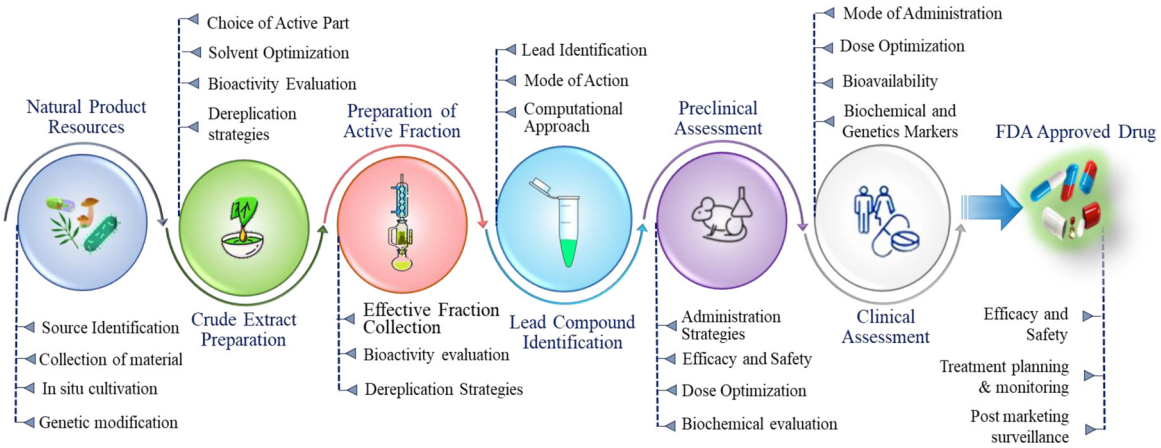

Fig. 2. Schematic representation of strategies used for the drug development from natural products.

control software and sensitive detectors, which help researchers conduct more scientifically to design and develop new structures from natural drug discovery (Koparde et al., 2018).

HTS is an efficient screening technology that utilizes the microplate format as the experimental tool carrier. This automated strategy expedites the experimental process and collects data with sensitive and rapid detection instruments at the molecular and cellular levels (Macarron et al., 2011). The corresponding database supports the overall operation of the technical system, and an enormous of samples are tested simultaneously, after which the experimental data is analyzed and processed by computational tools (Lahlou., 2013).

High-throughput screening methods are also used to characterize new drug molecules in their pharmacokinetic and toxicological data. The effectiveness of HTS for identifying target-specific compounds can be attributed to its narrow focus on a single mechanism (Szymański et al., 2011). As a result, HTS has the potential to reduce drug development costs by allowing for the early rejection of unsuitable molecules (Szymański et al., 2011).

5.3. Genomics

Compared to traditional methods of physical identification and local traditional (vernacular) names, techniques such as DNA barcoding use genomics data to enable a more robust and exact identification of the resources of natural products. DNA barcoding has been employed for natural product inventories, whereas authentication of herbal products is also an integrative approach to identify plant species (Thomford et al., 2018). Microarray analysis of gene expression is a novel transcriptomic technique that allows the rapid and accurate study of many transcripts (Lv et al., 2017). Researchers will be able to examine changes in numerous gene expressions and genome annotations simultaneously, anticipating target structure and understanding disease genetics with this transcriptome approach. As a result, a new research trend emerged to show drug action mechanisms, forecast drug resistance, and uncover biomarkers for various disorders (Ataya., 2019). This is a powerful tool for deciphering the molecular mechanisms and biological networks underlying the pharmacological activities of natural compounds. The sequencing of the plant genome, on the other hand, has created an unprecedented opportunity for revealing new therapeutic targets (Thomford et al., 2018).

5.4. Proteomics

Natural product-based approaches to drug discovery can reveal the protein function and its expression and biosynthetic pathways based on therapeutic value resulting in consistent product efficiency (Martinez-Esteso et al., 2015; Russell et al., 2013). Proteomics research has widened the scope of protein study by looking at how protein function affects the phenotype and interaction of medication with its target. These investigations have also revealed illness pathophysiology, drug target validation, activity, toxicity, and adverse effects (Ataya., 2019). This is an effective way to explain the multitarget effects of complex natural product preparations and the discovery of multiple compounds and fractions, characterization of natural products, and ultimately, a molecular diagnostic platform (Kiriiri et al., 2020; Aslam et al., 2017). Protein-protein interactions and structure-function investigations benefit greatly from proteomics methods. Proteomic data, when combined with systems biology methodologies, is exceptionally well adapted to guide the development of novel antiviral therapy regimens that allow for rapid characterization of host-pathogen interactions (Cakir et al., 2021).

5.5. Metabolomics

Natural product metabolomic profiling aims to discover and measure the range of distinctive metabolites of respective sources. The discovery of chemicals that impart medicinal effects of herbs has been made possible by metabolomic profiling of natural products utilizing methods such as ultra-high-performance liquid chromatography–quadrupole TOF/MS (UPLC–MS). In this connection, Perkowska et al., 2021 employed the UPLC-MS method to detect pharmacologically active compounds like scopolin, skimmin, and esculin (Coumarins), which have neuroprotective, anticoagulant, anticancer, antiviral, and anti-inflammatory properties. Tang et al. (2019) employed LC-ESI-QTOF/MS to detect and quantify bioactive substances such as hydroxybenzoic acid (Gallic acid), hydroxycinnamic acid (Caffeic acid, p-coumaric acid), epicatechin, apigenin, kaempferol, and myricetin, among others. While Quatrin et al. (2019) used two separate mass spectrometer analyzers (LC–TRAP–MS/MS and LC–Q-TOF–MS/MS) to characterize and identify tannins, flavanols, anthocyanins, and matrix-bound polyphenols from jaboticaba fruit peel, the quantification was done using HPLC–DAD approach.

Metabolomics using nuclear magnetic resonance (NMR) spectroscopy or high-resolution mass spectrometry (HRMS), or combined approaches consisting of upstream liquid chromatography (LC), such as LC–HRMS, which can separate several isomers found in NPs extracts (Atanasov et al., 2021). LC—HRMS/MS identified Piperamides in the *Piper* fruit extracts by Luca et al., 2021. The L-DOPA was quantified by Aware et al., 2017 using the RP-HPLC method from *M. macrocarpa* Wall. (Leguminosae), the most effective medication available for treating Parkinson's disease. Moreover, metabolomics profiling of different *Mucuna* species present in India was successfully studied previously by Rane and Suryawanshi et al. using RP-HPLC and LCMS, respectively (Rane and Suryawanshi, 2019; Suryawanshi et al., 2019). Several alkaloids, including sanguinine, hydoxyvittatine, hippeastrine, dideoxypancratistatin, and lycoricidine with promising pharmacological applications, were detected from *P. parvum* Dalzell (Amaryllidaceae) bulb aqueous extract using LCMS-QTOF MS (Patil et al., 2020).

