Doctor of Botanical Medicine

Enhancing Methodological Approaches in Clinical Trials for Botanical Medicine.

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Contents:

Research Question

In clinical trials, what methodological enhancements can be implemented to improve the quality of botanical medicine research?

Keywords

Botanical medicine, pharmacognosy, phytotherapy, Botany ethnobotany, scientific approaches, herbal medicines, customary uses of herbs, contemporary advancements in pharmaceuticals, formulation methods, clinical examinations, alternative medicine

Introduction

Botanical medicine has become increasingly popular globally in recent years due to its perceived therapeutic benefits, leading to increased exploration and utilisation. Botanicals, which are frequently obtained from plants, fungi, or other natural origins, have long been an essential component of traditional healing systems, providing a wide range of compounds that may possess medicinal properties. For botanical medicine to be widely accepted in modern healthcare systems, it is crucial to have strong scientific evidence from clinical trials that establish the effectiveness, safety, and potential clinical uses of botanicals.

Therefore, the aims of this research appear will be to first acknowledge clinical research, identify the many medicines in relation to phyto-pharmaceutics and pharmacognosy, concluding with the many ways in which enhancements to methodologies surrounding botanical medicine and pharmacognosy practices would be beneficial to the quality of botanical medicine research.

Significance of Evidence-Based Botanical Medicine

The concept of evidence-based medicine is a fundamental framework in modern healthcare that involves integrating the most reliable evidence from scientific research into clinical decision-making. Simultaneously, it aims to utilise scientific rigour to evaluate, authenticate, and eventually integrate botanical interventions into conventional clinical practice. The importance of such lies in its ability to connect traditional knowledge systems with modern scientific methodologies. This helps to support the therapeutic claims made about botanical remedies, while also ensuring the safety and effectiveness of patient care.

Justification for the Research

Although there is increasing interest in botanical medicine throughout the world, and most noticeably within the World Health Organisation, the field faces various methodological obstacles that hinder the smooth incorporation of botanicals into evidence-based practice. Botanical medicines, i.e. pharmacognosy, phyto-therapeutics, and or magistrates' formulations in the case of Spain, present unique complexities when being studied in clinical trials. Clinical trials are crucial for generating evidence in modern medicine, (Sena, Currie, McCann, Macleod, & Howells, 2014). These complexities involve various factors, such as the variability of plant constituents, difficulties in standardising and controlling the quality of botanical preparations, intricacies in designing trials, potential interactions between herbs and

drugs, and the incorporation of traditional knowledge into scientific frameworks, to name but a few.

Therefore, these complexities require a comprehensive analysis and adjustment of current methodologies to guarantee the dependability, accuracy, and applicability of evidence obtained from botanical clinical trials.

Similarly, by combining the available data to create a comprehensive picture of multiple studies, systematic reviews, and meta-analyses, it is possible to obtain priceless insights that can influence the future course of botanical medicine research by highlighting patterns, variances in results, and areas that need more study (Wardani et al., 2023).

As a Homeopathic Practitioner of over 25 years, it is in the best interest of allied healthcare practitioners such as myself, to advocate for advances in methodological research, that would only serve to conclude stronger evidence and findings, and benefit patients who receive our treatments.

Thesis Objectives and Structure

The main objective of this thesis is to investigate and suggest methodological approaches that would aid in the clinical validity of the medicines being studied. For example, the significance of utilising HPLC is highly beneficial due to its quantifying ability, which consequently would aid in the regulating of the active compounds within a botanical, thus streamlining and standardising the medicinal properties and product being created. Ultimately, the quality assurance and standardisation of botanicals would consequently be beneficial for the industry.

The aim of the proposed strategies explained in the latter part of this paper, is to reduce biases, enhance standardisation, consequently enhancing the quality and credibility of research and conclusions in the field of botanical medicine. They will be pre-empted by medicines in phytotherapy, pharmacognosy and legal frameworks surrounding botanical medicine in Spain, as evidence to the fledged field of botanical medicine. Thus, evidently highlighting the importance of ensuring that clinical research around botanical medicine is of a high standard, to maintain, and continue to provide healing products to the public.

Literature review

Botanical Medicine

Botanical medicine, sometimes referred to as herbal medicine or phytotherapy, is the practice of using substances derived from plants for therapeutic purposes. Its fascinating story begins with its historical development, which can be traced back to ancient civilizations where traditional healing methods honoured the healing qualities of nature's abundance (“Traditional, Complementary and Integrative Medicine,” 2019). Botanical medicine is still gaining traction in the modern healthcare system because many people looking for natural, holistic alternatives to conventional therapies, find value in its perceived natural approach

(“Traditional Medicine Has a Long History of Contributing to Conventional Medicine and Continues to Hold Promise,” 2023).

The History of Botanical Medicine

Many historical societies have recorded using plants for medical purposes, including the Egyptians, Mesopotamians, Greeks, Romans, Indians, and Chinese (Šantić, Ž., Pravdić, Bevanda, & Galić, 2017)). These cultures developed herbal remedies based on empirical observations, folklore, and traditional knowledge. By carefully recording medicinal plants and their uses, notable individuals like Hippocrates and Dioscorides made important contributions that laid the groundwork for later developments in herbal medicine (Zunic, Skrbo, & Dobraca, 2017).

Herbals became well-known reference books in the Middle Ages and Renaissance, featuring colourful illustrations of therapeutic plants. The Age of Exploration made it easier for botanists to communicate across continents, which led to the creation of botanical gardens and pharmacopoeias, which further enhanced the field of botanical medicine.

Pharmacognosy and Bioactive Substances

The study of the identification, extraction, and characterization of bioactive compounds found in plants is the focus of pharmacognosy, or the science of natural products (Sasidharan, Chen, Saravanan, Sundram, & Latha, 2010). Scholars have uncovered the various medicinal benefits of phytochemicals such as phenolic compounds, flavonoids, terpenoids, and alkaloids (Kumar et al., 2023). These substances have a variety of pharmacological effects, including antibacterial, anti-inflammatory, antioxidant, and even anticancer effects.

Opportunities and Challenges

There are still several obstacles in the way of botanical medicine's potential and growing interest. Ensuring consistency and efficacy across herbal products is hampered by regulatory complexities pertaining to standardisation, quality control, and safety standards (Indrayanto, 2023). Attention must also be paid to sustainability, fair access to traditional knowledge, and ethical sourcing (Tilburt, 2008).

These difficulties however, present opportunities for growth. To address these shortcomings, initiatives are being made to create standardised protocols, strong quality assurance measures, and encourage collaborations between modern practitioners and traditional healers (Headquarters, 2006). Combining conventional wisdom with research-proven methods has great potential to develop new treatment modalities and improve patient outcomes.

In conclusion, this brief review of the literature surrounding botanical medicine highlights the history of botanical medicine, identifies pharmacognosy and identifies the difficulties that the industry is faced with today. The advancement of botanical medicine's place in contemporary healthcare will depend on how well it handles ethical and regulatory issues now present.

Methodology

The main objective I had to perform, was a comprehensive analysis and combine different academic journals, research studies, clinical trials, and professional viewpoints that are pertinent to the topic, and to compile the current medicinal products in relation to pharmacognosy and phyto-therapeutics.

