ECRONICON OPEN ACCESS

EC CLINICAL AND MEDICAL CASE REPORTS

Review Article

A Comprehensive Review of Specific Herbal Medicines with Immunomodulatory Effects, and COVID-19

Nicholas A Kerna[1,2]*, Joseph Anderson II[3], Kevin D Pruitt[4,5], Hilary M Holets[6,7], ND Victor Carsrud[8], Raymond Nomel[9], Uzoamaka Nwokorie[10] and John V Flores[6,7]

[1]*SMC–Medical Research, Thailand*

[2]*First InterHealth Group, Thailand*

[3]*International Institute of Original Medicine, USA*

[4]*Kemet Medical Consultants, USA*

[5]*PBJ Medical Associates, LLC, USA*

[6]*Beverly Hills Wellness Surgical Institute, USA*

[7]*Orange Partners Surgicenter, USA*

[8]*Lakeline Wellness Center, USA*

[9]*All Saints University, College of Medicine, St. Vincent and the Grenadines*

[10]*University of Washington, USA*

***Corresponding Author:** Nicholas A Kerna, (mailing address) POB47 Phatphong, Suriwongse Road, Bangkok, Thailand 10500. Contact: medpublab+drkerna@gmail.com

Received: September 21, 2021; **Published:** November 30, 2021

DOI: 10.31080/eccmc.2021.04.00483

Abstract

In contemporary times, herbal medicine is used as an adjunct to conventional therapy and for health promotion. Herbs that have long been considered curative or prophylactic should be further studied in clinical trials. Can these time-tested natural therapies be used and trusted in exceptional circumstances, such as the ongoing COVID-19 pandemic?

Traditional medicines have led to a revolution in and evolution of modern medicine. Herbs, such as *Echinacea purpurea*, *Curcuma longa*, *Allium sativum, Althaea officinalis, Andrographis paniculate, Commiphora molmol, Cymbopogon citratus, Eucalyptus globulus,* have shown immunomodulatory effects. Many plant-based formulations with potential immunomodulatory activity have been isolated and utilized—even without supportive evidence-based findings. Thus, more initiative toward human trials should be undertaken to understand better how herbs promote human health and prevent or cure specific illnesses and diseases.

Moreover, and most importantly, the interests of indigenous communities—which are the primary source of rich traditional knowledge and the natural reserve of herbal plants—should be safeguarded.

Keywords: *Mangosteen; Natural Remedy; Phytotherapeutic; Thai; Traditional; Vedas*

Abbreviations

ASEAN: Association of Southeast Asian Nations; BFAD: Bureau of Food and Drugs; CITES: Convention on International Trade in Endangered Species of Wild Fauna and Flora; GACP, 2003: Good Agricultural and Collection Practices 2003; GMP: Good Manufacturing Prac-

tices; HATC: Herbal Anatomical Therapeutic Chemical; Hcov-NL63: Human Coronavirus NL63; HM: Herbal Medicine; MERS: Middle East Respiratory Syndrome; SD: Synthetic Drug; UMC: Uppsala Monitoring Center; URG: Uniform Regulation Guidelines; WHO: World Health Organization

Introduction

Etymologically, "herb" is derived from the Latin word *herba* and the French word *herbe*—referring to any part of a woody or non-woody plant [1]. In the absence of scientific knowledge, the early human civilization turned instinctively toward nature, searching for cures for their ailments [2].

The immeasurable value of plants in healthcare became known with the gradual technological advancement and expansion of scientific knowledge. Presently, herbal medicine is no longer folklore; it has become a distinct branch of medicine, reinforced by scientific evidence. Ethnobotany is the study of traditional plants regarding their medicinal properties [3]. However, herbal combinations with chemically defined active substances or isolated constituents are not categorized as herbal medicines [4].

The practice of alternative and complementary medicine is flourishing. Traditional therapies and allopathic care have joined forces, searching for preventions and cures for numerous illnesses and diseases. Many mainstream drugs are derived from plant sources, such as aspirin, digoxin, quinine, opium, morphine, salicylic acid, and dicoumarol.

History of herbal medicines

Until the sixteenth century, which introduced us to iatrochemistry, plants were the main 'drugs' used to prevent and cure diseases [5]. Even now, the study of phytochemicals is an intriguing aspect of the pharmaceutical industry's research and development. About 80% of the world's population depends on herbal medicines, and the global market for herbal remedies is growing [6].

The late-nineteenth and early-twentieth centuries saw the regression of medicinal plants from therapeutic science. During this period, the shortcomings of herbal medicine and the harmful actions of enzymes due to the inadequate or improper processing of medicinal plants were identified and considered potentially harmful. Moreover, herbal medicines or phytotherapeutic agents generally do not have immediate or substantial pharmacological action; hence, they are not recommended for emergency treatment. Instead, these are used more often to treat chronic diseases.

The early-twentieth century saw the inventions for the preservation and stabilization of medicinal plants, specifically those with labile components. Efforts were extended in cultivating medicinal plants, applying effective manufacturing techniques, and employing favorable processing methods to extract the ingredients [4].

The "early footprints" of traditional medicine

The archaeological find of Sumerian clay tablets depicts that humans have been using medicinal plants for millennia [7]. (Sumer is a venerable Mesopotamian civilization). An ancient Chinese book (circa 2500 BCE) recorded numerous remedies made of dried plant products. The Indian Vedas mention the medicinal properties of spices. A papyrus, written in 1550 BCE, lists plant-based therapeutic remedies. The Iliad and Odyssey (by Homer, circa 8th century BCE) also refer to medicinal plants [5].