5.6. CRISPR/Cas9 system

This advanced approach has been utilized in recent years because of its convenient implementation, high efficiency, and wide application in gene mutation and transcriptional regulation in animals and plants. In recent years, CRISPR/Cas has been regarded as a breakthrough in plant biology (Jaganathan et al., 2018). However, several plant secondary metabolic pathways (viz. alkaloid, terpenoid, flavonoids, phenolic, saponin, etc.) have been engineered to employ CRISPR/Cas-editing via knock-out knock-in, point-mutation, fine-tuning of gene-expression and targeted-mutagenesis (Abhijit, 2021). This genome-editing tool further extends its applicability by incorporating the tools of synthetic and system biology, functional genomics, and Next Generation Sequencing (NGS) to produce genetically-engineered medicinal crops with advanced traits facilitating the production of pharmaceutical and nutraceuticals. CRISPR/Cas 9 has become an advantageous tool for next-generation drug development by accelerating the identification and verification of drug targets (Atanasov et al., 2021). CRISPR-Cas 9 system allows researchers to quickly determine the pathogenic effects of oncogenes, tumor suppressors, and other factors in a particular context. Similarly, through HDR "knock-in" mutant alleles, the impact of disease-related allele mutations can be tested.

5.7. Computer-aided drug development (CADD)

CADD involves predictive algorithms, computing resources, and 3D visualization tools to design, optimize, and develop small molecule therapeutics against diseases.

There are three primary roles of CADD in pharmaceutical industries: (1) the screening of large libraries of molecules to predict

minimal best small molecules to further test in actual experiments; (2) lead identification by designing novel small molecules; and (3) lead optimization for affinity or pharmacokinetic/ pharmacodynamic (PK/PD) properties. The implementation of omics will be enabled by using computing frameworks, including bioinformatics and other statistical techniques, to elucidate pathophysiological effects, target specificity, and molecular effects and to elucidate the pharmacodynamic, pharmacokinetics, and toxicological characterizations of natural products. Flurbiprofen is currently one of the most effective drugs for treating Rheumatoid arthritis, which was discovered by ligand-based drug design (Sharma et al., 2021). Some diseases involve multiple genes, multiple target pathways, and network regulation. There is a complex interaction between the virus and the human genome and proteome. Traditional research methods for single targets have been difficult to apply to related therapeutic drug research. Pharmacogenomics provides new strategies for studying multi-gene and multi-target disease prevention and treatment and opens golden avenues for new drug research. Furthermore, natural products usually have the characteristics of multi-functional and multi-targets. Strategies employing in-silico methods can detect drug toxicity early along with the drug discovery process. If this approach is combined with *in-vitro* and *in-vivo* biological experiments, this can reduce the time and cost of drug discovery and improve safety evaluation (Sharma et al., 2021).

5.8. Artificial intelligence (AI)

The earlier pharmaceutical organization had technical challenges and encountered economic issues in drug development; the further intervention of artificial intelligence intensified the drug development process. The interaction of a medicament and its target can be measured using AI-based approaches, which provide faster drug target validation and help optimize drug structure design (Paul et al., 2021; Khan et al., 2021). At present, many companies have begun to apply artificial intelligence to the process of drug development. In the field of AI-assisted drug discovery, many start-up companies have developed much faster than large pharmaceutical companies. These start-up pharmaceutical companies are continually introducing new drugs to the market, which expedites the developmental process limitless.

6. Choice of a drug molecule and its implementation

A drug development program begins with a disease or clinical condition with no viable medicinal products. This unmet clinical necessity is the project's fundamental driving impetus. Often in academia, initial research is focused on inhibiting the enzyme related to the particular disease or identifying and isolating a compound that develops a hypothesis that can produce a therapeutic outcome in the ailing condition. This activity leads to selecting a target that may require further confirmation before going to the lead discovery phase, which is necessary to justify a drug discovery effort. In the process of drug discovery, rigorous research is focused on searching for a drug-like small compound with therapeutic benefits that can evolve into pre-clinical. Also, it is based on understanding the root cause of the disease to be treated, information on how the genes that cause the disease are altered, the interaction of proteins with the affected cells, and changes brought about by these affected cells. Further, if that screened drug passes the pre-clinical criteria successfully, it can be tested in clinical development and eventually marketed.

6.1. Target identification

Identifying and confirming targets is a crucial stage in developing a novel medicine. Target identification plays a pivotal role in the drug discovery and development process. A target is a general term that can refer to a wide range of biological entities, such as proteins, genes, and RNA. A good target should be effective, safe, and appropriate to clinical and commercial needs and be 'druggable' (Hughes et al., 2011). The small molecule, which is destined to become a drug molecule, must pass a series of tests and experiments to demonstrate that it is absorbed into the bloodstream, delivered to the correct action site in the body, metabolized adequately, does not cause toxicity, and further this can be considered safe and successful (Siddiqui et al., 2017). The failure of drugs in clinical studies is primarily due to two main reasons: the desired drug is toxic and unsafe and does not work effectively. The Discovery of the target is categorized into two methods; system and molecular approach. The approaching target is selected based on available data acquired from in-vivo and clinical studies in the system. A molecular approach focused on identifying 'druggable' targets whose activity can be influenced by interactions with small compounds, proteins, and antibodies. Thus, this is the conformist approach to strategizing the target discovery (Yang et al., 2012).

A data mining approach is employed to screen the target drug, which uses a bioinformatics methodology that blends biological principles with computer tools or statistical approaches and is mainly used to discover, select, and prioritize targets in biomedical science. This makes the procedure rapid to identify the targets based on the available data. For instance, in the case of autosomal dominant Alzheimer's disease (AD), amyloid precursor protein (APP) or presenilin 1 and 2 (PSEN 1 and 2) are targeted genes because if a mutation occurs in the respective genes, it results in AD (Bekris et al., 2010). Whereas, in sporadic AD, APOE $\varepsilon 4$ is the targeted gene for identifying disease. Using microarray data analysis, microarray data mining uses bioinformatics techniques to find entities and biological pathways that describe a phenotype, such as a human disease. Primary research and target identification, biomarker determination, pharmacology, toxicogenomic, target selectivity, development of prognostic tests, and disease-subclass resolution are all applications of microarrays in drug discovery (Butte, 2002).

