International Journal of Pharmacognosy and Herbal Drug Technology (IJPHDT)
ISSN: 3049-1630, Vol.02, Issue No. 09, 2025 (pp.31-43)
AKT PUBLICATION
ORIGINAL ARTICLE
https://www.aktpublication.com/index.php/ijphdt

Novel Therapeutic Mediators: The Intersection of Pharmacognosy and Ethnopharmacology

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ABSTRACT

Methodically screening and successfully validating new natural materials as medicines begins with the intersection of these two fields, ethnopharmacology and pharmacognosy. New natural remedies have been developed as a result of traditional knowledge of plants, minerals, and animals. Ethnomedicine is the source of many of the most clinically significant medications used today, including morphine, quinine, and artemisinin. The pharmacological properties, modes of action, and safety profiles of bioactive chemicals are evaluated by controlled, biopharmaceutical, pre-clinical, and in vivo research. There is substantial evidence of bioactives (such as flavonoids, terpenoids, polyphenols, alkaloids, saponins, and resveratrol) modulating corresponding molecular pathways, as well as regulating enzyme activity and receptor interactions, as well as large-scale anti-inflammatory, antioxidant, antimicrobial, antidiabetic, and anticancer activity. Although animal experiments are excellent for reproducibility and mechanistic insights, they are complicated by interspecies heterogeneity, extract variability, bioavailability, and ethical issues that call for additional in vitro, computer model, and clinical trials. Standardised extracts, the creation of bioactive formulations that target multiple modes of action, and the environmentally responsible sourcing of medicinal plants that connect traditional and modern pharmacotherapy should be the main priorities of the future. These studies demonstrate the translational potential of agents derived from ethnopharmacology, validating the wisdom of our ancestors' traditions while also offering the chance to safely explore beneficial phytotherapeutics to meet the health care needs of contemporary society.

Key Words:

Pharmacognosy, Ethnopharmacology, Phytotherapeutics, Anti-Inflammatory, Antioxidant, Anticancer, Antidiabetic.

Article History:

Received June 22, 2025

Revised July 28, 2025

Accepted Aug. 18, 2025

Published Sep. 04, 2025

DOI: https://doi.org/10.64063/3049-1630.vol.2.issue9.3

1. INTRODUCTION

Natural products have long been fundamental to medicine, whether through traditional methods or contemporary pharmacotherapy[1]. Communities have been using plant, mineral, and animal derivatives to heal illnesses for thousands of years; this ethnomedical knowledge has been transmitted from one generation to the next. The wealth of this experience has benefited science, since we have used it to develop novel drugs such as morphine from Papaver somniferum, quinine from Cinchona officinalis, and artemisinin from Artemisia annua. Together, the fields of pharmacognosy and ethnopharmacology offer a methodical way to research and validate these treatments. Pharmacognosy focusses on the chemical characterisation and pharmacological testing of bioactive natural chemicals, whereas

ethnopharmacology describes, analyses, and comprehends the cultural, historical, and medical aspects of these goods. In addition to preserving native culture, their convergence speeds up the development of novel therapeutic agents to address urgent global health issues2. In addition to highlighting the relevance and applicability of ethnomedicinal practices in the treatment of contemporary diseases like cancer, diabetes, inflammation, and infections, researchers can show the scientific validity of these practices by fusing traditional knowledge with experimental validation. This approach to promote drug discovery while yet adhering to tradition emphasises how basic pharmacognosy or ethnopharmacology along with animal-based research are required at this point.

1.1. Background and Context

The study of drugs or bioactive natural compounds with an emphasis on their chemical makeup, pharmacological characteristics, and therapeutic applications is known as pharmacognosy [4]. Ethnopharmacology, on the other hand, investigates traditional medical systems by looking at the cultural and anthropological roots of natural products. They work together to connect contemporary medication discovery with traditional medical expertise. The efficacy of this multimodal method is demonstrated by examples like the separation of morphine from Papaver somniferum and artemisinin from Artemisia annua. In recent years, animal testing has become a crucial component of preclinical research to confirm the pharmacodynamic effectiveness and safety of natural bioactives. This allows researchers to investigate mechanisms of action and potential therapeutic applications in a controlled setting.

1.2. Objectives of the Review

The primary objective of this review is:

- To review animal-based evidence supporting therapeutic effects of ethnopharmacological agents.
- To analyze experimental models used for validating traditional remedies.
- To identify bioactive compounds and their pharmacological mechanisms.
- To evaluate strengths, limitations, and translational relevance of animal studies.
- To highlight potential novel phytotherapeutics for future drug development.