Dioscorides is known as the father of "pharmacognosy"—pharmacognosy being the study of drugs and substances of plant origin. In 77 CE, Dioscorides wrote *De Materia Medica*, which recorded 944 drugs, of which 657 are of plant origin [8]. Unani, Indian Vaids, and European and Mediterranean traditional medicine practitioners have used herbs for over 4,000 years. Even the early civilizations of Rome, Egypt, Iran, Africa, and America used herbs for healing (as well as in rituals and ceremonies). The more developed and systemic traditional systems, such as Indian Ayurveda and Traditional Chinese Medicine, utilized herbal plants almost exclusively, as noted in ancient texts [1].

Herbal medicine in immunotherapy

Pathogenic microorganisms are constantly presenting new challenges, such as in the recent COVID-19 pandemic. It is well recognized that specific medicinal plants exert immunomodulatory effects by stimulating immune cells and organs—enhancing cytokine production, inhibiting inflammation, and exerting antiallergic effects [9]. Table 1 lists some herbs with immunomodulatory properties.

Herb	Mechanism of action
Ophiocordyceps lanpingensis (a tonifying Chinese medical plant) [11]	Ameliorates renal dysfunction by inhibiting oxidative stress and enhancing IgG immune response
Mahuang Fuzi Xixin decoction (a Chinese formula) [11]	Exerts a therapeutic effect on allergic inflammation by regulating Th1 and Th2 immune responses
Withania somnifera (powdered root) [12]	Enhances WBC count, improves antibody titer, inhibits delayed hypersensitivity, and enhances phagocytic activity of peritoneal macrophages
Allium sativum (garlic) [13]	Lowers IL-1, IL-6, TNF, IL-8 and boosts IL-10
Aloe vera [14]	Reduces TNF-α and IL-6
Chlorophytum borivilianum (root extract) [15]	Improves both humoral and cell-mediated immunity
Curcuma longa (turmeric/curcumin) [16]	Inhibits nuclear factor kappa B pathway and target of rapamycin (TOR) pathway, thus controlling the release of pro-inflammatory cytokines
Echinacea purpurea [17]	Regulates pro-inflammatory cytokine release

Table 1: *Herbs having immunomodulatory properties.*

Traditional herbal therapy has recently been revived, and various herbs are being scientifically investigated for potential therapeutic applications. The bioactive components of specific herbs increase host defense mechanisms. This increase in intrinsic immunity protects the body against infections and has an antitumor effect. Moreover, the herbal constituents have an antiproliferative effect on tumor cells, helping the host endure damage by toxic chemicals (that are used to destroy cancer cells). Immunomodulatory therapy has proven to be a valuable alternative to conventional chemotherapy, significantly when host defenses mechanisms are impaired, or selective immunosuppression must be induced [10].

The polyphenolic compounds of green tea are antiangiogenic, preventing tumor growth. Soy isoflavones detoxify pro-carcinogens. Vitamin C modulates immune function and has a therapeutic effect in neurodegenerative diseases. Cancer risk is mitigated by green tea, soy food, and Brassica vegetables [9]. However, there are some fundamental differences between herbal medicines (HMs) and chemically synthesized drugs (SDs) as listed in Figure 1.

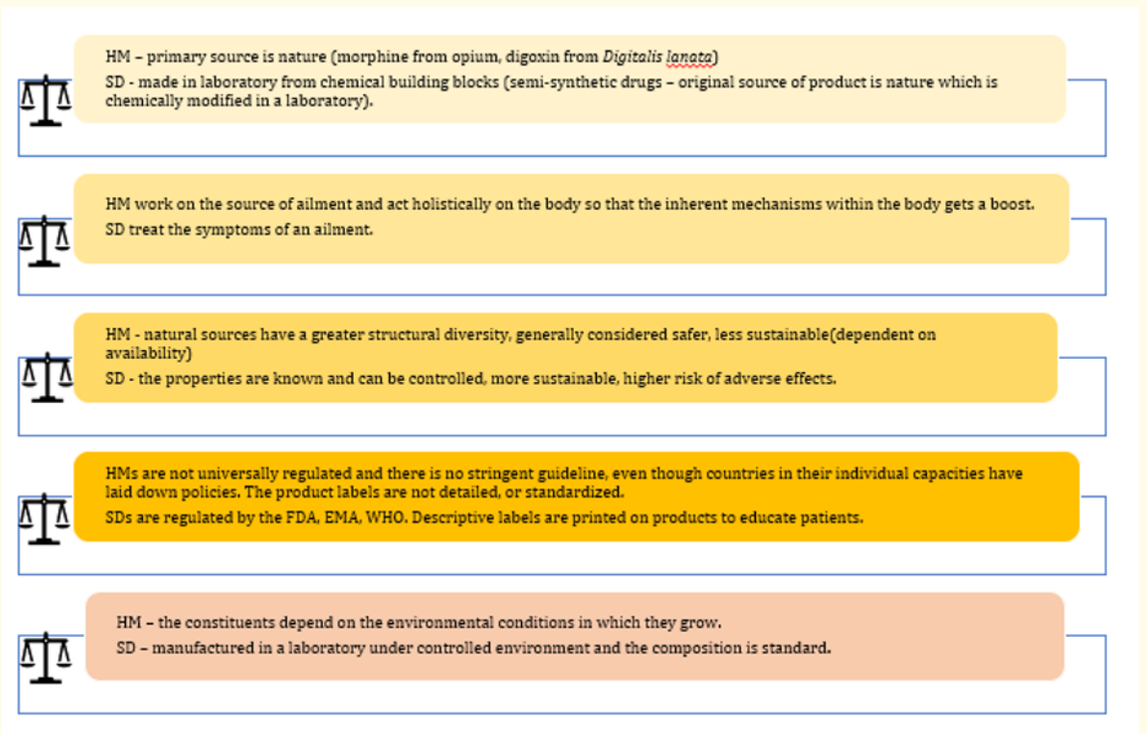

Figure 1: *Fundamental differences between herbal medicines (HMs) and synthetic drugs (SDs).*