6.2. Target validation

Target validation confirms that the target's assignation can be therapeutically valuable. The target must then be fully prosecuted after being identified. Validation methods include everything from *in-vitro* tools to full animal models to know the effectiveness of the desired target. This is the initial phase of the drug discovery process and includes several steps, methods, and a wide range of techniques to validate the results. Only after validation of results target can enter into the drug development process. There should be a clarified understanding of the clinical usage of the screened therapeutic drug to deliver the right medicine to the concerned person (Wyatt et al., 2011). Target validation also includes; the target product profile, which is an imperative deliberated planning and decision-making tool that is used to define; the population of the patient, acceptable levels of safety, acceptable levels of efficacy, route of dosing and its schedule, formulated drug properties, and acceptable levels of cost of the formulated drug (Wyatt et al., 2011). To discover the targets, various methodologies are focused includes; gene transfection, RNAi, DNA microarray, RT-PCR, gene knock-out, RNA sequencing, and MARCM technique (Shangguan, 2021). Thus, target validation includes the expression of target protein in the targeted locus and genetics associated with that particular disease, followed by a small clinical trial to check the efficacy with a lack of pathway knowledge to assess potential therapeutic benefit.

7. Preclinical assessments for therapeutic authentication

A medication candidate must go through a long set of laboratory and animal studies before being investigated in people to determine

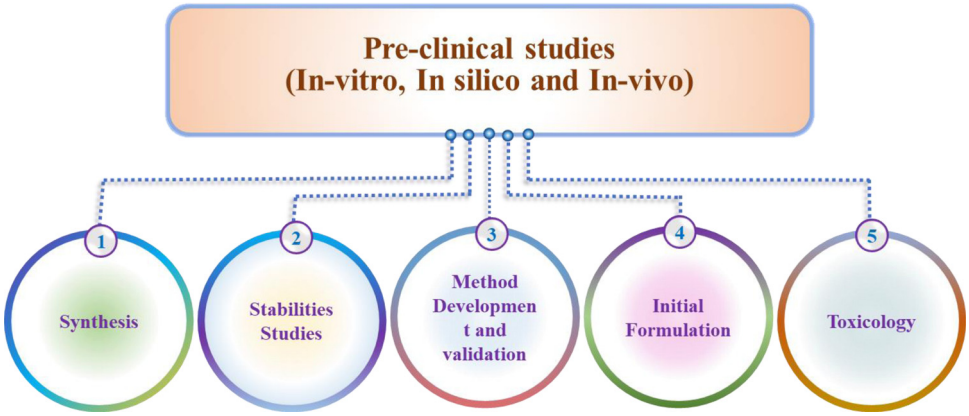

Fig. 3. Consecutive steps in Preclinical assessment of drug.

its therapeutic and harmful effects as depicted in Fig. 3. It's critical to evaluate whether pre-clinical pharmacodynamic and safety models have accurately predicted human responses and when they haven't to enhance drug development outcomes. Many *in-vitro*, in vivo, and *in-silico* screening assays and tests have been carried out following good laboratory practice criteria during pre-clinical testing. The formulation phase may begin early or late in this stage, depending on product strategy, and may even last until Phase II. In Phase III, a final formulation is constantly tested for one specified indication (Shegokar, 2020). In pre-clinical studies, the most appropriate and similar model for the intended population must be used to ensure data accuracy, reliability, and comparability. To address the inimitable requirements of the targeted indication and regulatory standards for a drug product, thorough testing and studies are often conducted using *in-vitro,* in vivo*, ex vivo*, and simulation models. Few drugs, including alagebrium, eplerenone, macitentan, sildenafil, vericiguat, and Ivabradine are the drugs that failed in clinical trials due to adverse effects or no possible outcomes in the tested parameters especially tested for heart failures with reduced left ventricular ejection fraction (Tamargo et al., 2019).

7.1. *In-vitro evaluation methods*

The potential of certain compounds to destroy living cells by necrosis or apoptosis is confirmed by a cell cytotoxicity study. This is a vital tool in pharmaceutical research to identify the compounds causing risk to humans. Markers present in the cytoplasm are the critical indicator entities for identifying viable cells either by an enzyme that behaves as biological markers or artificial markers such as fluorescent or radioactive markers. Those are introduced into the cell to check the cell viability (Riss Niles et al., 2019). The marker enzyme primarily assessed is lactate dehydrogenase which converts pyruvate to lactate with the conversion of NAD^+ to NADH (Decker and Lohmann-Matthes, 1988). Apoptotic markers mostly checked to study cell cytotoxicity are cytochrome-c, Bcl-2/Bcl-xl/Mcl-1, and activated caspases (2, 3, 7, 8, and 9), externalized phosphatidylserine, p53, photo-p53, pH2AX, Apo-1/Fas, fas ligand, and cytokeratins (Ward et al., 2008). These markers are used in the early phase of drug discovery for successful outcomes in pre-clinical research.

Cellular interactions and their interaction with the extracellular matrix are the critical criteria for the function and development of complex organisms. Due to some lacuna in traditionally used 2D culture cell models, 3D models better understand and mimic the cellular behavior by providing more relevant information. 3D tools provide a promising podium for the *in-vitro* building of *in-vivo* behavior for validation and development of various therapies and better precision in drug discovery. VITVO is one of the 3D *in-vitro* models which resembles like *in-vivo* environment and is applied for oncology research (Candini et al., 2019). 3D culture models are more advantageous as they provide cell-cell with extracellular matrix interactions, nutrient oxygen, tissue-specific stiffness, and waste gradients of metabolites (Langhans, 2018); it also provides perspective to co-culture multiple types of cells. Even 3D cultures are used in tissue engineering as they provide more predictive and precise information with promising cellular responses than 2D cell cultures (Edmondson et al., 2014).