1.3. Importance of the Topic

There are many reasons why this is a very important topic. First of all it gives some scientific validation to the ethnomedicinal heritage. Second, it provides natural solutions that are non harmful and effective for many current common issues such as: inflammation, diabetes, infection, and cancer. Third, the idea is in support of sustainable drug discovery reflecting the use of drug discovery on the bioactives natural resources are being used for drug discovery. Overall, the inclusion of animal models into ethnopharmacological studies allows a connection between traditional medicine and pharmacotherapy to form, leading to new therapeutics that are both grounded in cultural wisdom and scientifically tested[5].

2. PRECLINICAL VALIDATION OF ETHNOPHARMACOLOGICAL AGENTS IN ANIMAL MODELS

Ethno pharmacological relevanceTowards developing traditional medicinal claims through evaluation of pharmacological effects, mechanisms of actions, and safety, animal-based ethnopharmacology utilizes a variety of experimental models to validate the ethnomedicinal use of each product. The anti-inflammatory activity is evaluated by carrageenan- and formalin-induced inflammation models, and the hepatoprotective and antioxidant potential are tested by CCl_4- and acetaminophen-induced liver injury models with biochemical and histopathological markers[6]. They discuss the antidiabetic effects validated using different STZ- and alloxan-induced diabetic models, neuropharmacological effects inferred from behavioral studies like open-field, elevated plus maze, and forced swim tests, and safety based on OECD guidelinebased toxicity studies. Extracts are found to have effects including but not limited to, flavonoids from Centella asiatica which may be anti-inflammatory, Phyllanthus emblica polyphenols which may be hepatoprotective by reducing oxidative stress and hepatotoxicity, Tinospora cordifolia alkaloids and its protection towards bacterial and fungal infection, Gymnema sylvestre saponins which possess anti-hyperglycaemia activity in blood, and curcumin from Curcuma longa which proves antitumor activity via regulating apoptotic and inflammatory pathways. Together, these studies demonstrate mechanistic validation of ethnomedicinal knowledge and support natural bioactives as sources for drug discovery.

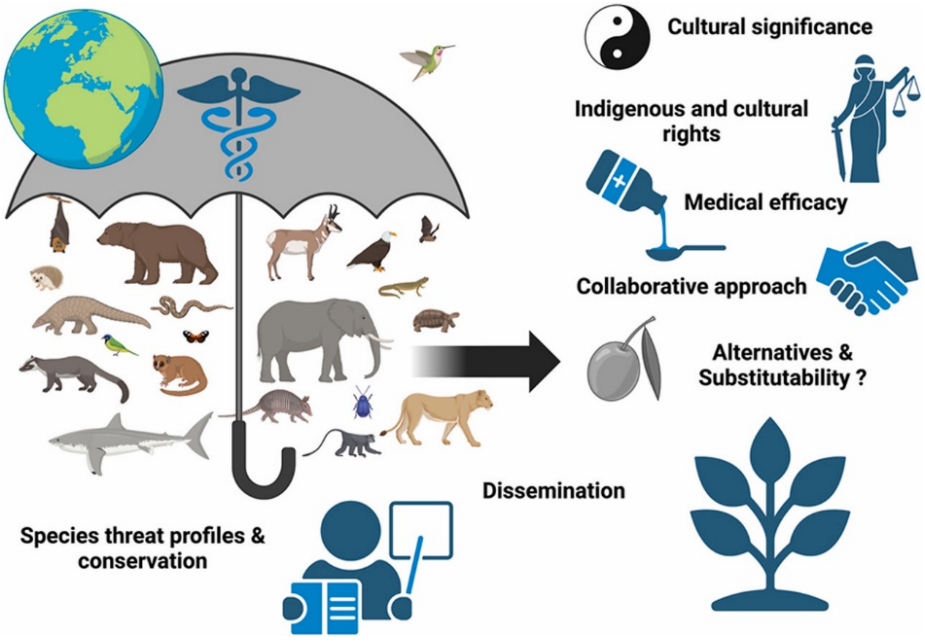

Figure 2: Integrating Species Conservation with Ethnopharmacological Practices and Cultural Significance[7]

2.1. Methodologies in Animal-Based Ethnopharmacology

Animal models serve as indispensable tools for validating traditional ethnopharmacological claims, as they provide controlled conditions to assess pharmacological effects, mechanisms of

action, and potential toxicity of bioactive compounds. A variety of models are employed depending on the therapeutic focus:

- **For anti-inflammatory activity:** Carrageenan-induced paw edema model is one of the classical methods for evaluation of acute inflammation by measuring the paw swelling after carrageenan injection, whereas formalin-induced inflammation model permits the assessment of both the early (neurogenic) and late (inflammatory) phase of pain and swelling. These models are useful for screening extracts from plants and animals for anti-inflammatory activity[8].
- **Antioxidants and hepatoprotective studies:** Models of oxidative stress and liver pathology, such as carbon tetrachloride (CCl_4)- and acetaminophen-induced hepatotoxicity, facilitate the assessment of protective machinery of natural substances against the liver. Conventional Biomarkers The other common biomarkers that are studied include serum levels of ALT, AST and changes seen in histopathological sections.
- **Diabetic model:** Type I and Type II diabetic models (demonstrated in vitro assay) induced by streptozotocin (STZ)-and alloxan, which selectively damage pancreatic β-cells. These models are used for evaluating the hypoglycemic and insulin-sensitizing effect of plant bioactives and animal formulations.
- **Neuropharmacological testing:** Behavioral approaches such as the open-field test (locomotor activity), elevated plus maze (anxiety), and forced swim test (depression-like symptoms) can be used to assess the neuroactive potential of compounds as a surrogate for CNS effects[9].
- **Toxicity studies:** Acute, sub-acute and chronic toxicity studies carried out as per OECD guidelines are important in determining the safe doses. Such as LD_{50} estimation, hematology profile, biochemical tests, histopathology for organ specific toxicities.

In total, these complementary methodologies integrate old world ethnomedicine with new world pharmacological validation, allowing for both therapeutic activity and bioactive safety.

2.2. Findings from Animal-Based Studies

Animal studies have provided supportive evidence for the therapeutic assertions related to traditional ethnomedicines and have given mechanistic explanations for pharmacological effects:

- **Anti inflammatory agents:** Centella asiatica extracts rich in flavonoids inhibited carrageenan-induced paw edema in a significant manner. This ability to inhibit pro-inflammatory mediators (prostaglandins, cytokines) confirmed the anti-inflammatory activity of C. asiatica. Hence, confirms this plants conventional application in inflammation, wound and rheumatic treatment[10].
- **Antioxidant Activity:** Significant hepatoprotective effect of ethanolic extracts of Phyllanthus emblica (amla) were observed in CCl_4-induced rats. The observed protection was related to the literature about positive effects of polyphenolic compounds that reduced lipid peroxidation, increased the activity of antioxidant enzymes (e.g., superoxide dismutase and catalase), and help liver architecture restoration.

- **Antimicrobial activity:** The major alkaloids (BA3,BA4) present in the fraction of Tinospora cordifolia, which are enriched in the alkaloids, improved survival in infected murine models following bacterial challenges. The extract reduced bacterial load as well as enhanced immune responses through macrophage modulation and its cytokine release, which justifies its ethnomedicinal use in the treatment of fevers and infections.
- **Antidiabetic activity:** All three fractions of saponins from Gymnema sylvestre reduced blood level of glucose in STZ-induced diabetic rats. This effect was associated with insulin secretion stimulation, enhanced glucose uptake on peripheral tissues, and regulation of enzymes of carbohydrate metabolism, confirming its folk uses as a "sugar destroyer".
- **Effects related to cancer:** Anti-Tumorigenic effects of curcumin in a xenograft mouse model531 More Prabstract. This mechanism was in line with its traditional anticancer and anti-inflammatory remedy, suppressing NF-κB signaling pathway, inducing apoptosis, and inhibiting angiogenesis[11].

These observations may emphasize the scientific validation of traditional animal-based ethno pharmacological practices and support the consideration for future natural compound research and drug development.

2.3. Critically Evaluate Strengths and Weaknesses

- **Strengths:** Animal models used in ethnopharmacology provide important advantages such as controlled experimental conditions, reproducibility, and a chance to study both therapeutically relevant effects and mechanistic pathways in vivo. They offer preliminary pharmacokinetic, pharmacodynamic, and toxicity data that can be crucial for modernizing the translation of traditional remedies into 21st-century therapeutics. Additionally, animal models allow for broader evaluation of complex extracts and bioactive (and often poorly soluble) compounds that may not be readily assessed in vitro[12].
- **Weaknesses:** As some research is performed using animal models, the exact translation to human biology is not always achievable and can raise some questions surrounding valid questions. For instance, STZ-induced diabetes or CCl_4-induced hepatotoxicity only simulate features of human disease and thus lack the desired predictive power. Variability in extract preparation, dosing, and bioavailability contributes to complications in reproducibility between studies. Animal experimentation, by no means perfect and ethically dubious in its necessity, also presents a challenge for the field and calls for refinement and alternatives where possible. Therefore, although animal, based validation is invaluable, it needs to be complemented by sophisticated in vitro systems, computational modelling, and ultimately, well designed clinical trials. In conclusion, the aforementioned approaches will make the translation into human therapeutics more robust.