Academic databases such as National Center for Complementary and Integrative Health (NCCIH), PubMed, National Library of Medicine, World Health Organisation, and Google Scholar were carefully examined. Peer-reviewed journals, books, conference proceedings, and relevant web resources were the overwhelming focus of this thorough search. To find pertinent literature, search terms like "botanical medicine," "herbal medicine," and "phytotherapy" were carefully used.

The selection of articles was conducted with great care, considering factors such as their direct relevance to the development, effectiveness, difficulties, advancements of botanical medicine, and how best they would support the point being made within the paper. I utilised, a tight inclusion criterion, as I only included English-language studies, with an overwhelming amount of research that had been published in the last ten years, with a select few falling within the 15–20-year range, to ensure current research was included. Furthermore, the range of data that can be analysed may be limited by the dependence on previously published works.

Botanical Medicine and Magistral formulations

Within the complex realm of healthcare, two separate but interrelated approaches – botanical medicine and magistral formulations - provide distinct benefits to the overall health of patients. One approach utilises tailored medications with high accuracy, (Biagi et al., 2016) while the other taps into the healing properties found in nature (Arias, Leon, Jaimes, & Bustos, 2021). This convergence creates a powerful combination, enabling patient-focused healthcare through customised treatments and holistic remedies.

Magistral Formulations

Magistral formulations represent the pinnacle of personalised medicine, as the medicines are carefully prepared by chemists to specifically cater to the individual requirements of each patient (Vicente, Ballensiefen, & Jönsson, 2020). Bespoke medications offer tailored solutions for allergies, dosages, and addressing the limitations of commercially available forms, (Pereira et al., 2016). They aim to provide optimal therapy by surpassing the conventional one-size-fits-all approach (England, 2016).

Botanical medicine harnesses the innate therapeutic properties of plants and their derivatives, encompassing a wide range of practices including traditional herbalism and indigenous healing traditions (“Traditional, Complementary and Integrative Medicine,” 2019). By combining traditional knowledge and scientific investigation, this resource explores the extensive collection of medicinal plants, providing a wide range of natural treatments designed for specific health issues (Cheikhyoussef, Shapi, Matengu, & Mu Ashekele, 2011) (Niemeyer, Bell, & Koithan, 2013).

Although magistral formulations and botanical medicine employ different methods, they both prioritise individualised and natural approaches to healthcare. This common ideology is evident in two primary ways:

Magistral formulations prioritise individualised treatment plans, ensuring each medication is perfectly matched to the patient's distinct biochemical composition and health issues. '*Magistral medicines are medicinal products prepared in a pharmacy for an individual patient or animal in accordance with a prescription from a doctor or veterinarian*' ("Magistral Medicines," n.d.).

Botanical medicines also acknowledge the unique nature of health experiences and supports the use of personalised remedies tailored to specific conditions and patient preferences (Benzie & Wachtel-Galor, 2011).

Botanical medicine flourishes by harnessing the inherent therapeutic variety of plants, highlighting the capacity of natural substances to facilitate the process of healing (Petrovska, 2012). Magistral formulations predominantly employ synthetic constituents but can also incorporate natural ingredients as per prescription, appealing to patients who prefer natural therapeutic alternatives.

Both avenues provide a wide range of treatment choices, enabling patients to actively engage in their healthcare journey. Magistral formulations offer exceptional versatility in tailoring medications, while botanical medicine offers a wide range of plant-derived remedies, catering to various health requirements and preferences.

This connection provides patients with a wide array of treatment choices, while placing importance on individualised care and utilising the healing properties of natural substances. This collaboration facilitates a comprehensive approach to healthcare, advocating for personalised and holistic principles in patient-focused treatment strategies.

By combining the advantages of both approaches, healthcare providers can enable patients to actively engage in their journeys towards well-being, promoting a future where precision medicine and natural remedies collaborate to maximise patient outcomes.

Preclinical research to Clinical Trials

The transition from preclinical research to clinical trial results in phytotherapy, is a crucial process that establishes the basis for transforming potential plant-based molecules, into effective therapeutic treatments. Preclinical investigations frequently reveal the prospective advantages of these substances. Nevertheless, the progression to definitive clinical results poses difficulties, emphasising the intricacy of converting preclinical potential into efficacious therapies. Here, I will examine specific instances that clarify the relationship between preclinical data and clinical trial results in the field of phytotherapy.

Resveratrol for Maintaining Cardiovascular Health

Preclinical studies on resveratrol, a molecule found in red grapes, have demonstrated its encouraging antioxidant and anti-inflammatory characteristics, indicating prospective advantages for cardiovascular well-being, (Singh, Liu, & Ahmad, 2015).

However, unfortunately, the process of translating the preclinical discoveries into definitive clinical results posed further difficulties. Human clinical trials investigating the impact of resveratrol on cardiovascular health produced inconclusive findings. Although many trials demonstrated modest enhancements in cardiovascular risk indicators such as blood pressure or cholesterol levels, following studies were unable to reliably reproduce results. The inconclusiveness of the clinical data, has highlighted the intricacy of converting preclinical potential into real human reactions.

Green Tea Catechins for Weight Control

In relation to green tea, preclinical studies have indicated that green tea catechins have potential for weight control and improving metabolic health, as seen by Kwak & Shin, (2022). Whereas, animal studies have shown the capacity of these substances to increase the breakdown of fat, decrease hunger, and boost the body's response to insulin (Hussain et al., 2022). This has paved the way for further investigation into their possible use in fighting obesity.

Studies evaluating the impact of green tea catechins on weight reduction and metabolic factors in people, demonstrated moderate and variable results. Several trials documented modest decreases in body weight and enhancements in metabolic indicators. Nevertheless, the degree and regularity of these impacts differed among people, highlighting the difficulties in converting preclinical discoveries into reliable clinical efficacy.

Cannabidiol (CBD) in the treatment of epilepsy.

In relation to CBD, preclinical studies on cannabidiol (CBD) demonstrated its ability to decrease the frequency of seizures in animal models of epilepsy. These investigations have shown that CBD can regulate the activity of neurons and provide anti-seizure effects, which has potential for managing epilepsy. Similarly, with commercial products on the market, the global cannabidiol market was worth ‘$9.4 billion in 2023 at a compound annual growth rate (CAGR) of 37.8%. [With] the cannabidiol market [expecting] to grow to $31.85 billion in 2027 at a CAGR of 35.7%’ (Markets, 2023), one would believe that there are therapeutic benefits to the persons taking the pharmaceutics, (Kwee et al., 2022) (Calapai et al., 2019).

Promising results were obtained from clinical trials examining the effects of CBD in persons with treatment-resistant epilepsy. The administration of targeted CBD formulations resulted in a notable decrease in the occurrence of seizures, which subsequently led to the authorization of drugs containing CBD for specific types of epilepsy. The positive results of these clinical trials have confirmed the earlier findings, showcasing the promise of CBD in effectively treating seizures, (Arias, Leon, Jaimes, & Bustos, 2021).

Rhodiola rosea for managing stress.