Gene expression studies are of utmost importance to study gene or protein expression to understand gene function and its potential mechanism. In diseased conditions, the regulation of the marker genes is crucial in understanding the diseased stage by studying variation in the expression pattern. Even novel genes involved in several cellular processes can be identified in gene expression studies, thus making investigation easy. DNA microarray is an excellent system for evaluating the expression pattern of several genes simultaneously (Chengalvala et al., 2007). Expression studies assess the therapeutic targets by evaluating the upregulation and downregulation of particular genes of interest. For example, in lipopolysaccharide-induced inflammation, TNF-α, interleukin 1β, cyclooxygenases 2 (COX2), and inducible nitric oxide synthase (iNOS) expression of these mentioned genes is studied to check the effect of drug-treated dose on human U937 macrophages cell line (Rafiee et al., 2019). In the case of inflammation studies, the expression of COX2, iNOS, and necrotic factor genes increases, and the effect of a particular drug can be studied by evaluating the expression pattern as effective treatment can be concluded if the expression of genes significantly decreases. Thus, the advances in genomics help obtain gene expression profiling and help screen and identify the efficacy of particular drug entities in disease conditions and their treatment.

Clinical interest is studying the biological system mechanism that responds to physiological and pathophysiological stimuli. Metabolite profiling is a promising candidate in drug development studies by identifying the route of elimination, safety concerns of drugs, and evaluating drug-drug interaction mechanisms (Ufer et al., 2017). In metabolomics fingerprinting, the role of metabolites (drug, microbiome) over the complex system is well studied (Kosmides et al., 2013). Human absorption, distribution, metabolism, and elimination (hADME) studies are performed to obtain metabolite profiling data useful in drug development studies and many pharmaceutical industries use. Thus, metabolic fingerprinting, profiling, and footprinting help understand and evaluate particular diseases and help diagnose illness and risk evaluation. Thus, cell cytotoxicity, cell culture system, expression studies, and metabolomics helps in drug identification studies with toxicity evaluation in pre-clinical studies.

7.2. In-vivo evaluation methods

Rodent and non-rodent mammalian models define the pharmacokinetics and overall safety and discover toxicity patterns. *In-vitro* testing should be reduced because it does not mimic the natural physiological environment and slows the drug discovery process. Compounds can be placed through high-throughput *in-vivo* tests right away, such as cassette dosing, cassette analysis, or a quick rat screen. Assays such as metabolic stability, response phenotyping, CYP-450 inhibition and induction, plasma protein binding, and others can be used to *in-vitro* profile candidates with the appropriate *in-vivo* pharmacokinetic profile (Singh, 2006). Pre-clinical animal studies have been suggested to closely follow the established techniques used in human clinical trials, where defined reporting criteria for statistical power have been imposed, randomization processes, and stratification variables (Laajala et al., 2016). The sample size is crucial for avoiding false-positive findings and determining positive effects in intervention studies. During the drug discovery and development stages, operative and efficacious pharmacokinetics/pharmacodynamics investigations are necessitated with input from scientific professionals in complementary fields in the pharmaceutical business. In most situations, pharmacology laboratories within a disease area do the pharmacodynamic portion of PK/PD research (e.g., animal dosing and response measurement). In contrast, Drug metabolomics and pharmacokinetics laboratories conduct concentration measurements and pharmacokinetics evaluations (Tuntland et al., 2014).

Even though PD is clinically and pathologically diverse, the onset of motor symptoms that lead to clinical diagnosis requires a significant loss of putaminal dopaminergic innervation (Cenci and Bj€orklund, 2020). Accordingly, motor impairments develop when striatal motor areas lose more than 50% of their dopaminergic input in rodent and macaque PD models. A full-blown parkinsonian-like illness seems only after deleting more than 80% of putaminal dopaminergic fibers (Francardo et al., 2011). Several drugs have been shown to cause Parkinson's-like symptoms in animal models, including 6-hydroxydopamine, 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine, Rotenone, and paraquat. The efficacy of a pharmacological entity can be determined by looking at dopamine levels in the brain (Cenci and Bj€orklund, 2020). Traditional transgenic models have played an essential role in investigating carcinogenesis, tumor pathogenesis, and studies into the emergence of therapeutic resistance. Traditional retroviral infection, microinjection of DNA constructs, and the so-called "gene-targeted transgene" strategy are used to silence tumor-suppressor genes in transgenic mice (Lampreht Tratar et al., 2018).

Nonhuman primates like marmosets and mouse lemurs, also very tractable as laboratory models, could conduct basic, pre-clinical testing using CRISPR/Cas9 genome editing. Notably, the mouse lemur develops a neurodegenerative condition similar to AD on its own, which could indicate that it can offer a correct AD model. Even AD-associated APP and PSEN1 transgenic mice were housed in an enriched habitat; they executed restored cognitive skills compared to when housed in regular circumstances (Tadenev and Burgess, 2019). Thus, getting better-diseased models makes it more beneficial to evaluate the efficacy of drugs, especially in complex diseases. Hence, *in-vivo* studies eventually goal to accurately design a model to choose a desired biological effect of a drug in animals to expect treatment outcomes in patients and recognize and illustrate all toxicities related to a drug to predict risk assessment.

7.3. Clinical assessments of drug and its therapeutic administration

It is not always the case that, if the drug passes pre-clinical trials, they are an efficient entity to interact better with human bodies. The drug should pass the clinical trials done with humans. Clinical trials are intended to monitor the outcomes of human volunteers under the unadulterated form of "experimental" settings supervised by the researchers (Umscheid et al., 2011). These are research studies used to evaluate new medications and prevailing drugs, equipment, and other treatments. Many clinical trials appear innovative to sense, spot, and enumerate illness severity. Even few studies find out the preventive measure to the root cause of the particular disease. These procedures are still being tested on humans, and the same rules are applicable. A clinical trial design is frequently preferred because it allows for intervention randomization, essentially eliminating selection bias caused by an imbalance of unknown/immeasurable confounders (Umscheid et al., 2011). Once pre-clinical tests prove that a novel drug/therapy is likely to be operative and not toxic in people, it is approved for human use. They are then tested for clinical trials with an appropriate study population requirement. In clinical studies, placebos are essential for demonstrating that a novel treatment is more operative than a control group. The placebo response relates to the degree of clinical improvement reported by patients allocated to the placebo group (Evans et al., 2021). Clinical trials usually include four testing phases, and once the drug passes the designed phases, it can be further approved for treatment.