3. THERAPEUTIC POTENTIAL OF ETHNOPHARMACOLOGICAL AGENTS: EVIDENCE FROM ANIMAL STUDIES

Ethnopharmacological drug development from animal studies has confirmed the treatment potentials of various plant-extracted bioactives in a diverse manner while reciting their mechanistic nature in combat against diseases. However, flavonoids, terpenoids and phenolic compounds have strong anti-inflammatory and analgesic activities by suppressing the mediators

such as TNF-α, IL-6, and cyclooxygenases in different models of arthritis as shown by Boswellia serrata[13]. Compounds like Silybum marianum that are concentrated with polyphenols protect against liver injury induced by toxins, restore antioxidant enzymes, and inhibit lipid peroxidation. Alkaloids that boost immune responses have antimicrobial and immunomodulatory properties from Andrographis paniculata. Momordica charantia demonstrates antidiabetic effects by avoiding decreased blood glucose through β-cell regeneration and higher insulin secretion or other compounds that inhibit carbohydrate-digesting enzymes. In addition to that, some anticancer molecules: curcumin, resveratrol and vincristine have been shown to induce apoptosis, inhibit angiogenesis and suppress metastasis in murine models. In sum, these results strengthen the rationale for the traditional use of these plants and offer mechanistic avenues toward modern phytotherapeutics.

- **Anti-Inflammatory and Analgesic Agents**

Numerous animal-based ethnopharmacological studies have confirmed the potent anti-inflammatory and analgesic activities of plant-derived phytochemicals, especially flavonoids, terpenoids and phenolic compounds. These bioactives work by reducing pro-inflammatory mediators, including TNF-α, IL-6, prostaglandins, and cyclooxygenase enzymes. Examples include the significant reduction in arthritis severity in rodent models from resin extracts of Boswellia serrata by inhibition of leukotriene biosynthesis and reduction in joint inflammation. Likewise, additional flavonoids-rich extracts displayed anti-inflammatory and analgesic activities, indicating their potential to modify both acute and chronic inflammation reactions, therefore justifying their traditional use to treat rheumatism, arthritis, and pain management[14].

- **Antioxidant and Hepatoprotective Agents**

Oxidative stress is a common underlying factor in liver injury, cardiovascular disease and neurodegenerative disorders, highlighting the importance of these agents as a potentially valuable target for ethnopharmacological research, as antioxidant and hepatoprotective agents. Silybum marianum (milk thistle) is an example of a plant extract rich in polyphenols and flavonoids, known to be extremely effective in protecting liver tissues against injurious toxins in CCl_4 and acetaminophen models[15]. Such extracts restore the activities of antioxidant enzymes, minimize lipid peroxidation and restore histopathological architecture of the liver. These results validate their traditional use in hepatic afflictions and expand their therapeutic importance by establishing antioxidant phytochemicals as proactive agents in protecting several organ systems from oxidative damage.

Figure 3: Hepatoprotection[16]

- **Antimicrobial and Immunomodulatory Agents**

The field of ethnopharmacology has also recognized antimicrobial and immune-modulating effects of several plant-derived compounds such as alkaloids, glycosides, and essential oils[17]. For instance, Andrographis paniculata extracts have been reported to boost immune responses via macrophage activation and modulation of cytokine secretion in mice. This in turn translates more significantly into an enhanced defence against bacteria and viruses. In addition to antimicrobial activity, multiple plant extracts serve immunomodulatory roles that could be used as treatments for various immune-associated diseases, including autoimmune diseases and chronic infections. The dual mechanism of direct pathogen inhibition, as well as functional host immune suppression, highlights their potential therapeutic versatility[18].