Herbal medicine against COVID-19

The capacity to mutate makes a virus unaffected by or impervious to specific synthetic drugs, and is the leading cause of drug resistance. Controlling the persistent COVID-19 pandemic has become a race against time—with truncated timeframes to develop novel antiviral mediators. Thus, medical researchers are looking towards nature for a cure or determent. Moreover, they have been able to repurpose many herbal medicines that are effective against SARC-CoV-2 (Table 2).

Herb	How does it act?
Echinacea purpurea	Acts on the virus membrane and shows a direct virucidal activity
Curcuma longa	Reduction in pro-inflammatory cytokines (symptomatic relief)
Allium sativum [24]	Symptomatic relief from the common cold, proven antiviral activity (against cytomegalovirus, influenza B virus, Herpes simplex virus type 1 and type 2, the human parainfluenza virus (HPIV) type 3, vaccinia virus (VACV or VV), the human rhinovirus type 2 (HRV2))
Althaea officinalis [25]	Suppresses cough and has a soothing effect on the upper respiratory tract
Andrographis paniculata [26]	Alleviates symptoms of uncomplicated upper respiratory tract infections
Commiphora molmol [27]	Anti-inflammatory or antinociceptive action
Cymbopogon citratus [28]	Relief therapy for the flu, having an anti-inflammatory effect on the respiratory tract
Eucalyptus globulus [26]	Relieves symptoms associated with upper respiratory infection by exerting a soothing effect on the respiratory tract

Table 2: *Potential herbal agents to combat COVID-19.*

The severity of the disease is associated with the pro-inflammatory response of the human body. The cytokine storm is related to viral virulence and host resistance, leading to the release of mediators, such as interleukin-2, interleukin-7, granulocyte colony-stimulating factor, interferon-c, inducible protein-10, monocyte chemoattractant protein-1, macrophage inflammatory protein1-α, and tumor necrosis factor α (TNF-a) [11]. In this regard, herbalists apply the herbs as prophylaxis and to control the symptoms of the disease.

The plants used in Traditional Chinese Medicine are effective against SARS-Cov and Middle East Respiratory Syndrome (MERS) [18]. Another well-known herb is curcumin (*Curcuma longa*), which is also a popular Indian spice. Nano encapsulated curcumin has been reported to lessen COVID-19 symptoms (fever, cough, and dyspnea) and reduce mortality [19]. Curcumin inhibits the activation of the nuclear factor kappa B pathway, which stimulates the production of pro-inflammatory cytokines. It also inhibits the target of the rapamycin pathway, which is another regulator of nuclear factor kappa B [18]. The roots of this perennial herb have antiviral and antimicrobial properties, anti-inflammatory potential, and relieve and prevent respiratory disorders [16].

Echinacea purpurea (purple coneflower) has antiviral activity. However, its primary mode of action has yet to be confirmed by human studies. It is claimed by some health care profeesionals to be immunostimulatory (enhances the release of pro-inflammatory cytokines (such as IL-1, IL-10, and TNF-α) [20] and is considered an immunosuppressant and virucidal [17].

Liquid elderberry extract (*Sambucus nigra*) has an *in vitro* antiviral action against the influenza virus and other respiratory bacterial pathogens. Preclinical evidence shows that it inhibits the replication and viral attachment of the human coronavirus NL63 (HCoV-NL63) and, thus, may be helpful in the initial stages of the infection [21].

Golden root (*Rhodiola rosea*) demonstrates an immunoregulatory effect, governing the differentiation of immune cells and inflammatory signaling pathways and controlling the secretion of inflammatory factors [22].

E. purpurea reduces the severity of acute respiratory infections. It also lowers the risk of recurrent infections and the incidence of complications [23]. Thus, it should be taken at the first signs of a respiratory infection.

Traditional Thai herbs with immunomodulatory action

The most significant ethnic minorities in Thailand—the Karen and the Hmong—have vast traditional knowledge regarding medicinal plant uses [29]. Since ancient times, they have been using various herbs for symptoms, such as fever (*Strobilanthes cusia* and *Acorus calamus)* and cough (*Zingiber officinale*, *Blumea balsamifera,* and *Elephantopus scaber*), which are, incidentally, the most common features in mild COVID-19 [30]. Thus, these plants are potential adjuvant therapies against the SARS-CoV-2 virus.

Andrographis paniculate has been shown to have antiviral activity, specifically against coronaviruses [31].

Sesame (*Sesamum indicum*), known as the "queen of oilseeds", is an annual herbaceous plant cultivated for its edible seed. Its essential oil modulates T-cell immune responses, lowers interferon-gamma, and increases interleukin-4 [32]. Also, it contains polyunsaturated fatty acids (linoleic acid, oleic acid, palmitic acid, and stearic acid), while its bioactive components (sesamin, sesamolin, and sesamol) act as antioxidants [33].

A study that specifically considered Thai herbs found that *Boesenbergia rotunda* and its purified compound, panduratin A, have a potent inhibitory effect against SARS-CoV-2 replication. The compound was found to be effective in both the pre-entry and post-infection stages [34].