8. Modern practices for higher production

Pharmaceuticals are consumed in massive amounts yearly around the globe to prevent, mitigate, diagnose and cure diseases in humans. Pharmaceutical organizations are the significant economic columns of developed countries. Nowadays, people cannot live well without drugs, predominantly in the established nations, whereas this year, the use of drugs for COVID and related disorders is too much higher than the regular requirement. The development of new chemical drugs relies purely on modern technology having a limit and numerous effects on the human body. The development process requires 15–20 years, driven by various technology platforms, to become a marketable therapeutic agent, which is reduced massively in this era. The increase in demand for the drug is fulfilled by the various modern and traditional practices used for higher production of herbal medications, which must be economically feasible and do not affect the biodiversity or food chain. Though the development of a new drug is a complex, costly and lengthy process with a low success rate, whereas capital investment gets double that of the year, only a few of the drugs get approved by the Food and Drug Administration (FDA) (Pan et al., 2013). The development of new methodologies for higher production of purified drugs requires modern technology, which will decrease the cost and time of drug production, which is valued in this modern era. This will involve a comprehensive understanding of the metabolic flux within plants or animals, which helps to drive operations to increase production. Also, some omics technologies such as transcriptomics, genomics, secretomics, metabolomics, and proteomics, along with the combined application of novel engineering strategies, are some recent advances in synthetic biology. Several methods for producing natural products are further involved in higher production, including A) plant tissue cultures techniques B) Animal Cell techniques C) Microbial techniques, also represented in Fig. 4.

8.1. Plants tissue cultures techniques

Nowadays, plant tissue micropropagation focuses on the commercial production of secondary metabolites concerning human welfare. In these techniques, various strategies of genetic interference are included for their effective production. A study reveals that around 420,000 plant species are present on Earth in the current situation; more than 35,000 plant species are used for medicinal purposes as drugs to manage different diseases (Pan et al., 2013). About 80% of the cardiovascular, immunosuppressive, anticancer, and antimicrobial drugs are derived from plant sources (Atanasov et al., 2021). Tremendous use of plant-based drugs increases the exploitation of plant

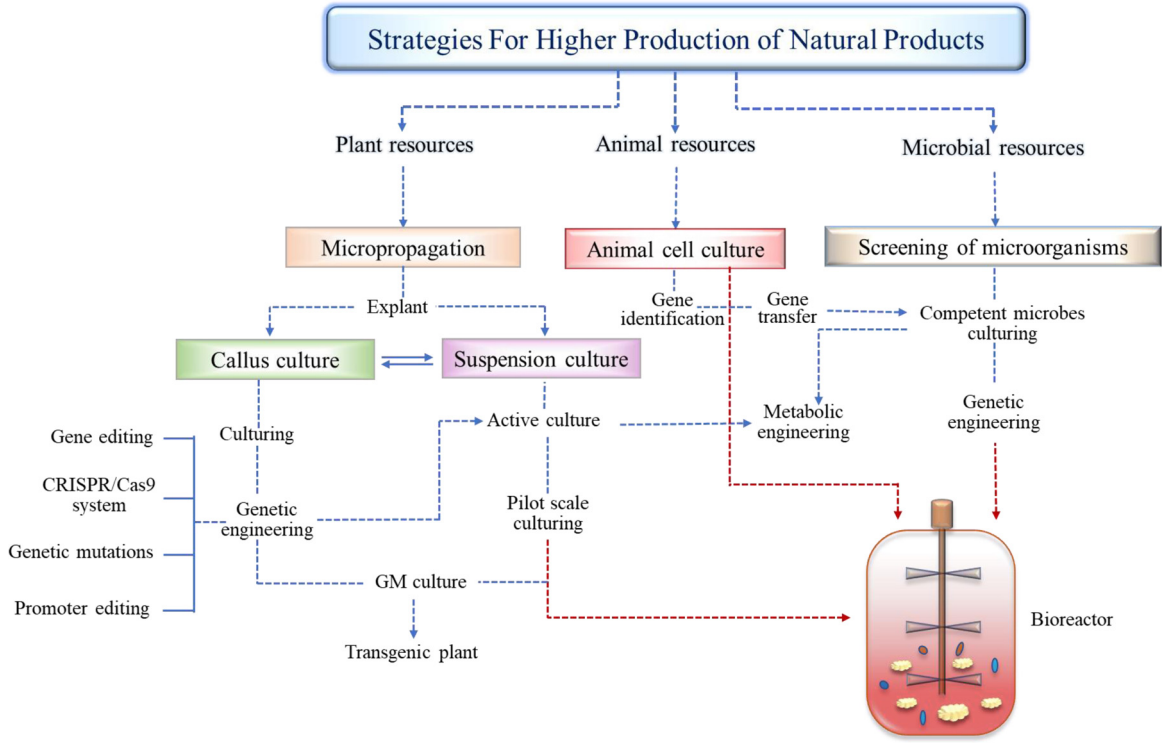

Fig. 4. Various strategies employed for higher production of natural products.

species, which may create a burden on plant existence; this issue can prevail using plant culture techniques. The primary three techniques are used for higher production practices in the modern era, including shoot culture/callus culture, cell suspension culture, and hairy root culture (Wu et al., 2021). There are various industrially important bioactive compounds were extracted by using the plant tissue culture technique were studied by Chandran et al. in their review article (Chandran et al., 2020)

8.1.1. Shoot culture/callus culture

It is a common, reliable, economically feasible technique used to prepare multiple disease-free plantlets, seed production (somatic embryogenesis), cell suspension culture, and production of a large number of phytoconstituents from biomass. The sterile explant from the plant can be cultured in controlled conditions of light, temperature, and humidity to produce undifferentiated cells. The invention of transgene and its consistent expression through the various generation of plants supported by several genetic tools is gaining interest these days for the consistent production of desired compounds. Plant genetic engineering allows plants to produce therapeutic antibodies and other recombinant proteins with selected properties; this recent invention adds a new and quickly developing dimension (Torres et al., 1999). Callus technology may assist in safeguarding rare and endangered plant species by allowing phytochemicals to be extracted directly from calli without sacrificing the entire plant. Hundreds of plant species were studied for their calli production; some of the economically and medicinally essential phytochemicals have been shown in the table (Table 1). Whereas *Catharanthus roseus* (L.) G. Don (Apocynaceae) is one of the valuable medicinal plants rich in metabolites traditionally utilized to control cancer, hypertension, diabetes, and microbial infections were isolated using different callus culture, cell suspension, and hairy root culture techniques (Heijden et al., 2004; Aslam et al., 2010; Moreno et al., 1995). *Coleus forskohlii* (Lamiaceae) is Indian Ayurvedic medicine and industrially important plant which acts as an activator of adenylate cyclase (Forskolin) and is also reported for pharmacological activities where optimized using elicitors like salicylic acid and methyl jasmonate in callus culture and root culture (Mastan et al., 2019).

