International Journal for Multidisciplinary Research (IJFMR)
E-ISSN: 2582-2160 ● Website: www.ijfmr.com ● Email: editor@ijfmr.com

Naturalproduct/ Phytopharmacology

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ABSTRACT:
Natural products (NPs) have long been used as a rich source of bioactive compounds for drug development. Recent technological advancements have revitalised natural products research as evidenced by increased publications in this field. In this editorial review, we highlight key points from the 2020 British Journal of Pharmacology (BJP) practical guide, which outlines standards for natural products research reports, and provide papers published in BJP between years 2020 to 2023 that demonstrate adherence to these guidelines. Looking ahead, we discuss the potential of chemical proteomics approaches to elucidate natural products mechanisms of action and identify therapeutic targets for future research. By fostering innovation, we aim to advance natural products research and contribute to the development of novel therapeutics that will have a significant impact on healthcare.

INTRODUCTION

Natural products are the part of the human living system since the time origin. Plants give numerous products for human needs, most of them good and beneficial. Everything such as food, shelter, clothes, medicines, fuels, etc. comes out from plants directly and indirectly. Plant are the milestones of all living entities on this planet and an important resource for all living organisms as well as humans. Medicinal plants as a part of traditional remedies possess the key role of human health care. Neanderthal made medicine by using medicinal plant and it is shown in molecular evidence. Modern human also implies medicinal plant and their part for the treatment of disease in the form of herbal medicine. It is not possible to pinpoint the percentage of traditional medicine use around the globe, evidence showed that the majority of the population in developing nations consistently based upon natural medicine and 50% of population rely on natural products in developed countries. Most of organic molecules has been developed from the plant part. From 1981 to 2002, 45% of drugs have been approved for infectious diseases that are obtained from the natural product as well as tropical forests contributed as 25% for the development of medicine. A phenolic compound such as phenolic acid flavonoids, tannins, stilbenes, coumarins, lignans, and lignins are mainly present in part of natural products that show multiple biological effects. In our routine nutraceutical diet like turmeric, cardamom, garlic, onion, ginger, tulsi, cloves, etc. contain medicinal value which is historically used for treatment of various diseases . (1)

Nature always stands as a golden mark to symbolize the significant phenomenon of sembiosis. Natural products derived from vanous sources of plant, animal and minerals have been the basis of treatment of human disease.(2)

The term medicinal plant includes various types of plants which contain substances that can be used for therapeutic purposes, or which are precursors for chemo-pharmaceu tical semi-synthesis. These medicinal plants consider as a rich resources of ingredients which can be used in drug development and synthesis.(2)

A plant is designated as 'medicinal' due to its use as a drug or therapeutic agent or an active ingredient of a medicinal preparation. Medicinal plants may be defined as a group of plants that possess some special

properties or virtues that qualify them as articles of drugs and therapeutic agents and are used for medic-inal purposes.(2)

The term herbal drugs denotes plants or plant parts that have been converted into phytopharmaceuticals by means of simple processes involving harvesting, drying, and storage. Hence they are capable of variation. This variability is also caused by differences growth, geographical location, and time of harvesting. Medical herbs and its application. (2)

Several problems not applicable to synthetic drugs often influence the quality of herbal drugs. For instance.(2)

- Herbal drugs are usually mixtures of many constituents.
- The active principle(s) is (are) in most cases unknown.
- Selective analytical methods or reference compounds may not be available commer cially.(2)

VARIOUS SOURCES OF NATURAL PRODUCTS

Natural products come from a wide variety of sources, including plants, microorganisms (like bacteria and fungi), marine organisms, and animals. These substances, found in nature without significant human modification, are used in many fields, from medicine to agriculture and cosmetics. (3)

Major sources of natural products:

1. **Plants:** Plants are a rich source of natural products and have been used for medicine, food, and materials for centuries. Examples include morphine from the opium poppy and quinine from the Cinchona tree bark, as noted by Frontiers.(4)
2. **Microorganisms**: This category includes bacteria, fungi, and other microbes. Microorganisms are crucial sources of natural products like antibiotics, and they are actively studied for new drug candidates.(5)
3. **Marine organisms**: The ocean is a source of unique natural products from organisms such as sponges, algae, and corals. The diversity of marine life offers a vast and largely untapped reservoir for new compounds.(6)
4. **Animals**: While less common due to extraction challenges, some natural products are derived from animals. Examples include compounds used in research and traditional medicine.(7)
5. **Symbiotic and endophytic organisms**: These are microorganisms that live in or on other organisms, such as plants. They can produce unique natural products as part of their symbiotic relationship, making them an important, though specialized, source.(8)

CURRENT STATE OF NATURAL PRODUCTS

Natural products have been playing a vital role in health care for decades. Since ancient times, natural products represent the main source of compounds employed in drug discovery and development. From thousands of years nature has been a rich resource of beneficial biological agents and remarkable number of recent drugs has been resulting from natural sources grounded for their traditional medicine value. Natural products have played central part in treatment and prevention of human diseases during thousands of years. Remedies based on natural substances come from different sources, among them terrestrial plants and microorganisms, sea macro and microorganisms, as well as terrestrial invertebrates and vertebrates. Nature opened promising avenues for the treatment of great variety of diseases byproviding the mankind with a diversity of small bioactive compounds.The top most marketing drugs from the last century have been developed from natural products (Taxol from T. brevifolia, vincristine from Vinca rosea and

morphine from Papaver somniferum etc.). The prominent revival of interest has been witnessed among academic world as well as pharmaceutical companies in recent years for natural products as novel drugs sources. Around 40% of recent drugs in practice have been developed from natural products.(9)

SHORT SUMMARY OF THE TREND (2000 → 2025)

Nationally, India's herbal / AYUSH related exports have grown substantially since the early 2000s - driven by spices, raw medicinal plants (ashwagandha, tulsi, boswellia), herbal extracts and value-added Ayurvedic products. Several reports estimate steady growth in the decade 2010-2025 with rising global demand.

Maharashtra is a leading state for agri/processed agricultural exports and has increased its contribution to India's agro/food & related exports in FY 2024-25 (record year for the state). That same export push has supported greater shipments of turmeric/other spice & plant products and value-added herbal preparations from the state.

Central & sectoral bodies (NMPB/Ministry of AYUSH / APEDA / DGCIS) have been publishing data and schemes encouraging cultivation & export of medicinal plants and herbal products meaning both production and export infrastructure improved markedly after 2014 (Ministry of AYUSH) and especially in 2018-2025 with targeted programmes.