Andrographis paniculata is another popular medicinal plant that is used in several Asian countries. It is traditionally used as a bitter tonic in diarrhea and relieves the symptoms of common colds and upper respiratory tract infections [35]. In addition, its antiviral properties (phytoconstituent andrographolide) have been increasingly investigated for application against specific viruses (dengue, chikungunya, zika, and influenza), which has encouraged numerous reviews on its constituent, andrographolide, as a potential antiviral in the treatment of COVID-19 [36].

Mangosteen (*Garcinia mangostana*) is a tropical tree that produces a fruit rich in xanthones. The extracts of mangosteen pericarp (layer surrounding the seed) contain the components α-mangostin and γ-mangostin, which are anti-inflammatory, antioxidative, anticancer, antimicrobial, and neuroprotective. Also, it is abundant in vitamin C, which is vital for building an efficient immune system. Traditionally, mangosteen has been used as an antimicrobial to treat skin infections, wounds, and dysentery [37]. The evidence in favor is significant; a randomized control trial in humans revealed the immune-boosting capacity of mangosteen [38].

Quality control

Standardization and quality assurance are critical aspects of pharmacotherapy for chemically synthesized drugs as well as herbal pharmaceuticals. With the rising demand for herbal remedies, the market for these products has increased multifold. To prevent the influx of spurious drugs and maintain the optimal chemical ingredient in each product, diverse electrophoretic and chromatographic techniques are used. These techniques are more pertinent to herbal resources because the chemical components of plants vary with the climate and soil composition in which they are grown [39]. The World Health Organization (WHO) has established guidelines for identifying and evaluating these natural medicinal resources. There are many scientific and analytical means of quality controls, such as microscopic evaluation, identification (to remove adulterants), physiochemical (for example, moisture content helps in assuring preservation), and pharmacognostic [40].

Newer methods of quality control include DNA fingerprinting and barcoding for plant authentication—although this does not guarantee the clinical potency of herbs [41]. The challenge is more remarkable for products that contain multiple herbal compounds. A signifi-

cant constraint is a lack of knowledge about the chemical constituents of herbs and their pharmacological actions. An innovative method is PhytomicsQC, which utilizes liquid chromatography and mass spectrometry for chemical characterization and fingerprinting differentials of cellular gene expression and animal pharmacology [42].

Sustainability of local communities

The Asian continent is well known for its biodiversity and its rich natural health care traditions. Thus, this region has tremendous potential in the field of herbal medicine. Nevertheless, local communities must be more knowledgeable regarding the growing, harvesting, and processing of these herbs. Furthermore, these ethnic communities and bio-reserves must be protected from exploitation.

With humanity now leaning more towards natural cures, medicinal plants have become a commercial income-generating source. Moreover, ethnic and underprivileged communities can use herbal medicine skills and mastery to improve their socio-economic condition [43]. However, this sector needs to be further explored and strengthened because numerous plant species are found in the less accessible mountainous areas [44].

In some instances, this increasing interest in traditional herbal remedies is creating an imbalance in nature due to the over-harvesting of certain plants to meet the growing demand for plant-based drugs. Some of these medicinal plants have slow growth rates, are fewer in number, and have distinct and narrow geographic ranges, making them prone to extinction if due diligence is not observed and practiced [45]. The concerns and recommendations to save the herbal plant biodiversity are given in Table 3.

Concerns
• The increasing human population reduces forest cover while shrinking the free land for cultivation, and loss of habitat for plants [46].
• Rising demand for plant-based raw materials is leading to over-harvesting of the plants. Over-harvesting is more damaging to plants that are slow-growing and habitat-specific [45].
• Laws regulating natural resources are becoming weak in front of socio-economic reforms [47].
• Natural pathogens and predators deplete the natural store of medicinal plants, profoundly affecting rare ones [45].
• There is a lack of categorization and estimation of plants with medicinal properties - due to inaccessibility of the terrain, the inherent short life span of plants, and other reasons [48].
• Knowledge on the propagation of medicinal plants and technological advancements in agriculture is not keeping pace with increasing demand
• Such as the slow production rate of medicinal plants, long gestation periods, lack of suitable cultivation technology, unscientific harvesting, inadequate research on high-yielding varieties, poor quality control procedures, and scarcity of good manufacturers [49,50].
Recommendations
• The farming of medicinal plants should be encouraged. It would also help produce uniform raw material, leading to the manufacture of consistent and standardized finished products and drugs. It would also help identify species, control quality better, and carry the possibility of genetic modification [45].
• Agroforestry to be encouraged (medicinal plants prefer forest cover) [51].
• Policies and stringent laws should be in place to limit profit-seeking groups looking for medicinal plants. Biodiversity should be used in a controlled manner and not overexploited.
• The patent and compensation system should be more uniform throughout the world so that indigenous people and herbal medicine practitioners are benefited and protected [52].
• The production and marketing of medicinal products should be more regulated, and all stakeholders should be kept in the loop (local farmers, herbal healers, manufacturers, traders, exporters). Naive farmers should receive proper education so that they know the value of what they are producing. Illegal marketing and scrupulous go-betweens should be kept at bay.

Table 3: *The concern areas and recommendations to save the herbal plant biodiversity.*

Primarily, herbal medicines have a complementary or synergistic action on human physiology. They confer holistic therapy, which involves the mental and spiritual aspects of an individual. A medicinal plant may not cause any specific adverse effect unless toxic or harmful content is ingested. Specific herbs can help the body recover its strength and augment healing [53]. Also, since plant-based therapies are generally safer than many pharmaceutical drugs, they resonate with human ideology in contrast to synthetic medicines. Thus, the primary use of herbal medicines is for health promotion and prevention. Nevertheless, safety concerns should not be ignored. There should be a clear understanding of the content of each herbal medicine and its mechanism of action.