8.1.2. Cell suspension culture

Although there are various methods to grow Plant cells in-vitro, including hairy roots culture, callus culture, shooty teratoma, immobilized cells, and suspension cell cultures, researchers have concentrated their efforts primarily on suspension cell culture (Motolinía-alcántara et al., 2021). This is most suited to genetically modified plant production protocols and can be grown relatively simply in large-scale bioreactors for natural product synthesis (Hellwig et al., 2004). In cell suspension culture, single-cell or tiny aggregates of cells are formed by agitating friable callus tissue in shaker flasks or fermenters from the callus produced on a solid medium. Distinct elicitors and processors affect different phytochemicals production in cell suspension cultures; the different plants with respective metabolites have been shown in the table (Table 1). The use of elicitors, precursor, biotic and abiotic substances in medium or rDNA technology in a single cell is one of the best ways to increase the production of the desired product. Production of Taxol anticancer drug used in chemotherapeutic medication that slows or stops the development of cancer cells produced by using cell suspension culture is one of the successful significant claims in bioproduction of the drug (Atanasov et al., 2021). *Hypericum perforatum* L. (Hypericaceae) is traditional medicine reported for its antibacterial, antiviral, antifungal, antidepressant, wound-healing, antioxidant properties, etc., by using in vitro cell culture studies (Karuppusamy, 2009).

8.1.3. Hairy root culture

When a plant is infested with bacteria, it creates a variety of metabolites and responds by stimulating the expression of many defense-related proteins and compounds. Hairy roots culture is a type of transformed root culture produced by infecting wounded higher plant roots with *Agrobacterium rhizogenic*. This culture strategy is employed for the small and large-scale production of high efficiency, genetic and biochemical stability with a phytohormone-

Table 1
Scale-up of desired bioactive compounds from various plant species.