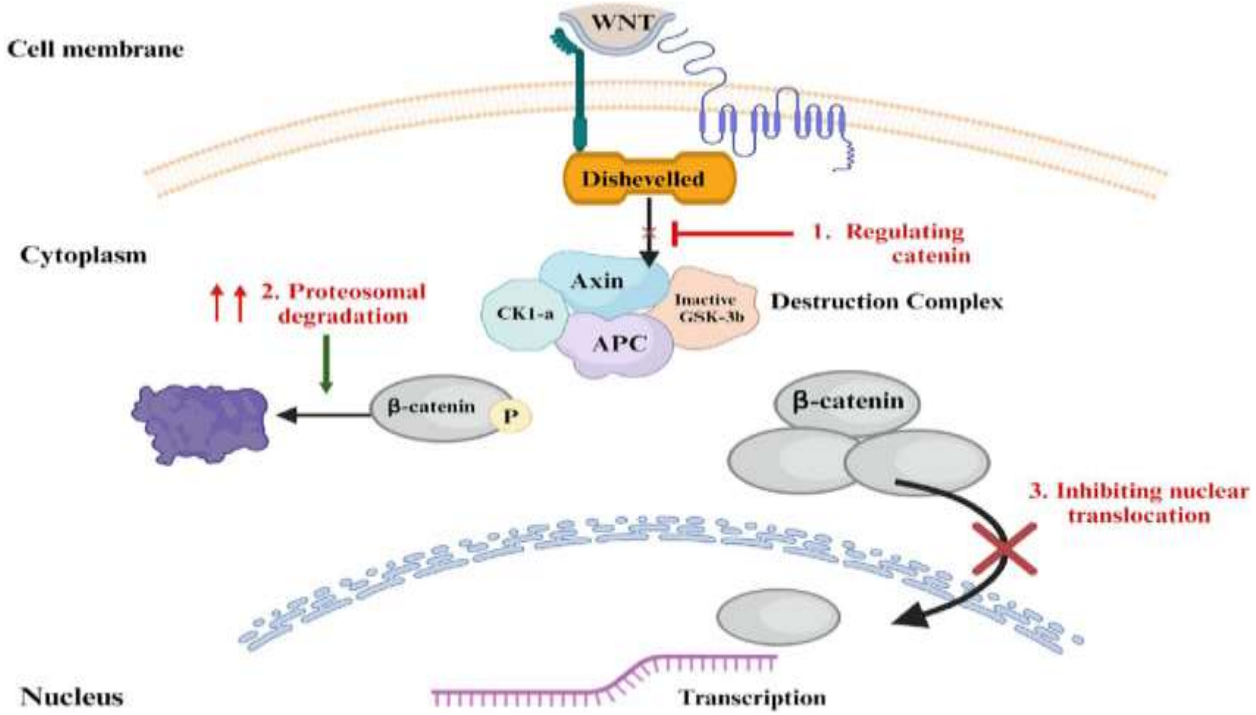
Short take: expect a gradual upward trend from 2000-2010, stronger growth 2010-2020, and noticeable gains 2020-2025- but precise yearwise Maharashtra figures must be pulled from customs / DGCIS/APEDA / state economic surveys because national aggregates mask state differences.

MECANISM OF NATURAL PRODUCTS

Natural products exert their effects through diverse mechanisms, including binding to specific cellular targets like enzymes, receptors, or ion channels, or interacting with nucleic acids to influence cellular processes. Many natural products act on complex cellular machinery, such as bacterial cell walls or ribosomes, and their complex structures can lead to polypharmacology, where a single compound affects multiple targets, which can be beneficial in fighting resistance. (10)

Molecular mechanisms:

1. **Enzyme inhibition**: Many natural products function by inhibiting specific enzymes. For example, penicillin works by inhibiting bacterial cell wall synthesis, while digoxin affects the sodium-potassium pump in cardiac cells.
2. **Receptor binding**: Some natural products bind to cellular receptors. Opioid alkaloids like morphine and codeine bind to opioid receptors to relieve pain.
3. **Ion channel modulation**: Certain natural products can modulate ion channels, which are critical for cell signaling. For instance, digoxin affects the sodium-potassium pump, a key ion transporter in the heart.
4. **Interaction with nucleic acids**: Some natural products can directly interact with DNA and influence processes like replication and transcription.
5. **Targeting cellular machinery**: Natural products can also target large, complex structures. Antibiotics often target essential machinery like the ribosome, DNA gyrase, or RNA polymerase.(10)



CLINICAL EVIDENCE

Phytopharmaceuticals — have long been used for therapeutic purposes. Modern clinical evidence supports their efficacy and safety for several health conditions. Below is an overview (11)

1. Meaning of Clinical Evidence

Clinical evidence refers to scientifically validated data obtained from human studies (clinical trials, observational studies, and meta-analyses) that evaluate the safety, efficacy, and pharmacological effects of natural products in treating diseases.(12)

TYPES OF CLINICAL STUDIES ON NATURAL PRODUCTS

Type Of Study	Description	Examples
Randmized Controlled Trials (RCTs)	Participants randomly received natural product or placebo; provides high quality evidence.	Curcumin vs.placebo in osteoarthritis.
Obeservational studies	Observes effects in real –word settings withot intervention.	Used of green tea and reduced cancer risk.
Meta-analysis and systematic reviews	Combined results of multiple studies to assess overall efficacy.	Ginkgo biloba in cognitive decline.