Preliminary investigations conducted on Rhodiola rosea, have proposed its potential in reducing stress reactions and improving resilience, (Ivanova Stojcheva & Quintela, 2022) (Tinsley, Jagim, Potter, Garner, & Galpin, 2023). Animal studies have indicated that Rhodiola extracts can regulate stress hormones and enhance stress tolerance, suggesting potential advantages for stress-related disorders.

Nevertheless, the clinical trials investigating the impact of Rhodiola rosea on stress and mental well-being provided inconclusive results. Although several experiments have reported slight enhancements in stress symptoms and mental exhaustion among those consuming Rhodiola supplements, other trials did not show notable distinctions when compared to a placebo. The variability in clinical outcomes has prompted inquiries regarding the translation of preclinical effects into consistent human responses.

To conclude, the connection between preclinical research and clinical trial outcomes in phytotherapy reveals both potential benefits and intricacies. Preclinical research is able to reveal potential, but the translation to definitive clinical findings is typically hindered by several variables, such as individual variances, inconclusive findings, lack of consistency throughout findings across multiple researches, and in some cases, simply not enough findings.

Most notably however, is the lack of research being conducted on specific botanicals for their therapeutics purposes; utilising the whole plant as medicine; as the therapeutic properties are often extracted for pharmaceutical gain, or pharmacognosy. This point of observation, is for a different research paper, however.

Gaining a comprehensive understanding of these complexities is crucial in successfully navigating the journey towards efficient botanical-based therapeutic treatments. This chapter highlights the importance of a thorough and careful methodology, as well as additional research efforts, to connect the potential benefits seen in preclinical studies with reliable and consistent effectiveness in phytotherapy.

Phyto-therapeutics

Using plant-derived compounds or herbal medications for their therapeutic effects in the prevention, treatment, or management of a variety of health issues is known as phyto-therapeutics. This method depends on the therapeutic qualities of plant-based substances, such as extracts, essential oils, and herbs.

Pharmacognosy on the other hand, is the study of medical medicines derived from plants and other natural sources to identify, isolate, and comprehend their qualities to develop therapeutic therapies.

Echinacea

Echinacea purpureau, is believed to augment immunological function, (Hudson, 2012). During a clinical experiment assessing its effectiveness, those who received echinacea exhibited a decreased occurrence and length of upper respiratory tract infections in

comparison to the placebo group (Karsch-Völk et al., 2014). This experiment demonstrated the capacity of echinacea as an immune-modulating agent in the management of common illnesses.

Ginkgo Biloba

The use of Ginkgo biloba extract, is thought to enhance cognitive abilities. During controlled research evaluating the effects of ginkgo biloba on memory and attention in older persons, it was shown that those who received ginkgo biloba showed slight enhancements in memory retention and attention span, when compared to the group that did not get it. This experiment demonstrated the potential efficacy of ginkgo biloba in promoting cognitive well-being, (Snitz, 2009).

St. John's Wort

Hypericum perforatum, often known as St. John's Wort, is acknowledged in the field of phytotherapy for its potential as an antidepressant, (Zheng & Cui, 2016). Trials assessing the effectiveness of St. John's Wort in mild to moderate depression, demonstrated that persons who received treatment with this herb saw notable improvements in depressive symptoms, when compared to those who received a placebo, (“St. John’s Wort and Depression: In Depth,” n.d.). This research indicates the possibility of using it as an alternate treatment for specific depressive illnesses (Klemow et al., 2011).

Curcumin

Curcumin, a biologically active chemical found in turmeric, is extensively researched for its anti-inflammatory characteristics. Clinical trials investigating its effectiveness in inflammatory illnesses, revealed a decrease in inflammatory indicators and intensity of symptoms in people with ailments, such as: osteoarthritis or inflammatory bowel diseases. These findings encourage the use of curcumin in the management of inflammatory conditions, (Hewlings & Kalman, 2017).

Valerian root

Valeriana officinalis, also known as Valerian root, is frequently used in phytotherapy to treat sleep disorders. Valerian root supplementation in controlled trials had positive benefits on sleep quality, including reduced time to fall asleep and improved total sleep quality, when compared to a placebo, (Chandra Shekhar, Joshua, & Thomas, 2023). These trials indicated the promise of this substance as a natural treatment for minor sleep problems (Bent, Padula, Moore, Patterson, & Mehling, 2006).

Milk Thistle

Silybum marianum, often known as Milk Thistle, is acknowledged for its alleged hepatoprotective qualities. Studies assessing the effectiveness of milk thistle extracts in treating liver illnesses, such as non-alcoholic fatty liver disease (NAFLD) or hepatitis, have shown that patients who received these extracts saw improvements in liver enzyme levels and liver function indicators, in comparison to the control group. This research substantiates its possible function in promoting liver health, (Flora, Hahn, Rosen, & Benner, 1998).

Pharmacognosy

Aspirin

Aspirin, originated from the historical utilisation of the willow tree, specifically Salix alba. The historical use of willow bark for pain alleviation can be traced back to ancient civilizations, as evidenced by the recorded information in the Ebers Papyrus of the ancient Egyptians. The acquisition of this conventional wisdom ultimately resulted in the identification of salicylic acid, the crucial component in aspirin, signifying a significant milestone in the advancement of modern pharmacotherapy, (Mahdi, Mahdi, Mahdi, & Bowen, 2006).

Morphine

The opium poppy, scientifically known as Papaver somniferum, contains a valuable pharmaceutical substance called opium. Across various cultures throughout history, this plant has been highly esteemed for its powerful component, morphine. The use of this substance as a powerful painkiller and sleep-inducing agent has been documented throughout various historical periods, spanning from ancient Mesopotamia to the Egyptian civilization. Currently, morphine is a crucial and essential means of relieving pain, closely connected to the historical importance of the opium poppy (ibid.) (“Opium Poppy,” n.d.).

Chemotherapy

Catharanthus roseus, commonly known as the rosy periwinkle, and Taxus brevifolia, also known as the Pacific yew, are two important and humble plants that play a crucial role in the fight against cancer. The botanical specimens contain powerful pharmacological compounds hidden within the petals and barks. Vincristine and vinblastine, chemotherapy drugs derived from the rosy periwinkle, have significant disruptive effects on cellular division, making them highly effective in treating leukaemia and Hodgkin's lymphoma. With, Paclitaxel, deriving from the Pacific yew, enhancing the stability of microtubules in cancer cells, thereby inhibiting their growth. Although there are concerns about the conservation of the Pacific yew, its undisputed role in cancer treatment continues to drive the search for alternative sources, (ibid.) (Weaver, 2014) (Italy, 2021).

Artemisinin

Artemisinin, derived from Artemisia annua (sweet wormwood), is a crucial element in artemisinin-based combination therapies/medicines (ACTs), which are the primary means of combating malaria (“The Use of Non-pharmaceutical Forms of Artemisia,” 2019) (Krishna, Bustamante, Haynes, & Staines, 2008) (Posadino et al., 2023). The discovery of artemisinin, credited to Chinese scientist Tu Youyou, was influenced by traditional Chinese herbal practices, and has made a substantial impact in saving countless lives. As a result, Tu Youyou was honoured with a Nobel Prize in Medicine.