To enumerate the interactions of herbal medicines with other pharmaceuticals requires a robust data analysis. Unfortunately, there is a dearth of scientific evidence at this time, although some such interactions have been recorded in the medical literature. Sporadic case reports with a low level of evidence tend to form the current knowledge base.

The study methods employed to deduce the interactions are not universal. To be considered are 1) the poor characterization of a specimen, 2) the possibility of adulterants, 3) the extraction procedures employed by researchers, 4) variation of the source of herbs, 5) seasonal variation in the phytochemical composition, 6) under-reporting, and 7) variation due to genetic factors involved in drug absorption and their metabolism.

A comprehensive review by Izzo (2012) compiled various articles on herb-drug interaction [54]. Examples of herbs showing interactions and the mechanisms thereof are listed in Table 4.

Herb	Mechanism of interaction
Aloe vera: - sevoflurane [55]	Inhibits platelet aggregation that causes blood loss during surgery, mainly when used with the anesthetic agent, sevoflurane.
Uncaria tomentosa (cat's claw) [56]	Inhibits cytochrome P34 A, thus increasing the plasma concentration of protease inhibitors (atazanavir, ritonavir, saquinavir)
Allium sativum (garlic) [57]	Garlic oil selectively inhibits CYP2E1
Zingiber officinale (ginger) [54]	Antiplatelet activity
Camellia sinensis (green tea) [58,59]	Diminishes the anticoagulant activity of warfarin. Reduces folic acid and the plasma level of statins.

Table 4: *Herbs that show drug interaction.*

The Chinese herbal medicine theory uses the following types of herb-herb interaction [41].

- *Reinforcement* - Use of herbs with similar action to improve overall efficacy.
- *Potentiation*- The addition of an adjunctive herb to a primary herb.
- *Restraint and detoxification*- The addition of an herb to detoxify another herb. Usually, herbal medicines do not contain any fatal toxins, but some components may have adverse effects. Nevertheless, these are still used for more significant benefits, with other herbs that neutralize or diminish the 'toxic' symptoms.
- *Counteraction*- One herb diminishes the therapeutic effect of another.
- *Incompatibility*- Combine herbs that are mutually incompatible and cause adverse effects.

Regulations for manufacturing and marketing

The WHO has established guidelines and policies for "Good Agricultural and Collection Practices 2003" (GACP, 2003), "Good Manufacturing Practices" (GMP), appropriate usage, and reporting of adverse events [60]. In 2019, it also released the "WHO Traditional Medicine Strategy 2014–2023" [61].

The Herbal Anatomical Therapeutic Chemical (HATC) classifies herbal medicines according to nomenclature and therapeutic activity. This classification also aids in pharmacovigilance. This herbal ATC was developed by the Sweden-based Uppsala Monitoring Center (UMC) as part of the WHODrug Global [62]. The UMC has listed adverse drug reactions, while the data are available in a single database.

To facilitate international commerce of herbal drugs, international treaties—like the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES—have been laid, regulating the trade, and prohibiting detrimental exploitation of rare species [63]. Some of the acts that guide and regulate the manufacturing and licensing of herbal products are as follows (for Asian countries):

- In India, herbal drugs are regulated under the Drug and Cosmetic Act 1940 and Rules 1945 India. AYUSH is the regulatory authority in the country. Manufacturing or marketing of herbal drugs requires licensing. The act also regulates composition, labeling, packing, quality, and export. Good manufacturing practices are described in the 'T' schedule of the act [64].
- In Malaysia, herbal products must be registered with the Malaysian Business Registrar or Suruhanjaya Syarikat Malaysia before marketing [65].
- In the Philippines, only traditional herbs that have been used for at least five decades and are well documented are marketed. These drugs should be registered with the Bureau of Food and Drugs (BFAD) before being manufactured, imported, or marketed. The Philippine National Museum or any recognized taxonomist of BFAD should first authenticate the plant, while for imported products, the country of origin should certify the authenticity [63].
- The ASEAN (Association of Southeast Asian Nations) countries follow the guidelines of the Health Science Authority (HSA) [66].

Recommendations for uniform regulation guidelines (URG)

Many countries have national acts, guidelines, and policies to regulate the practice of growing, processing, and marketing many herbal compounds, yet many other countries do not have defined regulations. There should be global collaboration to ascertain regulatory compliance, so those correct procedures are followed at every step—from plant selection to marketing to post-marketing surveillance. Also, the conservation of natural resources should be paramount. Any substandard marketing practices and exploitation of folk knowledge should be discouraged and controlled. Uniform pharmacopeias should be formulated to overcome these drawbacks. Standard guidelines for universal practices on herbal therapies are given in Figure 2 [67].

Figure 2: *Common guidelines for universal practices on herbal therapeutics.*

Conclusion

Herbal medicine is gaining popularity and acceptance due to its longstanding use and growing efficacy in treating various illnesses and promoting health. Researchers around the world are increasingly acknowledging herbs' numerous health benefits. More research is required to develop a thorough body of evidence for herbal medicine, which will also aid in understanding the pharmacology of the primary constituents of plant extracts. Combining herbal therapy and allopathic medicine may be a valuable key in combating newly emerging and resistant microorganisms. Specific herbs—such as curcumin, ginger, aloe vera, and green tea—are used widely for their health benefits. *E. purpurea*, *S. nigra,* and other herbaceous elements have proven immunomodulatory properties. Such herbs and herbal constituents should be studied further to determine their efficacy. Protocols should be developed for the prevention and treatment of particular illnesses and diseases.

