Chapter

Use of Medicinal Plants: Interindividual Variability of Their Effects from a Genetic and Anthropological Perspective

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Abstract

The use of plants for nutritional and therapeutic purposes has been constant over the centuries. The variability of enzymatic activity between individuals and populations in an attempt to adapt has been a conditioning mechanism, reflected in the incidence and prevalence of certain diseases, possible adverse effects of plant-derived nutrients and their interaction with medications, in addition to interference in natural selection and consequent geographical distribution of specific genetic polymorphisms in harmony with indigenous medicinal plants. The metabolizer type may influence the anticancer protective effect of certain plant-derived constituents, with interindividual variability to be considered. This chapter will deepen and develop the role of using plants in different geographic areas and populations over the centuries in producing the genetic variability of the metabolism of plant constituents in the context of environmental adaptation and ecogenetics. Possible therapeutic/adverse effects due to this variability will be discussed.

Keywords: medicinal plants, nutrigenetics, pharmacogenetics, ecogenetics, genetic variability, anthropology

1. Introduction

Since time immemorial, medicinal plants have been a fundamental aspect of human health and continue to play a vitally important role in different cultures worldwide. Primitive medicine before the Christian era was based from a therapeutic point of view, on a powerful psychological component supported by magical beliefs and rites combined with medicinal plants.

Today, however, it is known that medicinal plants' effects can vary significantly between individuals and interfere with medicinal substances. This variability involves aspects ranging from inherent to the medicinal plant to complex genetic and anthropological factors.

The interindividual variability of the effects of medicinal plants arises from the complex interaction between the plant phenotype and genetic and anthropological factors specific to each individual and community. It is essential to recognize and respect this variability in the use of medicinal plants for health purposes.

Nutrigenetics and pharmacogenomics make it possible to identify genetic markers associated with responses to specific food or medicinal plants. The patient's genetic background, cultural environment, and lifestyle must be considered when recommending medicinal plants or herbal medicines.

Furthermore, the importance of collaboration between therapists from alternative or traditional approaches and modern healthcare providers stands out for a holistic and personalized approach to recommending herbal medicines, within integrative medicine programs.

It is currently recognized as imperative to understand the modes of interaction between different medicines from conventional and traditional healthcare systems when used in treatment combinations. Both synthetic and natural medicinal chemical entities are metabolized by the same enzyme systems in the human body, resulting in pharmacokinetic and pharmacodynamic interactions, the properties of which are still largely unknown/unquantified.

This chapter will address these three aspects, plant, individual, and anthropological, which lead to interindividual variability and its effects, highlighting the growing importance of medicine that respects variability and, increasingly, is centered on the person.

2. Medicinal plant variability

The variability of the response to therapeutically beneficial plants begins with its natural variability. The plant has variability depending on its phenotype, the seed quality, the climatic conditions, and the terrain where it grows.

Chemical variation in a plant sample can influence the effectiveness of medicines formulated against a specific disease. Therefore, selecting raw materials based on their chemical composition is a prerequisite [1].

Preparations based on medicinal plants still require detailed scientific analytical studies for quantification of markers and active ingredients or just for chemical standardization purposes, so that they can guarantee the reproducibility of their effects in in vitro biological tests and in pre-clinical animal models. For the clinical evaluation stage, quality control is a completely indispensable practice in accordance with international standards.

The already validated quality control methods for some medicinal plants are present in monographs found in all European Pharmacopoeia: United States Pharmacopoeia, Chinese Pharmacopoeia, WHO Monographs, Japanese Pharmacopoeia, Brazilian Pharmacopoeia—they are universal reference works, updated in all countries on different continents.

Geographical origin and climatic conditions are the notable factors that affect the metabolome of a plant. Plants are adapted to different geographic, climatic, and soil conditions through genotypic and phenotypic changes. Genotypic change also influences plants' production and accumulation of secondary metabolites [2, 3].

Although the specialized metabolic profile is unique to individuals within a species or a closely related taxonomic group, it can be altered if its biosynthetic pathways are influenced by environmental conditions such as climate, soil, pathogen infection, and pest infestation. Therefore, regional variation may be due to different mixtures

or proportions of active compounds, which links the geography and climate of the medicinal plant habitat.