Digoxin

Digoxin, obtained from the plant Digitalis purpurea (foxglove), has played a crucial role in the treatment of heart failure and arrhythmias (Jamshed, Dashti, Ouyang, Mehal, & Banini,

2023) (David, M. N. V., & Shetty, M., 2023). William Withering, an English physician, recognised the effectiveness of this practice in the 18th century. He based his observations on local herbal knowledge and clinical experiences.

Quinine

Quinine, obtained from the bark of the Cinchona tree, has been a fundamental component in the treatment of malaria for many centuries (Achan et al., 2011).

Capsaicin

Capsaicin, derived from chilli peppers, acts as a sensory stimulant and a topical analgesic, efficiently alleviating pain in conditions like arthritis and neuropathic pain (Pasierski & Szulczyk, 2022). The use of herbal remedies for pain relief has its roots in various traditional medicinal practices, highlighting the long-lasting importance of knowledge based on herbs.

These accounts provide only a partial view of the vast field of plant-based therapeutics, where the abundant healing properties of nature intersect with scientific investigation. Every new discovery blurs the boundaries between ancient knowledge and modern scientific advancements, emphasising the lasting effectiveness of plant resources in enhancing health and well-being.

Legal framework for magistral formulations in Spain

Legal Basis and Adherence to Regulations

In Spain, the establishment of magistral formulations is supported by a strong legislative structure that clearly defines the duties, obligations, and particular instructions for compounding chemists. The law, which consists of the Spanish Royal Decree 175/2001 and Royal Decree 782/2013, provides comprehensive guidelines on the compounding, quality control, and dispensing of these customised pharmaceuticals (“Machine Translation of ‘Royal Decree 782/2013, on 11 October, on Distribution of Medicinal Products for Human Use.’ (Spain),” n.d.).

The Spanish Agency for Medicines and Health Products (AEMPS) plays a crucial role in supervising and controlling the preparation of magistral formulations. The AEMPS has a crucial responsibility in ensuring that chemists adhere to established processes, uphold quality standards, and maintain the utmost level of safety and effectiveness in these preparations.

Requirements for Quality Assurance and Documentation

Rigorous quality control methods are essential for the development of magistral formulations. Pharmacists must follow protocols that cover the acquisition of raw ingredients, compounding methods, and quality control evaluations. Comprehensive documentation of the compounding process, which includes batch records, ingredient specifications, and analytical test results, is kept to by the pharmacist, and clinic, to enable traceability and guarantee adherence to the set standards.

Pharmacists' Ethical Obligations

Pharmacists have a significant professional duty in synthesising magistral formulations, since they are responsible for ensuring the safety and effectiveness of medications leaving their pharmacy. Proficiency in compounding processes, pharmaceutical chemistry, and therapeutic compatibility is a prerequisite for them. The chemist's main responsibility goes beyond just creating pharmaceuticals; they are responsible for evaluating compatibility, stability, and ensuring the proper utilisation of compounded medications. Each magistrates formulation, is a personalised prescription of phyto-therapeutics, sometimes created, and sometimes of already formulated products.

Conformity to Good Manufacturing Practices (GMP)

Although magistral formulations are prepared on an individual basis, the procedure is influenced by the fundamental principles of Good Manufacturing Practices (GMP). Pharmacists are required to maintain Good Manufacturing Practice (GMP) standards in their compounding facilities, which involves assuring cleanliness, controlled conditions, and following established compounding processes. This alignment also guarantees the uniformity, dependability, and security of the manufactured formulas.

Uninterrupted compliance with changing regulations

The pharmaceutical regulatory environment is always changing, requiring ongoing compliance with developing standards and recommendations. Pharmacists participate in continuous training, educational seminars, and professional development activities to be updated on regulatory changes, guaranteeing consistent compliance and the delivery of superior compounded pharmaceuticals.

Spain's regulatory system for compounded drugs is in accordance with European Union legislation, including the European Commission Directives. This directive primarily pertains to the good manufacturing practice of sterile medical goods intended for extemporaneous use. Its impact spans Spanish rules, fostering harmonisation within the EU and guaranteeing compliance with standardised procedures for manufacturing sterile drugs.

The European Pharmacopoeia, well-known for establishing high-quality standards and detailed guidelines for pharmaceutical components and medicines, exerts a considerable impact on compounded drugs in Spain. By adhering to the standards set by the European Pharmacopoeia, compounded drugs are guaranteed to satisfy specific quality criteria, which ultimately enhances their safety and effectiveness.

Primary sources of evidence for the comprehensiveness of a regulatory framework.

The regulation of compounded drugs in Spain is principally based on two legislative instruments, namely Royal Decree 175/2001 and Royal Decree 782/2013. These documents are essential for the regulatory framework, outlining the rules and criteria for compounding operations in the nation.

The Spanish Agency for Medicines and Medical Devices (AEMPS) has a vital function in supervising and controlling compounded drugs. The AEMPS releases reports, conducts

inspections, addresses safety concerns, and provides regulatory updates pertaining to compounded drugs. These publications are essential sources of information, providing valuable knowledge about the changing regulatory environment and guaranteeing ongoing adherence to safety and quality requirements.

Scholarly literature and contributions to the professional field

The academic literature, which includes reviews and research papers specifically examining pharmaceutical legislation in Spain and Europe, is an invaluable source of knowledge. These papers provide insight into the criteria, regulations, and developing methodologies in compounded pharmaceuticals. Furthermore, the input from chemist organisations and professional bodies provides valuable insight on optimal procedures, hence aiding in the formulation and execution of laws.

Methodological Enhancements

Strong and reliable procedural methods are crucial to strengthen the basis for using herbal medicine, supported by evidence in clinical studies. Methodological enhancements, firmly grounded in principles of evidence-based medicine, seek to improve the dependability, accuracy, and applicability of outcomes from clinical trials including botanical substances.

Synthesising Multiple Sources of Evidence

The thorough evaluation of botanical therapies relies on the integration of many evidence sources, such as traditional knowledge, preclinical investigations, and clinical trial outcomes. These examples of integrating evidence act as solid bases, promoting a more profound comprehension and confidence in the healing capabilities of plant medicines.

Consolidating Conventional Wisdom

During a scientific experiment investigating the impact of a traditional herbal remedy on gastrointestinal diseases, working together with local healers revealed the historical use of some herbs in relieving digestive pain. The formulation's components and doses were guided by these discoveries, which harmonised ancient wisdom with contemporary clinical research. By incorporating traditional wisdom into the trial design, it was demonstrated how historical traditions might enhance and authenticate botanical therapies.

Thorough Compilation of Evidence

The conclusions of a meta-analysis, examining the effectiveness of botanical therapies in treating chronic pain, were greatly influenced by the incorporation of various sources of information. Preclinical research that synthesised data on the analgesic characteristics of a particular plant chemicals, were combined with clinical trial data that assessed the effectiveness in relieving pain. The complete synthesis confirmed the effectiveness of botanical therapies, showing consistent pain reduction results in different trials and contexts. This is how a compilation of evidence would lead to stronger methodological approaches to botanical medicine research.