Plant species (family name)	Compound name	Yield	References
A) Hairy root culture			
Coleus blumei Benth. (Lamiaceae)	Rosmarinic acid	871.8 mg/L	(Bauer et al., 2015)
Panax quinquefolium (L.) (Araliaceae)	Ginsenoside	35.12 mg/g	(Kochan et al., 2016)
Fagopyrum tataricum (L.) Gaertn. (Polygonaceae)	Rutin	0.85 mg/g	(Huang et al., 2016)
Trachyspermum ammi (L.) Sprague	Thymol	11.30 mg/g	(Vamenani et al., 2020)
Helicteres isora (L.) (Sterculiaceae)	Diosgenin	1034 μg/g	(Kumar et al., 2014)
Catharanthus roseus (L.) Apocynaceae	Vincristine	442.3 ng/mg	(Hanafy et al., 2016)
Pelargonium sidoides DC. (Geraniaceae)	Gallic acid	2430.3 μg/g	(Yousefian et al., 2021)
Pelargonium sidoides DC. (Geraniaceae)	p-coumaric acid	127.61 μg/g	(Yousefian et al., 2021)
Pelargonium sidoides DC. (Geraniaceae)	Vanillic acid	1664.04 μg/g	(Yousefian et al., 2021)
Pelargonium sidoides DC. (Geraniaceae)	Kaempferol	491.72 μg/g	(Yousefian et al., 2021)
Artemisia annua (L.) (Asteraceae)	Artemisinin	25.78 mg/L	(Patra and Srivastava, 2015)
Pelargonium sidoides DC. (Geraniaceae)	p-coumaric acid	127.61 μg/g	(Yousefian et al., 2021)
Stevia rebaudiana Bert. (Asteraceae)	Stevioside	7.13 mg/g	(Ahmad et al., 2020)
Stevia rebaudiana Bert. (Asteraceae)	Rebaudioside-A	0.27 mg/g	(Ahmad et al., 2020)
Stevia rebaudiana Bert. (Asteraceae)	Dulcoside-A	0.001 mg/g	(Ahmad et al., 2020)
Hyoscyamus niger (L.) (Solanaceae)	Anisodamine	0.67 mg/g	(Jaremicz et al., 2014)
Hyoscyamus niger (L.) (Solanaceae)	Scopolamine	5.3 mg/g	(Jaremicz et al., 2014)
Hyoscyamus niger (L.) (Solanaceae)	Hyoscyamine	1.6 mg/g	(Jaremicz et al., 2014)
Hyoscyamus niger (L.) (Solanaceae)	Cuscohygrine	26.5 mg/g	(Jaremicz et al., 2014)
Catharanthus roseus (L.) (Apocynaceae)	Vincristine	442.3 ng/mg	(Hanafy et al., 2016)
Agastache foeniculum Blue Giant Hyssop (Lamiaceae)	Rosmarinic acid	213.42 μg/g	(Nourozi et al., 2014)
Chlorophytum borivilianum Santapau & R. R. Fern. (Anthericaceae)	Hecogenin Stigmasterol	83.952 mg/g	(Bathoju et al., 2017)
Artemisia dubia Wall. ex Besser (Asteraceae)	Artemisinin	79 ± 3 μg/g	(Ali, 2012)
Dracocephalum kotschyi Boiss. (Lamiaceae)	Xanthomicrol	0.95 μg/g	(Nourozi et al., 2019)
Ocimum basilicum (L.) (Lamiaceae)	Rosmarinic acid	71.03 mg/g	(Srivastava et al., 2016)
Gentiana scabra Bunge (Gentianaceae)	Loganic acid	6.94 mg/g	(Huang et al., 2014)
Plumbago europaea (L.) (Plumbaginaceae)	Plumbagin	3.2 mg/g	(Beigmohamadi et al., 2020)
Polygonum multiflorum Thunb (Polygonaceae)	Physcion	353.23 μg/g	(Thiruvengadam et al., 2014)
Salvia austriaca Jacq. (L.) (Lamiaceae)	Abietan diterpenes	5.56 mg/g	(Kuźma and M., 2017)
Salvia austriaca Jacq. (Lamiaceae)	Abietan diterpenes	7.27 mg/g	(Kuźma and M., 2017)
B) Shoot culture/Callus culture			
Salvia officinalis (L.) (Lamiaceae)	Rosmarinic acid	26.24 mg/L	(Grzegorczyk and Wysokińska, 2010)
Mucuna Imbricata (L.) (Fabaceae)	L-DOPA	0.043 mg/g	(Suryawanshi et al., 2022)
Bacopa monnieri (L.) (Plantaginaceae)	Bacoside	10.15 mg/g	(Sharma et al., 2015)
Salacia chinensis (L.)	Mangiferin	8.493 mg/g	(Chavan et al., 2021)
Catharanthus roseus (L.) (Apocynaceae)	Ajmalicine	34 mg/L	(Thakore et al., 2017)
Leucojum aestivum (L.) (Amaryllidaceae)	Galantamine	3.1 mg/L	(Ivanov et al., 2019)
Dracocephalum forrestii W.W.Sm (Lamiaceae)	Rosmarinic acid	19.90 mg/g	(Weremczuk-Jeżyna et al., 2019)
C) Cell suspension culture			
Mucuna monosperma (Fabaceae)	L-DOPA	200 mg/L/h	(Inamdar et al., 2013)
Swertia minor (Griseb.) Knobl	Swertiamarin	1.45 mg/g	(Kshirsagar et al., 2021)
Ocimum basilicum (L.) (Lamiaceae)	Rosmarinic acid	15.73 mg/g	(Pandey et al., 2019)
Harpagophytum procumbens DC (Pedaliaceae)	Verbascoside	165.42 mg/L/day	(Georgiev et al., 2011)
Pueraria candollei var. mirifica Niyomdham	Deoxymiroestro	976 μg/g	(Udomsin et al., 2020)
Pueraria candollei var. mirifica Niyomdham	Isoflavonoid	587 μg/g	(Udomsin et al., 2020)
Ocimum basilicum (L.) (Lamiaceae)	Betulinic acid	14.63 mg/g	(Pandey et al., 2019)
Santalum album (L.) (Santalaceae)	Squalene	5.5 mg/g	(Rani et al., 2018)
Tolypocladium geodes Z.Gams(Ophiocordycipitaceae)	Malettinins B	18.2 mg/L	(Kebede et al., 2017)
Satureja khuzistanica Jamzad (Lamiaceae)	Rosmarinic acid	3.9 g/L	(Khojasteh et al., 2016)
Verbana officinalis (L.) (Verbenaceae)	Verbascoside	95.16 mg/g	(Kubica et al., 2020)
Catharanthus roseus (L.) G. Don (Apocynaceae)	cyclodextrins	162.30 mg/L	(Almagro et al., 2014)
Catharanthus roseus (L.) G. Don (Apocynaceae)	Ajmalicine	850.09 mg/L	(Almagro et al., 2014)
Crocus sativus (L.) (Iridaceae)	Crocin	0.22 mg/L	(Moradi et al., 2020)
Helicteres isora (L.) (Malvaceae)	Diosgenin	8.64 mg/L	(Shaikh et al., 2020)
Artemisia annua (L.) (Asteraceae)	Artemisinin	9.33 mg/L	(Salehi et al., 2019)
Camptotheca acuminata Decne (Nyssaceae)	Camptothecin	2.03 smg/L	(Yang et al., 2017)
Ocimum basilicum (L.) (Lamiaceae)	Rosmarinic acid	12.32 mg/g	(Açıkgöz, 2021)
Ocimum basilicum (L.) (Lamiaceae)	Chicoric acid	4.52 mg/g	(Açıkgöz, 2021)
Ocimum basilicum (L.) (Lamiaceae)	Rutin	6.78 mg/g	(Açıkgöz, 2021)
Ocimum basilicum (L.) (Lamiaceae)	Isoquercetin	4.12 mg/g	(Açıkgöz, 2021)
Vitis amurensis Rupr. (Vitaceae)	Resveratrol	53.881 mg/L	(Sun et al., 2016)
Vitis amurensis Rupr. (Vitaceae)	Resveratrol	72 mg/L	(Nivelle et al., 2017)
Vitis amurensis Rupr. (Vitaceae)	Resveratrol	66 mg/L	(Chastang et al., 2018)
Nicotiana tabacum (L.) (Solanaceae)	Nicotine	14.9 mg/L	(Awad et al., 2011)
Ophiorrhiza mungos (L.) (Rubiaceae)	Camptothecin	0.8 mg/g	(Deepthi and Satheeshkumar, 2016)
Satureja khuzistanica Jamzad (Lamiaceae)	Rosmarinic Acid	38.0 mg/g	(Sahraroo et al., 2016)
Vitis vinifera (L.) (Vitaceae)	Resveratrol	277.89 μg/g	(Sae-Lee et al., 2014)

independent growth approach. A mouse monoclonal antibody was produced in the tobacco plant as the first proof of concept for hairy root culture in antibody production by Wongsamuth and Doran 1997 (Wongsamuth and Doran, 1997). Enormous research on hairy root culture for the production of various compounds like human acetylcholinesterase, recombinant alpha-L-iduronidase, green fluorescent protein, and thaumatin sweetener has been mentioned in the table (Table 1) (N. Gutierrez-Valdes et al., 2020). A recent review of current development on the therapeutic potential of hairy root culture focused on bioactive compounds present in various plants (Shi et al., 2021; N. Gutierrez-Valdes et al., 2020). However, *Ocimum*, a traditionally important genus (Ayurveda, Unani, Siddha, and Homeopathy), was previously studied and well known for managing diabetes, liver problems, malaria, and rich source antioxidants by micropropagation (Pandey et al., 2021).

9. Scale-up and its commercialization

The accomplishment of product commercialization is mainly focused on the availability of resources, effective scale-up processes, and a profitable downstream method that will provide product profits to customers and create economic profit for investors (Bisaria and Panda, 1991). Preferably, after lab-scale production (0.5–10 L fermenters), scale-up is done in two stages, including pilot plant (pilot scale) with 100–10,000 L and demonstration plant (demo-scale) with 10,000–100,000 L (Crater and Lievense, 2018). Conversation of lab scale to pilot scale is a realistic scaled-down form of the manufacturing procedure, which is not integrated most of the time. Production of eco-friendly Polyhydroxybutyrate (PHB) at pilot and industrial scale for its diverse applications has been evidenced by Suryawanshi et al. (2020).