3. Examples of clinically proven natural products

Natural Products	Active Constituents	Clinical Evidance/Uses
Curcuma longa (Turmeric)	Curucumin	Shown in RCTs to reduce inflammation and pain in

		osteoarthritis and rheumatoid arthritis.
Panax ginseng	Ginsenosides	Improves mental performance, fatigue, and immune function in several clinical studies.
Ginkgo biloba	Flavone glycosiodes terpenoids	Used for memory enhancement and dementia; meta-analyses support mild benefit in Alzheimer's disease.
Allium sativum (Garlic)	Allicin	Clinical evidence supports cholesterol-lowering and antihypertensive effects.
Green tea (Camelli sinensis)	Catechins (EGCG)	Clinical trials show antioxidant, anti-obesity, and anticancer potential.
Aloe vera	Polysaccharides ,anthraquinones	Shown effective for wound healing, burns, and skin hydration.
Hypericum perforatum (St. John's Wort)	Hypericin ,hyperforin	Comparable efficacy to SSRIs in mild to moderate depression, but interacts with many drugs.
Milk thistle (Silybum marianum	Silymarin	Clinically beneficial in liver disorders like hepatitis and cirrhosis.
Echinacea purpurea	Alkylamides ,caffeic acid derivatives	Reduces severity and duration of common cold symptoms. (13)

4. Importance of Clinical Evidence

- Ensures scientific validation of traditional remedies.
- Confirms dose, efficacy, and safety in humans.
- Provides basis for regulatory approval (e.g., phytopharmaceuticals, nutraceuticals).
- Helps prevent adverse drug interactions and misuse.(14)

5. Integration with modern drug development

Drug discovery is a highly intricate and lengthy process that requires the identification of potential drug candidates that can effectively treat various diseases. The use of AI has brought a significant shift in the approach to drug discovery. AI has fundamentally transformed the pharmaceutical industry by speeding up the drug discovery process, improving precision, and decreasing costs. In this review, we will explore the different types of AI techniques used in drug discovery, including ML (to predict drug properties, identify potential drug candidates, and optimize chemical structures), DL (to analyze large-scale biological data, predict drug properties, and identify potential drug candidates), NLP (to analyze the scientific literature for potential drug candidates and to generate drug summaries), GM (to generate new molecules

that could potentially be drug candidates), and network-based approaches (to identify potential targets for drug development).(15)

1) Artificial Intelligence (AI) in Discovering New Drugs

In the field of medicine, there are two types of AI applications: physical and virtual. Physical applications include the following: robot-assisted surgery, AI-enhanced prosthetics, real-time patient monitoring, and automated laboratory processes.