The usefulness of combining conventional, preclinical, and clinical data in botanical clinical trials, is highlighted by concrete instances that demonstrate the integration of evidence sources in the methodology of the research being conducted. Aligning traditional knowledge with trial designs, establishing connections between preclinical and clinical results, and synthesising information from meta-analyses, greatly help to validate the findings of botanical therapies. The use of evidence integration in these integrated techniques, enhances our comprehension and assurance in the therapeutic capabilities of botanical medicines.

Implementing the principles of evidence-based medicine

Integrating evidence-based medicine (EBM) principles into the field of herbal medicines is crucial for enhancing the methodological structure of clinical trials. This entails customising study approaches to reflect the natural variances seen in botanical medicines, removing biases, and optimising outcome evaluations. For example, the inclusion of adaptive trial designs in randomised controlled trials, enables the modification of dosages or intervention arms based on the accumulation of data. This adaptable method not only guarantees flexibility but also maintains scientific precision, therefore optimising the efficiency of the study.

Synthesis of Varied Information Sources

To fully comprehend botanical remedies, it is essential to effectively combine several sources of knowledge. To conduct thorough assessments, it is crucial to integrate conventional knowledge, bridge the gap between laboratory research and practical outcomes, and provide frameworks for complete evidence synthesis. Researchers can enhance their studies on traditional herbal treatments by cooperating with local healers, which enables them to incorporate indigenous knowledge. This collaboration not only strengthens the rationale and hypotheses underlying the botanical intervention but also fosters a more comprehensive and integrated approach to trial design and implementation.

Standardised Cultivation and Harvesting Techniques

Improving/enhancing the approach of phyto-therapeutic research, frequently requires using standardised cultivation and harvesting techniques, which may have a substantial influence on the quality, uniformity, and long-term viability of herbal products.

The primary benefit of standardised cultivation and harvesting is the guarantee of consistent quantities of bioactive chemicals in plant materials. This methodology reduces the influence of external factors and ensures consistent harvesting methods, hence mitigating fluctuations in the concentration of bioactive chemicals in the finished product. As a result, maintaining consistency in herbal treatments, guarantees that the industry/researchers consistently have trustworthy, therapeutic samples in various batches, enhancing the effectiveness and dependability of such in clinical applications.

Furthermore, the adoption of standardised methods in planting and harvesting significantly enhances quality control and standardisation. This approach allows for accurate evaluation of efficacy and excellence, ensuring that herbal products across the board adhere to set

benchmarks. This rigorous oversight of the manufacturing process guarantees that clients constantly obtain herbal treatments that are both effective and safe.

In addition to quality monitoring, standardised cultivation and harvesting procedures are also essential in encouraging sustainable and ethical approaches in botanical medicine. Prioritising ecologically sustainable farming methods and equitable labour practices, not only promotes the creation of premium herbal goods, but also enhances the social and environmental welfare of the communities engaged in cultivation.

Moreover, this approach promotes the preservation of biodiversity, by promoting the cultivation of uncommon or threatened medicinal plants. Through the cultivation of these plants in controlled surroundings, researchers and practitioners actively contribute to the preservation of these species, therefore alleviating the strain on wild populations. This technique is in accordance with the principles of conservation biology and serves to protect the variety of medicinal plant species for future generations.

Standardised cultivation and harvesting procedures in botanical medicine research provide a comprehensive and versatile approach. They not only guarantee the uniformity of bioactive substances, providing dependable medicinal effects, but also endorse ethical methods, uphold sustainability, and make substantial contributions to biodiversity conservation efforts. These improved techniques allow the creation of herbal products that are of superior quality, highly efficient, and ecologically friendly.

Biomarker And Genetic Analysis

The use of biomarker and genetic analysis in botanical medicine research has several benefits, greatly influencing the customisation of therapy, evaluation of safety, and comprehension of therapeutic processes. These approaches enable customised therapies by identifying genetic and biochemical markers associated with treatment response, so optimising the effectiveness of therapy while minimising negative side effects. Furthermore, they enable the prediction and proactive handling of probable adverse responses, hence improving patient safety and overall medication administration.

Furthermore, the examination of biomarkers and genetic analysis explores the complex mechanisms that underlie botanical medicines, leading to a more profound comprehension of their therapeutic impacts on a molecular scale. Randomised control trials provide significant insights into the effectiveness of treatments across varied populations. However, biomarker and genetic analysis stand out, by focusing on individualised therapies that are tailored to a person's genetic and biochemical traits. This individualised strategy guarantees more precise and efficient interventions in contrast to conventional clinical studies that concentrate on general population reactions.

These modern approaches are highly effective in identifying the exact biochemical pathways that are affected by herbal treatments. They also disclose molecular interactions that are frequently not included in more general clinical research. This comprehensive understanding not only determines which groups of patients are likely to have positive effects from specific

herbal remedies, but also predicts possible negative consequences based on individual genetic and physiological characteristics.

In addition, the use of biomarker and genetic analysis plays a significant role in the process of drug discovery as it aids in the identification of novel therapeutic targets, hence potentially facilitating the development of groundbreaking herbal-based treatments. This advancement offers enhanced therapy alternatives and broadens the utilisation of herbal medicine in addressing diverse health concerns.

To summarise, the utilisation of biomarker and genetic analysis in botanical medicine research has brought about a significant transformation in the customisation of treatments, prediction of safety, comprehension of molecular pathways, and the advancement of innovative remedies. By utilising genetic and biochemical data, these approaches provide a new period of tailored, secure, and efficient botanical therapies, significantly influencing patient care and propelling the profession of herbal medicine.

Implementation of standardised procedures and rigorous quality control protocols (HPLC)

Strict attention to standardisation and quality control methods is necessary due to the extensive variety seen in botanical preparations, as stated prior. To ensure consistency across many clinical studies, it is essential to establish comprehensive protocols that govern botanical preparation techniques and enforce stringent quality control systems. For instance, while examining the effects of a particular herbal extract, one may apply accurate manufacturing instructions, extraction methods, and the use of High-Performance Liquid Chromatography (HPLC) to confirm the presence and amounts of active compounds. These procedures greatly aid in preserving consistency between batches, therefore guaranteeing the dependability and uniformity of testing results.

The advantages of High-Performance Liquid Chromatography (HPLC) in Botanical Medicine are substantial and diverse, enhancing the progress and dependability of research and development in this domain.

An inherent benefit of HPLC is its enhanced standardisation and quality control. This method facilitates the accurate detection and measurement of distinct bioactive chemicals present in plant extracts: including flavonoids, alkaloids, and terpenes. Precise measurements enable the standardisation of the extract's potency, guaranteeing consistent therapeutic benefits across different batches and formulations. Moreover, the capacity of HPLC to accurately distinguish between identical chemicals inside plants is essential.

Numerous plants possess chemically similar molecules with nuanced distinctions. The high-performance liquid chromatography (HPLC) has the capacity to separate and measure these distinct constituents, guaranteeing accurate identification and proper utilisation of the active substance, hence reducing the likelihood of mistakes in therapeutic administration.

HPLC, besides its ability to identify substances, also enables the detection of adulteration and contamination in botanical goods. HPLC can detect the presence of extraneous chemicals, such as fillers, contaminants, or adulterants, by accurately analysing the components of plant

extracts. This procedure ensures the genuineness of the goods and protects consumers from potentially hazardous substances.