Genetic diversity can help evaluate the evolution and conservation of varieties [4]. Genetic diversity is generally estimated through DNA sequences (polymorphisms between varieties) and cytological and morphological markers. However, morphological characteristics are often influenced by the environment. Therefore, molecular markers are relatively more stable and popular than morphological markers [5]. Inbreeding and evolution events can alter allele frequency and reduce genetic diversity [6]. Therefore, it is vital to accurately estimate the correlation between different germplasm resources to ensure high-efficiency utilization and management and to maintain adequate genetic variability for breeding diverse plant varieties [7].

Genetic diversity and population structure analysis have examined various plant species. An analysis of 1151 ramie germplasms using SSR and phenotypic markers reveals that the genetic diversity of wild germplasms is greater than that of domesticated germplasms. This finding of diversity and subpopulations [8] has been observed in several plants such as cannabis [9], sunflower from Iran [10], beans from Brazil [11], allowing technological advances. This wealth of variability is substantial and needs to be preserved by this observation of genetic diversity and the population structure of plants, whether they are sources of medicines, nutrition, or fiber.

2.1 The case for turmeric (*Curcuma longa* L.)

Curcuma longa L., rhizoma (turmeric root; **Figure 1**) with long-standing use, was approved in Europe as a traditional herbal medicinal product for the relief of digestive disturbances, such as feelings of fullness, slow digestion, and flatulence [12]. However, there are also studies showing a potential role as an immune modulator and anti-inflammatory [13–15].

The characteristic compounds are curcuminoids, of which curcumin makes up approximately 90% of the curcuminoid content in turmeric [16]. Chemically, curcumin is a diferuloylmethane, i.e., a beta-diketone derived from methane in which two of the hydrogens are substituted by feruloyl groups (**Figure 2**). These phenolic groups in the structure of curcumin explain the ability of curcumin to eliminate oxygen-derived free radicals [17]. However, as generally observed in medicinal plants' bioactive markers, the curcumin content of the *Curcuma longa* rhizome is very low, as it varies from 0.6 to 5% of the dry mass [18].

Recently, Chen et al. [19] studied the genetic and chemical variability among five Curcuma species, and the results showed that the similarity of the chemical composition of medicinal plants was the primary evidence for the selection of the original plants of Curcuma medicinal materials [19]. In this study, the ITS2 and trnK intron gene sequences were used to analyze the genetic distance between different Curcuma species—chemical composition by HPLC. The authors found that the correlation between genetic distance based on finite genetic sequence and chemical variability showed a relatively low level. The pharmacodynamic potential of new species can be predicted by analyzing the genetic distance between them of the same genus and known medicinal plants.

According to this research, genetic distance data could provide some reference clues for finding new medicinal plant resources.

The huge variety of secondary metabolites produced by plants used to treat various diseases and illnesses are often difficult to obtain in large quantities, limiting their industrial use.

Figure 1.
Curcuma plant (hand-drawn illustration: In Franz Eugen Köhler, Köhler's Medizinal-Pflanzen (1887)).

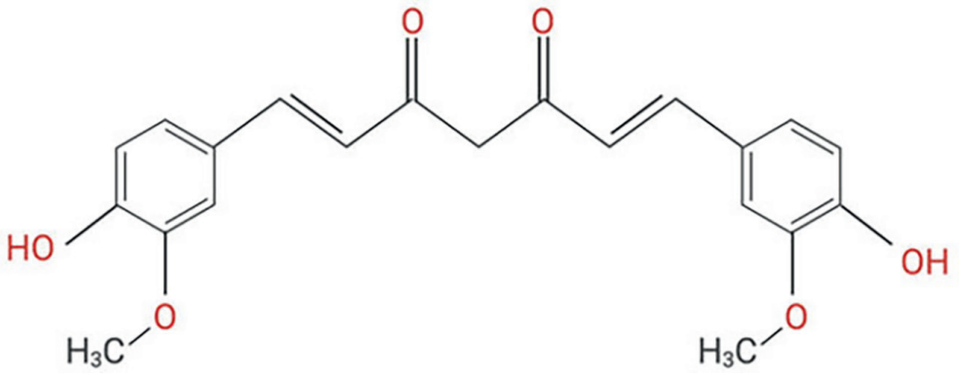


Figure 2.
Chemical structure of curcumin, (1E,6E)-1,7-bis(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione.

Cytochrome P450 enzymes (CYPs) are fundamental catalysts in the biosynthesis and metabolism of highly valued active metabolites. The technological development of high-throughput sequencing and high-resolution mass spectrometry has allowed new biosynthetic pathways and identified associated CYPs.