For example, AI in robot-assisted surgery can provide medical professionals with relevant information to assist them in making more informed decisions. While AI cannot replace human doctors, it can enhance their capabilities and improve patient care. Thus, AI-powered surgical robots enable surgeons to perform complex procedures with greater precision, control, and flexibility. These robots can reduce the risk of complications, minimize invasiveness, and shorten recovery times, leading to better surgical outcomes . On the other hand, AI-driven prosthetics are designed to adapt to the user's movements and respond to their neural signals. These advanced prosthetics significantly improve the quality of life for amputees, allowing them to perform complex tasks with greater ease and naturalness. AI-based monitoring systems continuously analyze patient data, such as their vital signs and electronic health records, to identify potential signs of deterioration or complications. This enables healthcare providers to intervene on time and avert adverse events. Studies have also shown that AI-based algorithms can outperform human doctors in certain diagnostic tasks, such as detecting certain types of cancer or interpreting pulmonary function tests . Some automated laboratory processes, such as AI-powered robotic systems that streamline and automate laboratory processes, include sample analysis, sorting, and preparation. This reduces the workload for laboratory staff and minimizes the risk of human errors, ensuring more accurate results.(16) Drug Discovery and Development belong to the Virtual Applications category, together with diagnostic assistance, personalized treatment plans, and virtual health assistants. Virtual AI applications aid healthcare professionals in diagnosing diseases more accurately and efficiently. AI algorithms can analyze medical imaging data, such as X-rays, CT scans, and MRI images, to detect abnormalities and assist in early disease detection . This capability translates to a significantly reduced chance of misdiagnosis and leads to better patient outcomes. The power of AI lies in its ability to process and analyze large amounts of medical data, spotting patterns that may not be immediately visible to humans. In doing so, AI can help improve diagnostic accuracy and develop personalized treatment plans. In particular, DL algorithms can identify anomalies or potential diseases in medical images, which can assist radiologists in their interpretations . For instance, AI has proven useful in the field of gastroenterology by detecting abnormal structures in endoscopy and ultrasound images, such as colonic polyps . Additionally, AI-powered wearable devices can remotely monitor patients and provide real-time data to healthcare professionals, offering early intervention opportunities. These devices have even been developed to detect and notify caregivers about seizures in epilepsy-suffering patients . Also, AI-powered virtual applications can analyze an individual's health data, including their genetics , medical history , lifestyle factors], and current health status, to create personalized treatment plans. These plans can optimize their medication dosage, predict their treatment response, and recommend targeted therapies, ensuring more effective and personalized patient care. AI can also contribute to precision medicine by analyzing a patient's genetic data and medical history to predict their disease risk, determine optimal treatment plans, and identify potential drug targets. Moreover, virtual health assistants, powered by AI, offer patients 24/7 support and personalized health advice . They can answer medical queries, remind patients about medication

schedules, and provide lifestyle recommendations, promoting patient engagement and proactive healthcare management. (17)

AI in designing drug molecules

Prediction of the target protein structure

While developing a drug molecule, it is essential to assign the correct target for successful treatment. Numerous proteins are involved in the development of the disease and, in some cases, they are overexpressed. Hence, for selective targeting of disease, it is vital to predict the structure of the target protein to design the drug molecule. AI can assist in structure-based drug discovery by predicting the 3D protein structure because the design is in accordance with the chemical environment of the target protein site, thus helping to predict the effect of a compound on the target along with safety considerations before their synthesis or production [18]. The AI tool, AlphaFold, which is based on DNNs, was used to analyze the distance between the adjacent amino acids and the corresponding angles of the peptide bonds to predict the 3D target protein structure and demonstrated excellent results by correctly predicting 25 out of 43 structures.

In a study by AlQurashi, RNN was used to predict the protein structure. The author considered three stages (i.e., computation, geometry, and assessment) termed a recurrent geometric network (RGN). Here, the primary protein sequence was encoded, and the torsional angles for a given residue and a partially completed backbone obtained from the geometric unit upstream of this were then considered as input and provided a new backbone as output. The final unit produced the 3D structure as the output. Assessment of the deviation of predicted and experimental structures was done using the distance-based root mean square deviation (dRMSD) metric. The parameters in RGN were optimized to keep the dRMSD low between the experimental and predicted structures [19]. AlQurashi predicted that his AI method would be quicker than AlphaFold in terms of the time taken to predict the protein structure. However, AlphaFold is likely to have better accuracy in predicting protein structures with sequences similar to the reference structures [20].