Furthermore, HPLC plays a crucial role in advancing research and development in the field of botanical medicine by facilitating the detection and analysis of new bioactive chemicals obtained from plants. This analytical approach is crucial in discovering new components in plants, which are necessary for the creation of innovative herbal treatments and for gaining a thorough grasp of the pharmacology of current botanical products.

HPLC offers significant advantages compared to older techniques such as UV spectroscopy, thin-layer chromatography (TLC), and bioassays. UV spectroscopy, although more time-efficient and cost-effective, lacks specificity and has challenges in distinguishing identical chemicals found in plant extracts. In contrast, HPLC provides greater resolution and can differentiate such compounds.

Similarly, while TLC is less complex, it only offers qualitative data and lacks the sensitivity and precision provided by HPLC for the accurate measurement of active chemicals. Bioassays, which rely on biological reactions, may exhibit lower specificity and reproducibility when compared to the direct chemical analysis facilitated by HPLC. HPLC offers significant benefits in the field of botanical medicine analysis, guaranteeing precision, specificity, and dependability in the identification and measurement of compounds.

Practical uses:

1. HPLC plays a vital role in quantifying the amount of curcumin in turmeric extracts, as part of the effort to use the healing properties of plants, (Jiang, Ghosh, & Charcosset, 2021) (Suresh, Behera, Selvaraja, & Pratap, 2020).
2. Identification of hypericin in St. John's wort for the treatment of moderate depression, (Zeliou, Kontaxis, Margianni, Petrou, & Lamari, 2017).
3. Quantifying the concentration of ginsenosides in ginseng to enhance cognitive function, (Hu, Chun, Kim, Cho, & Ku, 2019) (He, Zhang, Luo, Zhang, & Mu, 2016).
4. Identifying contaminants in herbal items sold on the market, (Balekundri & Mannur, 2020).

HPLC, or high-performance liquid chromatography, is an influential analytical method that has greatly improved research and development in the field of plant medicine. The capacity to precisely detect and measure active chemicals plays a crucial role in guaranteeing the quality, effectiveness, and safety of plant-derived treatments.

The utilisation of the methodological improvements in this chapter, goes beyond conventional scientific rigour. It provides healthcare providers with trustworthy evidence, enabling them to make educated decisions about incorporating botanical remedies into patient care. Furthermore, it enhances patient safety, by recognising possible hazards and customising therapies to meet individual requirements, so enhancing the entire healthcare experience.

Ultimately, improvements in the methodology of botanical medicine research act as drivers for advancement, promoting standardised, evidence-based, and patient-focused methods.

Through enhancing the dependability, security, and comprehension of herbal remedies, these developments enhance the legitimacy and potential of botanical medicine, providing innovative therapeutic alternatives while safeguarding traditional knowledge and natural resources. Adopting these improvements not only helps herbal medicine progress but also enhances the worldwide healthcare field by combining traditional knowledge and modern scientific rigour.

Recommendations for Further Research and Implementation

It is crucial to make available recommendations for further research and implementation to deepen comprehension and improve the incorporation of these strategies into mainstream healthcare.

Verification and substantiation of clinical effectiveness, and supporting data synthesis serves as essential foundations. It is essential to carry out clinical trials to verify the effectiveness, safety, and comparative advantages of botanical medicine. Utilising evidence from rigorous trials creates a strong basis for making well-informed clinical decisions.

Concurrently, it is crucial to enhance the regulatory framework. Consistent improvement of regulatory standards for botanical medicine guarantees compliance with quality and safety criteria. The collaboration among regulatory bodies, healthcare professionals, and researchers helps to simplify guidelines to enhance safety, adoption across countries within Europe, (Bilia & Costa, 2021), and effectiveness of medicines.

Furthermore, the incorporation of patient-centred integration and the exploration of combinatorial approaches show great potential. Education programmes targeting healthcare professionals and individuals promote understanding and endorsement of personalised pharmaceutical choices and holistic treatments.

Providing patients with information enhances the practice of collaborative decision-making in selecting treatment options. Furthermore, exploring the potential for synergy by combining compounded formulations with herbal medicine creates opportunities for novel treatment approaches.

Ultimately, the incorporation of evidence-based methodologies in the field of botanical medicine is crucial for the establishment of rigorous clinical trials. Strategies that prioritise evidence-based principles, strict quality control, integration of diverse information, and patient-centred approaches collectively enhance the dependability, safety, and effectiveness of botanical interventions. Ultimately, these strategies reshape healthcare paradigms by promoting more personalised and holistic patient outcomes.

Summary

This research explores the field of botanical medicine, focusing on improvements in research methods to improve the quality of botanical research. It observes that one can combine

traditional knowledge with rigorous scientific approaches. The study explores the importance of evidence-based methods, examining historical settings and discussing the main goals and structure of the thesis.

The literature review serves as a brief investigation of botanical medicine, examining its historical development, explaining concepts of pharmacognosy, and outlining evidence-based research approaches. In addition, it briefly examines methods aimed at enhancing research methodology, with a specific focus on evidence-based medical concepts, standardised procedures, and the synthesis of various material.

The practical implementation of botanical medicine is demonstrated using specialised formulations and the incorporation of plant-based therapy in clinical settings. The usefulness of botanical treatments is supported by examining notable botanicals such as Echinacea, Ginkgo Biloba, and Curcumin, thus highlighting the importance of having stringent, and quality research methodologies to improve the findings, and reliability of conclusions.

The paper similarly, focuses on the shift from preclinical research to clinical trials, showcasing instances like the use of Resveratrol for cardiovascular health and Cannabidiol (CBD) for epileptic therapy. It underscores the advancement of botanical medicine from laboratory investigations to practical implementation.

Moreover, the study examines medications that are derived from herbal sources, such as Aspirin, Morphine, and Artemisinin, providing a detailed analysis of their historical importance and current therapeutic functions.

The aim of this research paper, is to investigate methodological improvements and their potential benefits for enhancing botanical medicine research. It delves into tactics designed to strengthen the research in this field. The paper thoroughly investigates methods of standardisation in the process of cultivating and harvesting, the use of biomarker and genetic studies, along with the prowess that is HPLC. Each of these methods is thoroughly assessed for their contribution to enhancing the dependability, security, and comprehension of botanical medication.

The research concludes by acknowledging where further research and implementation of such can take place, along with the consequential benefits of such.

To summarise comprehensively, the paper delineates potential avenues for future research in the field of plant medicine. I hope that recommendations support the ongoing investigation, establishment of standards, and integration of traditional knowledge with modern scientific methods to enhance the field of botanical medicine.

The thorough investigation carried out and the combination of conventional knowledge with evidence-based methods in botanical medicine research are authenticated by the references provided throughout the text.