The global herbal medicine market needs to be a coordinated effort. There should be cooperation among the various governments and public health departments worldwide. Knowledge on herbs' efficacy, indications, contraindications, and drug interactions must be systemically investigated and accumulated, while the manufacturing and distribution of the medicines must be regularized to ensure safety.

Conflict of Interest Statement

The authors declare that this paper was written without any commercial or financial relationship that could be construed as a potential conflict of interest.

References

1. Introduction and Importance of Medicinal Plants and Herbs (2021).https://www.nhp.gov.in/introduction-and-importance-of-medicinal-plants-and-herbs_mtl

2. Stojanoski N. "Development of health culture in Veles and its region from the past to the end of the 20th century". Veles: Society of science and art (1999): 13-34.

3. Sharma P., *et al*. "Immunomodulators: Role of medicinal plants in the immune system". *National Journal of Physiology, Pharmacy and Pharmacology* 7.6 (2017): 552-556. http://njppp.com/fulltext/28-1487571016.pdf

4. Calixto JB. "Efficacy, safety, quality control, marketing, and regulatory guidelines for herbal medicines (phytotherapeutic agents)". *The Brazilian Journal of Medical and Biological Research* 33.2 (2000). https://pubmed.ncbi.nlm.nih.gov/10657057/

5. BB Petrovska. "Historical review of medicinal plants' usage". *Pharmacognosy Reviews* 6.11 (2012): 1-5. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3358962/

6. Ekor M. "The growing use of herbal medicines: issues relating to adverse reactions and challenges in monitoring safety". *Frontiers in Pharmacology* 4 (2013): 177. https://pubmed.ncbi.nlm.nih.gov/24454289/

7. Kelly K. "History of medicine". New York: Facts on file (2009): 29-50.

8. Thorwald J. "Power and knowledge of ancient physicians". Zagreb: August Cesarec (1991): 10-255.

9. Haddad PS., *et al*. "Natural health products, modulation of immune function and prevention of chronic diseases". *Evidence-Based Complementary and Alternative Medicine* 2.4 (2005): 513-520. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1297498/

10. Singh N. "A Review On Herbal Plants Used As Immunomodulators". *International Journal of Pharmaceutical Research* 13.02 (2021): 3602-3610. http://www.ijpronline.com/ViewArticleDetail.aspx?ID=20830

11. Xiao C., *et al*. "Medical Plants and Immunological Regulation". *Journal of Immunology Research Volume* (2018). https://www.hindawi.com/journals/jir/si/694170/

12. Davis L and Kuttan G. "Immunomodulatory activity of Withania somnifera". *Journal of Ethnopharmacology* 71 (2000): 193-200. https://pubmed.ncbi.nlm.nih.gov/10904163/

13. Singh UP., *et al*. "Role of garlic (Allium sativum L.) in human and plant diseases". *Indian Journal of Experimental Biology* 39.4 (2001): 310-322. https://pubmed.ncbi.nlm.nih.gov/11491574/

14. Liu P., *et al*. "Chemical constituents, biological activity and agricultural cultivation of Aloe vera- A review". *Asian Journal of Chemistry* 25.112 (2013): 6477. http://www.asianjournalofchemistry.co.in/User/ViewFreeArticle.aspx?ArticleID=25_13_1

15. Thakur M., *et al*. "Immunomodulatory activity of Chlorophytum borivilianum Sant. F". *Evidence-Based Complementary and Alternative Medicine* 4.4 (2007): 419-423. https://pubmed.ncbi.nlm.nih.gov/18227908/

16. Boskabady MH., *et al*. "The effects of Curcuma Longa L. and its constituents in respiratory disorders and molecular mechanisms of their action". In Studies in Natural Products Chemistry; Atta-ur-Rahman, Edition. Elsevier: Oxford, UK 65 (2020): 239-269. https://www.researchgate.net/publication/342401858_The_effects_of_Curcuma_Longa_L_and_its_constituents_in_respiratory_disorders_and_molecular_mechanisms_of_their_action

17. Sharma MSA., *et al*. "Induction of multiple pro-inflammatory cytokines by respiratory viruses and reversal by standardized Echinacea, a potent antiviral herbal extract". *Antiviral Research* 83.2 (2009): 165-170. https://pubmed.ncbi.nlm.nih.gov/19409931/

18. Rattis BAC., *et al*. "Curcumin as a Potential Treatment for COVID-19". *Frontiers in Pharmacology* 12 (2021): 1-14. https://pubmed.ncbi.nlm.nih.gov/34025433/

19. Valizadeh H., *et al*. "Nano-curcumin Therapy, a Promising Method in Modulating Inflammatory Cytokines in COVID-19 Patients". *International Immunopharmacology* 89 (2020): 107088. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7574843/

20. Burger RA., *et al*. "Echinacea-induced cytokine production by human macrophages". *International Journal of Immunopharma- Cology* 19.7 (1997): 371-379. https://pubmed.ncbi.nlm.nih.gov/9568541/

21. Back AT and Lundkvist A. "Dengue viruses-an an overview". *Infection Ecology and Epidemiology* 3 (2013): 19839. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3759171/

22. Pu WL., *et al*. "Anti-inflammatory effects of Rhodiola rosea L.: A review". *Biomedicine and Pharmacotherapy* 121 (2020): 109552. https://pubmed.ncbi.nlm.nih.gov/31715370/