The number of operational issues to be considered during the design and scale-up of large-scale manufacturing of plant-derived natural bioactive molecules. The culture systems ensure a steady supply of metabolites to efficiently produce desired molecules, whereas management of production conditions is now considered a technical challenge (Lonsane et al., 1992). Various scale-up parameters affect bioreactor productivity, including biomass formed, large-scale inoculum development, medium sterilization, and several other physical parameters consisting of aeration, agitation, heat removal, moisture content, pH, contamination control, heterogeneity, and waste management. Maintaining all these essential parameters in the demo scale is difficult, making the job more challenging and failing in the batch culture (Lonsane et al., 1992). Digitoxin and digoxin are pharmaceutical important compounds extracted from leaves of *Digitalis lanata* Ehrh. (Plantaginaceae) commonly used for the treatment of heart diseases were optimized for their scale-up using airlift reactors in a previous study (Spieler et al., 1985).

9.1. Factors affecting the performance of scale-up

Essential elements that contribute to the positive effect on scaling-up of pilot projects need to be considered to scale up the process. Numerous parameters influence the performance of the scale-up process, mainly including the grade of raw material and its sterilization, fermenter mixing time, broth hydrostatic pressure, gas-liquid volumetric mass transfer coefficient, broth handling, etc. (Taticek et al., 1991). Unsuccessful scale-up results in the diminution of time consumed, laboratory cost for scale-up work, and economic failure. Developing engineering techniques for discovering and producing new compounds, identifying metabolic building blocks, and improving genome editing capabilities through synthetic biology can yield significant benefits and solutions for long-term processes (Reisman, 2008). Recent process engineering strategies have revolutionized production systems for various products. The advancement in artificial intelligence technologies, data science and modeling, selective gene-editing tools, and the development of standardized synthetic regulatory elements contribute to the synthesis of NPs with the transformed microbial community in the future. Furthermore, these advancements have gained popularity due to several benefits, including a quick and versatile production of a diverse array of high-value products with fewer competing intermediates (Jackson, 2010).

Three main guiding ethics are serious to the effective scale-up of the plant metabolites production system. Skilled project teamwork based on chemistry, biology, and engineering molds; who builds process flow diagrams, energy, and material equilibriums, unit operation designs, and techno-economic models of the plant needs before the starting lab experiments (Jackson, 2010). It is tough to create identical conditions in the lab as they are at the lab level and require special attention because many components interact in the production environment, which majorly affects production. The third guiding principle includes being prepared for the challenges of microbial contamination, utility interruptions, equipment failure, variable raw material quality, fouling of process equipment, and surprising reduced performance at scale (Reisman, 2008). The hardware configuration and internal environment optimization for the commercialization of plant bioreactors were explained in detail by (Georgiev and Weber, 2014) in their research evidence.

9.2. The significance of scale-up

Scale-up is the important connection between transferring a laboratory-scale method to commercial-scale production. Scaling-up is not only up-gradation to a large-scale production scheme; it is the journey of developing a robust full-scale manufacturing plant that meets its commercial objectives with desired products (Ochoa-Villarreal et al., 2016). It is best to get optimum products in less-expensive functioning processes with efficiency and simplicity by increasing the capability of existing hardware. Scale-up helps to upgrade the resources that are simple to implement and easy to manage, which will also conserve energy by reducing the demand for physical equipment. Systems take advantage of processors intended specifically for numerical computation or high-end application program applications that are error-free, automatic, and cost-effective (Dhobale et al., 2018).

10. Conclusion and future prospective

Natural products will continue to be a reliable source for pharmaceutical drug invention. Finding the correct technique for drug development from biological substances is very crucial. Most findings are part of the constant effort from herbal remedies to commercial medications. This is a well-known fact that researchers explored chemicals that could perform a therapeutic approach from herbal medicines. Although indigenous knowledge concerning plants and pharmacological assisted drug development from natural products is more convenient, these approaches are time-consuming and have poor productivity. Plant-based novel therapeutics assist researchers in developing new medications by revealing harmful effects.

Innovative approaches are required for the development of medication from natural products. To accomplish these, novel methodologies focused on the natural product have aided in the discovery and development process, converting natural compounds into active pharmaceuticals. In this context, technical advancements have enabled the study of complicated chemical characteristics, leading to the development and synthesis of many molecules. Several breakthrough medications have been recently produced from natural substances or components derived from natural resources. These retained natural products at the center of medication development and recent technology advancements will help to boost the performance rate of novel therapeutic molecules. Consequently, natural substances will continue to perform an essential role in medication

development and in our efforts to address public health issues and achieve health-related sustainable and economic development.

However, substantial clinical competence and cognitive reasoning are required. Biological compounds generated from microorganisms' resources can have limitations, such as higher toxicological properties. The drug development from microbes is complex and requires superb dereplication strategies. Almost all valuable natural compounds result from the cellular biosynthesis of secondary metabolites. The primary approach for natural drug development consists of pathogenic factors, target receptors, and disease-induced animal models that are more convenient than the other drug development strategies. Infectious agents and hideous diseases limit the drug development process based on natural compounds. The perfect animal model needs to be established with arduous effort for such a challenging context. Intrinsic biomolecules also serve as a model for developing novel medications, enabling researchers to optimize natural molecules' activity and toxicity. Drug development from the natural product can make tremendous advances due to the continued exploration of disease-related mechanisms. With the advent of modernistic techniques, there is new hope for higher success rates of the new drug. As research progresses, more advanced molecular technologies are revealed, supporting the investigation of active chemical mechanisms. We can use network pharmacology and computational biology to quickly identify the active ingredients in natural remedies.

Further, the hypotheses are then confirmed using pharmacological testing. The next biotechnological advancement will expand natural products' biochemistry with molecular understanding. The remarkable improvement in biological sciences and technology has expedited drug development using cellular and molecular experiments from natural ingredients. Even though natural products play an essential function in developing new medications, natural product-based drug development faces several challenges. Natural product medication development is becoming increasingly complex. The key to success in natural product drug discovery and development will be an integrative approach that combines various discovery tools and the new discipline of integrative biology. More focus should be directed to innovative drug discovery methodologies and technology. The critical components for eventual accomplishment in this practice are thorough monitoring, critical analysis, and innovation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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