References:

Achan, J., Talisuna, A. O., Erhart, A., Yeka, A., Tibenderana, J. K., Baliraine, F. N., . . . D'Alessandro, U. (2011). Quinine, an old anti-malarial drug in a modern world: role in the treatment of malaria. *Malaria Journal*, *10*(1). https://doi.org/10.1186/1475-2875-10-144

Arias, S., Leon, M., Jaimes, D., & Bustos, R. H. (2021). Clinical Evidence of Magistral Preparations Based on Medicinal Cannabis. *Pharmaceuticals*, *14*(2), 78. https://doi.org/10.3390/ph14020078

Arias, S., Leon, M., Jaimes, D., & Bustos, R. H. (2021). Clinical Evidence of Magistral Preparations Based on Medicinal Cannabis. *Pharmaceuticals*, *14*(2), 78. https://doi.org/10.3390/ph14020078

Aspirin, morphine and chemotherapy: the essential medicines powered by plants. (2021, February 19). Retrieved from https://www.nhm.ac.uk/discover/essential-medicines-powered-by-plants.html

Balekundri, A., & Mannur, V. (2020). Quality control of the traditional herbs and herbal products: a review. *Future Journal of Pharmaceutical Sciences*, *6*(1). https://doi.org/10.1186/s43094-020-00091-5

Benzie, I. F. F., & Wachtel-Galor, S. (2011). *Herbal Medicine*. CRC Press. Retrieved from http://books.google.ie/books?id=7WDgesSflScC&printsec=frontcover&dq=Herbal+Medicine:+Biomolecular+and+Clinical+Aspects.+2nd+edition.&hl=&cd=1&source=gbs_api

Biagi, M., Pecorari, R., Appendino, G., Miraldi, E., Magnano, A., Governa, P., . . . Giachetti, D. (2016). Herbal Products in Italy: The Thin Line between Phytotherapy, Nutrition and Parapharmaceuticals; A Normative Overview of the Fastest Growing Market in Europe. *Pharmaceuticals*, *9*(4), 65. https://doi.org/10.3390/ph9040065

Bilia, A. R., & Costa, M. D. C. (2021). Medicinal plants and their preparations in the European market: Why has the harmonization failed? The cases of St. John's wort, valerian, ginkgo, ginseng, and green tea. *Phytomedicine*, *81*, 153421. https://doi.org/10.1016/j.phymed.2020.153421

Calapai, G., Mannucci, C., Chinou, I., Cardia, L., Calapai, F., Sorbara, E. E., Firenzuoli, B., Ricca, V., Gensini, G. F., & Firenzuoli, F. (2019, August 29). Preclinical and Clinical Evidence Supporting Use of Cannabidiol in Psychiatry. *Evidence-Based Complementary and Alternative Medicine*, *2019*, 1–11. https://doi.org/10.1155/2019/2509129

Cheikhyoussef, A., Shapi, M., Matengu, K., & Mu Ashekele, H. (2011). Ethnobotanical study of indigenous knowledge on medicinal plant use by traditional healers in Oshikoto region, Namibia. *Journal of Ethnobiology and Ethnomedicine*, *7*(1). https://doi.org/10.1186/1746-4269-7-10

David, M. N. V., & Shetty, M. (2023). Digoxin. In StatPearls. StatPearls Publishing.

England, N. (2016, September 7). NHS England » Improving Outcomes through Personalised Medicine. Retrieved from https://www.england.nhs.uk/publication/improving-outcomes-through-personalised-medicine/

He, J. M., Zhang, Y. Z., Luo, J. P., Zhang, W. J., & Mu, Q. (2016). Variation of Ginsenosides in Ginseng of Different Ages. *Natural Product Communications*, *11*(6), 1934578X1601100. https://doi.org/10.1177/1934578x1601100610

Headquarters, W. (2006, December 12). WHO monographs on selected medicinal plants. Retrieved from https://www.who.int/publications/i/item/9241545178

Hewlings, S., & Kalman, D. (2017). Curcumin: A Review of Its Effects on Human Health. *Foods*, *6*(10), 92. https://doi.org/10.3390/foods6100092

Hou, C. C., Chen, C. H., Yang, N. S., Chen, Y. P., Lo, C. P., Wang, S. Y., . . . Shyur, L. F. (2010). Comparative metabolomics approach coupled with cell- and gene-based assays for species classification and anti-inflammatory bioactivity validation of Echinacea plants. *The Journal of Nutritional Biochemistry*, *21*(11), 1045–1059. https://doi.org/10.1016/j.jnutbio.2009.08.010

Hu, J., Chun, Y., Kim, J., Cho, I., & Ku, S. (2019). Ginseng berry aqueous extract prevents scopolamine-induced memory impairment in mice. *Experimental and Therapeutic Medicine*. https://doi.org/10.3892/etm.2019.8090

Hussain, K., Yang, Y., Wang, J., Bian, H., Lei, X., Chen, J., . . . Liao, Z. (2022). Comparative study on the weight loss and lipid metabolism by tea polyphenols in diet induced obese C57BL/6J pseudo germ free and conventionalized mice. *Food Science and Human Wellness*, *11*(3), 697–710. https://doi.org/10.1016/j.fshw.2021.12.027

Indrayanto, G. (2023). Regulation and standardization of herbal drugs: Current status, limitation, challenge's and future prospective. *Profiles of Drug Substances, Excipients and Related Methodology*. https://doi.org/10.1016/bs.podrm.2023.11.003

Italy, U. M. (2021, November 19). Native Americans' many contributions to medicine - U.S. Embassy & Consulates in Italy. Retrieved from https://it.usembassy.gov/native-americans-many-contributions-to-medicine/

Ivanova Stojcheva, E., & Quintela, J. C. (2022). The Effectiveness of Rhodiola rosea L. Preparations in Alleviating Various Aspects of Life-Stress Symptoms and Stress-Induced Conditions—Encouraging Clinical Evidence. *Molecules*, *27*(12), 3902. https://doi.org/10.3390/molecules27123902

Jamshed, F., Dashti, F., Ouyang, X., Mehal, W. Z., & Banini, B. A. (2023). New uses for an old remedy: Digoxin as a potential treatment for steatohepatitis and other disorders. *World Journal of Gastroenterology*, *29*(12), 1824–1837. https://doi.org/10.3748/wjg.v29.i12.1824

Jiang, T., Ghosh, R., & Charcosset, C. (2021). Extraction, purification and applications of curcumin from plant materials-A comprehensive review. *Trends in Food Science & Technology*, *112*, 419–430. https://doi.org/10.1016/j.tifs.2021.04.015

Krishna, S., Bustamante, L., Haynes, R. K., & Staines, H. M. (2008). Artemisinins: their growing importance in medicine. *Trends in Pharmacological Sciences*, *29*(10), 520–527. https://doi.org/10.1016/j.tips.2008.07.004

Kumar, A., P, N., Kumar, M., Jose, A., Tomer, V., Oz, E., . . . Oz, F. (2023). Major Phytochemicals: Recent Advances in Health Benefits and Extraction Method. *Molecules*, *28*(2), 887. https://doi.org/10.3390/molecules28020887

Kwee, C. M., van Gerven, J. M., Bongaerts, F. L., Cath, D. C., Jacobs, G., Baas, J. M., & Groenink, L. (2022, October 14). Cannabidiol in clinical and preclinical anxiety research. A systematic review into concentration–effect relations using the IB-de-risk tool. *Journal of Psychopharmacology*, *36*(12), 1299–1314. https://doi.org/10.1177/02698811221124792