- **Antidiabetic and Metabolic Regulators**

Some plants traditionally used in the treatment of diabetes mellitus have been validated for their antidiabetic properties in animal-based studies. Momordica charantia (bitter melon) extracts were shown to exert powerful hypoglycemic effects in diabetic rats, but potentiation of insulin secretion, increased glucose uptake in peripheral tissues and stimulation of pancreatic β-cell regeneration appear to be the important mechanisms. In addition to other enzyme inhibitors of carbohydrates digestion (α-amylase and α-glucosidase) from plant source, which help in the postprandial glucose-reducing capacity. These results not only validate the role of plants in ethnomedicine for the management of diabetes but also pave the way for developing new generations of phytotherapeutics for metabolic syndrome, obesity and insulin resistance.

- **Anticancer and Chemopreventive Agents**

Ethnopharmacological relevanceNatural compounds are becoming increasingly more acknowledged as promising anticancer and chemopreventive agents. Bioactives like curcumin (plant species: Curcuma longa), resveratrol (grape species), and vincristine (plant species: Catharanthus roseus) have been shown to produce remarkable antitumor effect in animal models.

These compounds exert their biological activities, such as induction of apoptosis, inhibition of angiogenesis, suppression of metastasis and cell cycle arrest, via multiple signal pathways. For example, curcumin blocks NF-κB signaling and modifies apoptotic pathways and resveratrol blocks reactive oxygen species (ROS) generation and tumor development. Apart from the obvious support to the traditional uses of these plants, this integrated information would mechanistically provide the basis for the inclusion of these natural agents in contemporary cancer therapy and chemoprevention paradigms[19].

4. MECHANISTIC INSIGHTS AND PHARMACOLOGICAL PATHWAYS

Ethnopharmacological studies on animals not only validate the bioactivity of native treatments, but also provide insight into the molecular and cellular mechanisms responsible for their pharmacological effect(s). Such insights are vital for converting ancient wisdom into rigorously tested therapies. Flavonoids, alkaloids, terpenoids, polyphenols, saponins, and other bioactive compounds induce effects by regulating their metabolomic machinery through signaling pathways, enzyme activities, and receptor interactions that regulate physiological and pathological processes[20].

Specific flavonoids, for example, have potent antioxidative properties by promoting the intrinsic defense system, particularly via induction of enzymes such as superoxidase dismutase (SOD), catalase, and glutathione peroxidase levels, resulting in decreased reactive oxygen species (ROS) and inhibition of lipid peroxidation. Alkaloid compounds such as berberine act via activation of proximal AMP-activated protein kinase (AMPK) pathways to increase insulin sensitivity, improve lipid homeostasis and inhibit hepatic gluconeogenesis in models of diabetes. A close example is anti-inflammatory activity of terpenoids including ursolic acid whereby the authors demonstrated an inhibition of cyclooxygenase-2 (COX-2) and subsequently downregulation of NF-κB signaling leads to reduced expression of pro-inflammatory cytokines and adhesion molecules, Full size image.

The enhancing insulin sensitivity can be mediated through the upregulation and translocation of glucose transporter-4 (GLUT-4) in skeletal muscles and adipose tissues, improving peripheral glucose uptake, thereby contributing towards antidiabetic effects of saponins. Other polyphenols, such as resveratrol and curcumin also target cell survival pathways via modulation of apoptotic regulators (e.g., Bcl-2, Bax, caspases) and angiogenesis-related proteins (e.g., VEGF) which may provide mechanistic insight into their anticancer and chemopreventive effects[21].

Animal-based studies offer a mechanism-based rationale for the mode of action of ethnomedicine by delineating these pathways. The merging of traditional knowledge with modern pharmacology, which not only authenticates ethnopharmacological legends but also hastens the search for new drug candidates with well-defined molecular targets.

Table 1: Summary of Key Studies on Ethnomedicine and Network Pharmacology Approaches [22]

Author(s)	Study	Focus Area	Methodology	Key Findings

Wen et al. (2021)[23]	Multiscale mechanisms of Jiaoqi Powder in treating ulcerative colitis	Ulcerative colitis; Traditional Chinese medicine	Network pharmacology to identify bioactive compounds and map targets	Multiple bioactive compounds targeted inflammation, immune regulation, and intestinal barrier function; therapeutic efficacy mediated through synergistic molecular pathways
Wu et al. (2022)[24]	Effect and mechanism of active ingredients from an herbal couple on rheumatoid arthritis	Rheumatoid arthritis; Herbal combination therapy	System pharmacology with pharmacokinetic profiling and target network mapping in rat models	Herbal combination modulated key inflammatory and immune pathways, reducing joint inflammation; demonstrated utility of multi-component therapeutics and system-level analyses
Xie et al. (2024)[25]	Potential mechanisms of Heng-Gu-Gu-Shang-Yu-He-Ji therapy for osteoporosis	Osteoporosis; Ethnomedicine	Network pharmacology combined with transcriptomics	Identified molecular targets and signaling pathways regulating bone metabolism; therapy influenced osteogenesis and inhibited bone resorption; multi-omics integration validated predicted targets
Yeung, Heinrich, & Atanasov (2018)[26]	Bibliometric analysis of ethnopharmacology	Ethnopharmacology research trends; Medicine and food science interface	Bibliometric analysis of publications, collaborations, and research trends	Revealed evolution from descriptive to mechanistic/system-based studies; highlighted interdisciplinary nature and integration of modern pharmacological and computational techniques