- **AI in advancing pharmaceutical product development**

The discovery of a novel drug molecule requires its subsequent incorporation in a suitable dosage form with desired delivery characteristics. In this area, AI can replace the older trial and error approach [21]. Various computational tools can resolve problems encountered in the formulation design area, such as stability issues, dissolution, porosity, and so on, with the help of QSPR [22]. Decision-support tools use rule-based systems to select the type, nature, and quantity of the excipients depending on the physicochemical attributes of the drug and operate through a feedback mechanism to monitor the entire process and intermittently modify it .Guo et al. integrated Expert Systems (ES) and ANN to create a hybrid system for the development of direct-filling hard gelatin capsules of piroxicam in accordance with the specifications of its dissolution profile. The MODEL EXPERT SYSTEM (MES) makes decisions and recommendations for formulation development based on the input parameters. By contrast, ANN uses backpropagation learning to link formulation parameters to the desired response, jointly controlled by the control module, to ensure hassle-free formulation development [23].Various mathematical tools, such as computational fluid dynamics (CFD), discrete element modeling (DEM), and the Finite Element Method have been used to examine the influence of the flow property of the powder on the die-filling and process of tablet compression 21 ,22 CFD can also be utilized to study the impact of tablet geometry on its dissolution profile [24]. The combination of these mathematical models with AI could prove to be of immense help in the rapid production of pharmaceutical products.

- **Artificial Intelligence Applications**

One of the critical AI breakthroughs was IBM Watson, whose development led to DeepQA software, a computer system that mim-ics successful competition at the quiz show Jeopardy compared to top players at Jeopardy! Quiz show (www.jeopardy.com). They used unstructured and structured data to answer questions logi-cally through natural language- processing such as DeepQA, which utilizes various models that scored based on a training set using multilayer logistic regression and screening through a testing set [25]. In the drug discovery field, this IBM Watson system has been extensively used by Pfizer to accelerate the search for drugs of im-muno-oncology conditions.

Application of AI-assisted computational models in drug dis-covery investigated by José Jiménez-Luna. et al., in ligand-based quantitative structure-activity and property (QSAR/ QSPR) and De Novo drug design. In the case of QSAR/QSPR, the prediction of pharmacokinetic parameters and biological activity showed suc-cessful progress and molecular descriptors are used to present ma-chine-readable numbers that are indicative of molecules' structural features such as functional groups, pharmacophore distribution, and physicochemical properties [26]. Computer-assisted de novodrug design is challenging, with ligand and/or structure-based be-ing the most known approach to designing novel molecular profiles with effective pharmacological potency and properties [26,27]. AI can identify hit and lead compounds with faster validation of the drug target and can also assist in predicting a targeted protein 3D structure [28]. PDB bind is a database that details the protein-li-gand structure complex [29]. Leveraging artificial intelligence AI and machine learning with the biology knowledge of a single cell level can produce unprecedented solutions in drug discovery and development by enhancing biomarker prediction and the discov-ery of drug candidates with high-quality and disease-associated targets; for this purpose, HiFiBiO Therapeutics has established a novel translational platform of Drug Intelligence Science (DIS) in-tegrating AI/ML with single-cell technology , resulting in the translation of high-resolution outcomes related to drugs, targets and patients.(30,31)

Conclusion:

Natural products continue to play a crucial role in drug discovery and the development of therapeutic agents. Their structural diversity, biological activity, and natural availability make them valuable sources for novel pharmaceuticals. The study of natural products helps in understanding the chemical composition, pharmacological properties, and mechanisms of action of bioactive compounds derived from plants, animals, and microorganisms.

Advances in modern analytical techniques, such as chromatography, spectroscopy, and molecular biology tools, have enhanced the identification, isolation, and characterization of natural constituents. Moreover, increasing scientific evidence supports the therapeutic potential of natural products in treating various diseases, including cancer, infections, inflammation, and metabolic disorders.

Overall, natural products remain an indispensable foundation for new drug leads, complementary medicine, and the discovery of safer and more effective therapeutic agents. Continued research is essential to explore their full potential, ensure quality and safety, and develop standardized formulations for clinical use.

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