Machine Translation of "Royal Decree 782/2013, On 11 October, On Distribution Of Medicinal Products For Human Use." (Spain). (n.d.). Retrieved from https://www.global-regulation.com/translation/spain/1466696/royal-decree-782-2013%252c-on-11-october%252c-on-distribution-of-medicinal-products-for-human-use.html

Magistral medicines. (n.d.). Retrieved from https://laegemiddelstyrelsen.dk/en/pharmacies/pharmacies/magistral-medicines/

Mahdi, J. G., Mahdi, A. J., Mahdi, A. J., & Bowen, I. D. (2006). The historical analysis of aspirin discovery, its relation to the willow tree and antiproliferative and anticancer potential. *Cell Proliferation*, *39*(2), 147–155. https://doi.org/10.1111/j.1365-2184.2006.00377.x

Markets, R. A. (2023, October 3). *Global Cannabidiol (CBD) Market Report 2023: Market is Set to Grow by Over $22 Billion to 2027 - Long-term Forecast to 2032*. https://www.prnewswire.com/news-releases/global-cannabidiol-cbd-market-report-2023-market-is-set-to-grow-by-over-22-billion-to-2027---long-term-forecast-to-2032-301945474.html#:~:text=The%20global%20cannabidiol%20market%20grew,at%20a%20CAGR%20of%2035.7%25.

Niemeyer, K., Bell, I. R., & Koithan, M. (2013). Traditional knowledge of Western herbal medicine and complex systems science. *Journal of Herbal Medicine*, *3*(3), 112–119. https://doi.org/10.1016/j.hermed.2013.03.001

Opium Poppy. (n.d.). Retrieved from https://museum.dea.gov/exhibits/online-exhibits/cannabis-coca-and-poppy-natures-addictive-plants/opium-poppy#:~:text=The%20poppy%20plant%2C%20Papaver%20somniferum,and%20their%20semi%2Dsynthetic%20substitutes.

Pasierski, M., & Szulczyk, B. (2022). Beneficial Effects of Capsaicin in Disorders of the Central Nervous System. *Molecules*, *27*(8), 2484. https://doi.org/10.3390/molecules27082484

Pereira, A. C. D. S., Miranda, E. S., Castilho, S. R. D., Futuro, D. O., Teixeira, L. A., & Paula, G. R. D. (2016). Magistral drugs in hospitalized newborns and children. *Revista Paulista De Pediatria (English Edition)*, *34*(4), 403–407. https://doi.org/10.1016/j.rppede.2016.02.012

Petrovska, B. (2012). Historical review of medicinal plants′ usage. *Pharmacognosy Reviews*, *6*(11), 1. https://doi.org/10.4103/0973-7847.95849

Posadino, A. M., Giordo, R., Pintus, G., Mohammed, S. A., Orhan, I. E., Fokou, P. V. T., . . . Cho, W. C. (2023). Medicinal and mechanistic overview of artemisinin in the treatment of human diseases. *Biomedicine & Pharmacotherapy*, *163*, 114866. https://doi.org/10.1016/j.biopha.2023.114866

Šantić, Ž., Pravdić, N., Bevanda, M., & Galić, K. (2017). The historical use of medicinal plants in traditional and scientific medicine. *Psychiatria Danubina*, *29 Suppl 4*(Suppl 4), 787–792.

Sasidharan, S., Chen, Y., Saravanan, D., Sundram, K., & Latha, L. (2010). Extraction, Isolation And Characterization Of Bioactive Compounds From Plants' Extracts. *African Journal of Traditional, Complementary and Alternative Medicines*, *8*(1). https://doi.org/10.4314/ajtcam.v8i1.60483

Sena, E. S., Currie, G. L., McCann, S. K., Macleod, M. R., & Howells, D. W. (2014). Systematic Reviews and Meta-Analysis of Preclinical Studies: Why Perform Them and How to Appraise Them Critically. *Journal of Cerebral Blood Flow & Metabolism*, *34*(5), 737–742. https://doi.org/10.1038/jcbfm.2014.28

Snitz, B. E. (2009). <emph type="ital">Ginkgo biloba</emph> for Preventing Cognitive Decline in Older Adults<subtitle>A Randomized Trial</subtitle>. *JAMA*, *302*(24), 2663. https://doi.org/10.1001/jama.2009.1913

Suresh, H., Behera, A. R., Selvaraja, S. K., & Pratap, R. (2020). Quantification of Curcuminoids in Turmeric Using Visible Reflectance Spectra and a Decision-Tree Based Chemometric Approach. *Journal of the Electrochemical Society*, *167*(16), 167528. https://doi.org/10.1149/1945-7111/abd603

The use of non-pharmaceutical forms of Artemisia. (2019, October 10). Retrieved from https://www.who.int/news/item/10-10-2019-the-use-of-non-pharmaceutical-forms-of-artemisia

Tilburt, J. (2008). Herbal medicine research and global health: an ethical analysis. *Bulletin of the World Health Organization*, *86*(8), 594–599. https://doi.org/10.2471/blt.07.042820

Tinsley, G. M., Jagim, A. R., Potter, G. D. M., Garner, D., & Galpin, A. J. (2023). Rhodiola Rosea as an Adaptogen to Enhance Exercise Performance: A Review of the Literature. *British Journal of Nutrition*, 1–27. https://doi.org/10.1017/s0007114523001988

Traditional medicine has a long history of contributing to conventional medicine and continues to hold promise. (2023, August 10). Retrieved from https://www.who.int/news-room/feature-stories/detail/traditional-medicine-has-a-long-history-of-contributing-to-conventional-medicine-and-continues-to-hold-promise

Traditional, Complementary and Integrative Medicine. (2019, November 25). Retrieved from https://www.who.int/health-topics/traditional-complementary-and-integrative-medicine#tab=tab_1

Vicente, A. M., Ballensiefen, W., & Jönsson, J. I. (2020). How personalised medicine will transform healthcare by 2030: the ICPerMed vision. *Journal of Translational Medicine*, *18*(1). https://doi.org/10.1186/s12967-020-02316-w

Wardani, R. S., Schellack, N., Govender, T., Dhulap, A. N., Utami, P., Malve, V., & Wong, Y. C. (2023). Treatment of the common cold with herbs used in Ayurveda and Jamu: monograph review and the science of ginger, liquorice, turmeric and peppermint. *Drugs in Context*, *12*, 1–10. https://doi.org/10.7573/dic.2023-2-12

Weaver, B. A. (2014). How Taxol/paclitaxel kills cancer cells. *Molecular Biology of the Cell*, *25*(18), 2677–2681. https://doi.org/10.1091/mbc.e14-04-0916

Zeliou, K., Kontaxis, N. I., Margianni, E., Petrou, C., & Lamari, F. N. (2017). Optimized and Validated HPLC Analysis of St. John's Wort Extract and Final Products by Simultaneous Determination of Major Ingredients. *Journal of Chromatographic Science*, *55*(8), 805–812. https://doi.org/10.1093/chromsci/bmx040

Zunic, L., Skrbo, A., & Dobraca, A. (2017). Historical Contribution of Pharmaceutics to Botany and Pharmacognosy Development. *Materia Socio Medica*, *29*(4), 291. https://doi.org/10.5455/msm.2017.29.291-300

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