23. Aucoin M., *et al*. "The effect of Echinacea spp. on the prevention or treatment of COVID-19 and other respiratory tract infections in humans: A rapid review". *Advances in Integrative Medicine* 7.4 (2020): 203-217. https://pubmed.ncbi.nlm.nih.gov/32837894/

24. Silveira D., *et al*. "COVID-19: Is There Evidence for the Use of Herbal Medicines as Adjuvant Symptomatic Therapy?" *Frontiers in Pharmacology* 11 (2020): 1-44. https://www.frontiersin.org/articles/10.3389/fphar.2020.581840/full

25. EMA (2016c). "European Union herbal monograph on Althaea officinalis L., radix," in EMA/HMPC/436679/2015 Committee on Herbal Medicinal Products (HMPC) (London: European Medicines Agency) (2016c). https://www.ema.europa.eu/en/documents/herbal-monograph/final-european-union-herbal-monograph-althaea-officinalis-l-radix_en.pdf

26. WHO. Monographs on selected medicinal plants 2 (Geneva: World Health Organization) (2002). http://apps.who.int/iris/bitstream/handle/10665/42052/9241545178.pdf;jsessionid=BC0DFB602E5A4372D83467D9025036EC?sequence=1

27. Su S., *et al*. "Anti-inflammatory and analgesic activity of different extracts of Commiphora myrrha". *Journal of Ethnopharmacology* 134 (2011): 251-258. https://pubmed.ncbi.nlm.nih.gov/21167270/

28. Silva FFM., *et al*. "Analysis of chemical composition of the essential oil of holy grass (Cymbopogon citratus) obtained through extractor for water vapor trail with built with materials of acquisition and easy low cost". *Holos* 30 (2014): 144. https://www.proquest.com/docview/1612531245

29. HHDC (2018). Information on Ethnic Group Populations in 20 Provinces (In Thai) (2021).

30. Phumthum M., *et al*. "Medicinal Plants Used for Treating Mild Covid-19 Symptoms Among Thai Karen and Hmong". *Frontiers in Pharmacology* 12 (2021): 699897. https://www.frontiersin.org/articles/10.3389/fphar.2021.699897/full

31. Shi TH., *et al*. "Andrographolide and its Fluorescent Derivative Inhibit the Main Proteases of 2019-nCoV and SARS-CoV through Covalent Linkage". *Biochemical and Biophysical Research Communications* 533.3 (2020): 467-473. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7447262/

32. Khorrami S., *et al*. "Sesame seeds essential oil and Sesamol modulate the pro-inflammatory function of macrophages and dendritic cells and promote Th2 response". *The Medical Journal of the Islamic Republic of Iran* 32.1 (2018): 1-8. https://pubmed.ncbi.nlm.nih.gov/30788333/

33. Pathak N., *et al*. "Value addition in sesame: A perspective on bioactive components for enhancing utility and profitability". *Pharmacognosy Reviews* 8.16 (2014): 147-155. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4127822/

34. Kanjanasirirat P., *et al*. "High-content screening of Thai medicinal plants reveals Boesenbergia rotunda extract and its component Panduratin A as anti-SARS-CoV-2 agents". *Scientific Reports* 10.1 (2020): 1-12. https://pubmed.ncbi.nlm.nih.gov/33203926/

35. Hu XY., *et al*. "Andrographis paniculata (Chuān Xīn Lián) for symptomatic relief of acute respiratory tract infections in adults and children: A systematic review and meta-analysis". *PLoS One* 1.8 2(2017): e0181780. https://pubmed.ncbi.nlm.nih.gov/28783743/

36. Andrographis paniculata (Burm. F.) Wall. Ex Nees, Andrographolide, and Andrographolide Analogues as SARS-CoV-2 Antivirals? A Rapid Review Xin Yi Lim, Janice Sue Wen Chan, Terence Yew Chin Tan et al". *Natural Product Communications* 16.5 (2021): 1-15. https://journals.sagepub.com/doi/full/10.1177/1934578X211016610

37. Pedraza-Chaverri J., *et al*. "Medicinal properties of mangosteen (Garcinia mangostana)". *Food and Chemical Toxicology* 46 (2008): 3227-3239. https://pubmed.ncbi.nlm.nih.gov/18725264/

38. Tang YP., *et al*. "Effect of a mangosteen dietary supplement on human immune function: a randomized, double-blind, placebo-controlled trial". *Journal of Medicinal Food* 12.4 (2009): 755-763. https://pubmed.ncbi.nlm.nih.gov/19697997/

39. Balekundri A and Mannur VK. "Quality control of the traditional herbs and herbal products: a review". *Future Journal of Pharmaceutical Sciences* 6 (2020): 67. https://fjps.springeropen.com/articles/10.1186/s43094-020-00091-5

40. Quality control methods for herbal materials (2011).

41. Che CT., *et al*. "Herb-Herb Combination for Therapeutic Enhancement and Advancement: Theory, Practice, and Future Perspectives". *Molecules* 18.5 (2013): 5125-5141. https://pubmed.ncbi.nlm.nih.gov/23644978/

42. Lou SK., *et al*. "An integrated web medicinal materials DNA database: MMDBD (Medicinal Materials DNA Barcode Database)". *BMC Genomics* 11 (2010): 402. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2996930/

43. Myers N. "The world's forests and human population: the environmental interconnections". *Population and Development Review* 16 (1991): 1-15. https://www.jstor.org/stable/2808073

44. Farooquee NA., *et al*. "Indigenous knowledge systems and sustainable management of natural resources in a high altitude society in Kumaun Himalaya, India". *Journal of Human Ecology* 16 (2004): 33-42. https://www.tandfonline.com/doi/abs/10.1080/09709274.2004.11905713

45. Kala CP., *et al*. "Developing the medicinal plants' sector in northern India: challenges and opportunities". *Journal of Ethnobiology and Ethnomedicine* 2 (2006): 32. https://ethnobiomed.biomedcentral.com/articles/10.1186/1746-4269-2-32

46. FAO. State of the World's Forest. Rome: Food and Agricultural Organization (2003). https://www.fao.org/3/y7581e/y7581e.pdf

47. KIT. Bulletin 350. Royal Tropical Institute, Amsterdam, The Netherlands; 2003. Cultivating a Healthy Enterprise (2003).