5. DISCUSSION

Ethnopharmacological agents reported in this review were found to have therapeutic effects in animal-based studies that confirm anti-inflammatory, antioxidant, antimicrobial, antidiabetic, and anticancer effects and display promising evidence of their pharmacological pathways. Nevertheless, factors such as dissimilarities between animal and human physiology, inconsistency in extract preparation and ethical considerations highlight the necessity for supplementary in vitro studies, computational methods and/or clinical validation[27]. However, future studies need to concentrate on the standardization of extracts, the bioactive formulation of upstreams, the multi-target actions of compounds, and sustainable supply chains to integrate a wealth of traditional knowledge with contemporary, value-added science-based therapeutics.

5.1. Interpretation and Significance of Findings

Ethnopharmacological agents from various plants have shown promise in different therapeutic areas, as evidenced by animal model studies. Mechanistically flavonoids, terpenoids, and phenolics have demonstrated anti-inflammatory and analgesic effects whereas polyphenol-rich extracts have been shown to offer protection against oxidative stress and liver injury. Alkaloids have an immunity booster and antimicrobial properties. Antidiabetic plants (e.g., Momordica charantia and Gymnema sylvestre) enhance insulin secretion and glucose uptake; anticancer agents (e.g., curcumin and vincristine) trigger apoptosis and limit angiogenesis. These results confirm traditional knowledge while delivering mechanistic understanding of pharmacological pathways, underlining their importance to contemporary drug discovery[28].

5.2. Gaps and Limitations

Despite promising results, limitations exist. Human physiology is not fully replicated in animal models, and lack of reproducibility is mostly related to variations in preparation, dosing, and bioavailability of the extracts.22 There is limited data and ethical concerns associated with animal experiments regarding the long-term safety, both of the vaccines and the other treatments being considered. The complications highlight the importance of supporting in vitro studies, computer modeling, and, ultimately well designed clinical trials to promote strong translational success[29].

5.3. Future Perspectives and Research Directions

Future studies should ideally be conducted in the clinical setting, along with standardized extracts, improved formulations of bioactives and multi-target mechanisms. Medicinal plants need to be sourced sustainably and preserved well, but well-established in vitro and computational techniques need to be integrated to elucidate in depth the mechanistic details[30]. This synergistic approach will expedite the generation of novel safe and evidence-based phytotherapeutics connecting traditional medicine and modern pharmacology.

6. CONCLUSION

This review illustrates the significance of the drug discovery points where pharmacognosy and ethnopharmacology have historically met, and emphasized the relationship between pharmacological studies, postulated possible mechanisms of action and traditional ethnomedicine. Animal studies provide robust evidence of the medicinal efficacy of numerous plant bioactives, and have supported various anti-inflammatory, antioxidant, antimicrobial, antidiabetic, and anticancer effects, while identifying possible pharmacological mechanisms by regulating important signalling pathways, enzymes, and receptors. As such, such evidence validates ethnopharmacological knowledge and spectacularly indicates the significance of the relationship between the development of natural products and modern drug discovery or drug development. Nevertheless, anthropocentric limitations related to the difference in physiology between animals and humans, variances and configurability in extract preparation and bioavailability, and ethical considerations justify in vitro studies, computational studies, and well-designed human anatomical studies (clinical trials) as essential parts of modern medical and agro-pharmaceutical research and discovery. Future direction should involve standardization of extracts, formulation optimization with bioactive(s), possible exploration of multi-target/multi-component mechanisms of action (MoA), along with ethical and sustainable sourcing and development of medicinal plants. Separately but cohesively, natural compounds that combine traditional knowledge with modern pharmacological studies offer traditional medicine practitioners a valuable opportunity to development safe, effective, and evidence-based phytotherapeutics, thereby combining culture with pressing 21st century health needs.

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