48. Kala CP. "Assessment of species rarity". *Current Science* 86 (2004): 1058-1059.

49. Hamilton AC. "Medicinal plants, conservation and livelihoods". *Biodiversity and Conservation* 13 (2004): 1477-1517. https://link.springer.com/article/10.1023/B:BIOC.0000021333.23413.42

50. Schippmann U., *et al*. "Impact of cultivation and Gathering of Medicinal Plants on Biodiversity: Global Trends and Issues. Rome: Inter-Department Working Group on Biology Diversity for Food and Agriculture, FAO (2002). https://www.fao.org/3/AA010E/AA010e00.htm

51. Rao MR., *et al*. "Medicinal and aromatic plants in agroforestry systems". *Agroforestry Systems* 61 (2004): 107-122. https://www.researchgate.net/publication/226462494_Medicinal_and_aromatic_plants_in_agroforestry_systems

52. Koo B., *et al*. "Intellectual property. Plants and intellectual property: an international appraisal". *Science* 306.5700 (2004): 1295-1297. https://pubmed.ncbi.nlm.nih.gov/15550646/

53. Karimi A., *et al*. "Herbal versus synthetic drugs; beliefs and facts". *Journal of Nephropharmacology* 4.1 (2015): 27-30. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5297475/

54. Izzo AA. "Interactions between Herbs and Conventional Drugs: Overview of the Clinical Data". *Medical Principles and Practice* 21 (2012): 404-428. https://pubmed.ncbi.nlm.nih.gov/22236736/

55. Lee A., *et al*. "Possible interaction between sevoflurane and Aloe vera". *Annals of Pharmacotherapy* 38 (2004): 1651-1654. https://pubmed.ncbi.nlm.nih.gov/15292490/

56. López Galera RM., *et al*. "Interaction between cat's claw and protease inhibitors atazanavir, ritonavir and saquinavir". *European Journal of Clinical Pharmacology* 64 (2008): 1235-1236. https://pubmed.ncbi.nlm.nih.gov/18712519/

57. Hajda J., *et al*. "Garlic extract induces intestinal P-glycoprotein, but exhibits no effect on intestinal and hepatic CYP3A4 in humans". *European Journal of Pharmaceutical Sciences* 41 (2010): 729-735. https://www.researchgate.net/publication/47382303_Garlic_extract_induces_intestinal_P-glycoprotein_but_exhibits_no_effect_on_intestinal_and_hepatic_CYP3A4_in_humans

58. Taylor JR and Wilt VM. "Probable antagonism of warfarin by green tea". *Annals of Pharmacotherapy* 33 (1999): 426-428. https://pubmed.ncbi.nlm.nih.gov/10332534/

59. Werba JP., *et al*. "The effect of green tea on simvastatin tolerability". *Annals of Internal Medicine* 149 (2008): 286-287. https://pubmed.ncbi.nlm.nih.gov/18711168/

60. Guidelines on good agricultural and collection practices (GACP) for medicinal plants. WHO guidelines on good agricultural and collection practices. Geneva GACP 1-71 (2003). http://apps.who.int/iris/bitstream/handle/10665/42783/9241546271.pdf?sequence=1

61. WHO Traditional Medicine Strategy 2014-2023. Traditional Medicine Strategy 2019 (2021). https://www.who.int/publications/i/item/9789241506096

62. Guidelines for ATC classification and DDD assignment 2013. WHO Collaborating Centre for Drug Statistics Methodology". *Drug Statistics Methodology* (2012). https://www.whocc.no/filearchive/publications/1_2013guidelines.pdf

63. Geneva: WHO Library Cataloguing-in-Publication Data, World Health Organization; 2005. [Last cited on 2014 Apr 29]. Guidelines on the Registration of Traditionally used Herbal Products, Department of Health, Republic of Philippines, Report of a WHO Global Survey (2021). https://apps.who.int/iris/bitstream/handle/10665/92455/9789241506090_eng.pdf

64. Malik V, editor. 23rd edition. Lucknow: Eastern Book Company. Law Relating to Drugs and Cosmetics (2013).

65. Ishak R and Mohamad J. "Guidelines on Registration of Traditional and Health Supplement Products". Revised ed. Version 1.0. Kuala Lumpur. Malaysian Biotechnology Corporation SDN BH (2011). http://www.biotechcorp.com.my/wp.content/uploads/2011/11/guidelines-on-registration-of-traditional-health-supplement-product-Dec-2011-Revision.pdf

66. Health Sciences Authority. Regulatory guidelines (2021). https://www.hsa.gov.sg/docs/default-source/hprg-tpb/guidances/guidance-on-therapeutic-product-registration-in-singapore_aug21.pdf

67. Ramadoss MSK and Koumaravelou K. "Regulatory compliance of herbal medicines–A review". *International Journal of Research in Pharmaceutical Sciences* 10.4 (2019): 3127-3135. https://pharmascope.org/index.php/ijrps/article/view/1609

Volume 4 Issue 12 December 2021