Current challenges and possible strategies to overcome limitations associated with CYP engineering to improve the biosynthesis of target secondary metabolites were highlighted [20].

2.2 Variability, scientific research, and use: example of cannabis

Cannabis contains several secondary metabolites belonging to different chemical classes including cannabinoids, terpenoids, flavonoids, and steroids among 545 identified compounds [21–28].

The term "variety" is the adaptation of a species resulting from changes in its habitat due to accidental factors such as climate change, soil changes, diseases, insect attacks, nematodes, and other similar influences [29]. The term "cultivar" is a combination of "cultivated variety," abbreviated to "cultivar" [29].

Unlike varieties, cultivars are not products of natural evolutionary processes. Instead, they are bred through deliberate breeding or agricultural techniques for improved, uniform characteristics [30]. This distinction is crucial as it highlights the human intervention in developing specific plant traits and characteristics.

Cannabis is typically classified into three species: *Cannabis sativa*, *Cannabis indica*, and *Cannabis ruderalis* (**Figure 3**). These species display genetic differences in growth characteristics, cannabinoid profiles, and terpene compositions. Thus, patients, growers, and dispensaries differentiate the three species. However, poly hybrids between these species have been developed worldwide with varying percentage contributions from each species and are currently commonly purchased as "*Cannabis sativa*". Each of the three species has a wide range of cultivars and varieties, each with its unique genetic makeup. These genetic differences result in variations in plant morphology, cannabinoid content (e.g., THC and CBD levels), and terpene profiles, leading to different effects and uses.

For medical applications, researchers largely adopt a chemotaxonomic perspective that describes three chemical phenotypes or chemotypes based on the content

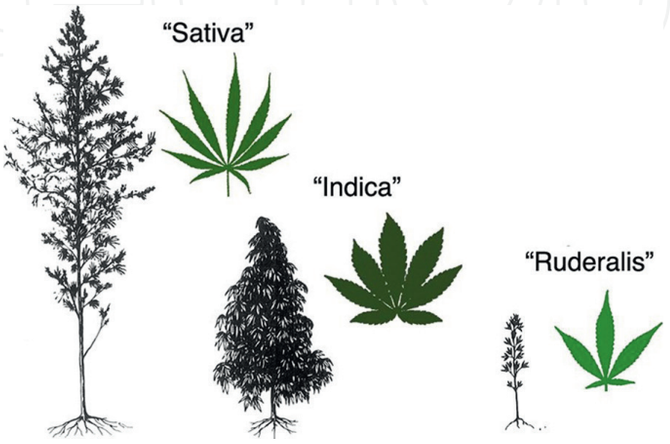


Figure 3.
Cannabis sativa, Cannabis indica, and Cannabis ruderalis have different heights, shapes, leaf structures, content of psychoactive molecules, and geographic origins (source: [31]).

of two main cannabinoids (**Figure 4**): psychoactive tetrahydrocannabinol (THC) and non-psychoactive cannabidiol (CBD; [32]). THC-dominant strains have a THC/CBD ratio > 1, intermediate strains have THC/CBD ≈ 1, and CBD-dominant strains have THC/CBD < 1. Although most clinical research studies focus on THC and CBD, increasing evidence shows that whole plant extract has additional benefits compared to individual cannabinoids.

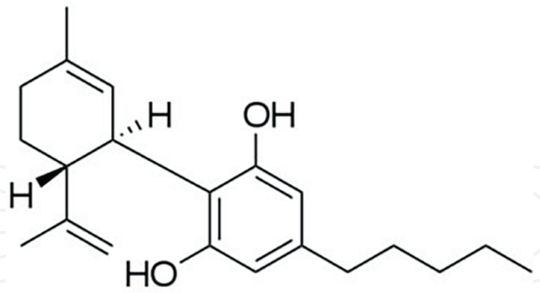
As early as 2020, Reimann-Philipp et al. highlighted that medical cannabis patients receive clinical benefits from the diverse plant's secondary metabolites, which contain a variety of other cannabinoids besides THC and CBD, several different combinations of cannabinoids and terpenoids that can be used to classify chemovars [33].

In state-regulated medical cannabis programs, no conventional naming system correlates breeder-reported names with their active ingredient profiles, and these "strain" names are invalid (as well as appropriate for microbial agents) as chemical differences are referred to as chemovars. The taxonomy of cannabis, a versatile plant with a long history of human use, has been the subject of constant debate and review, especially with the advancement of molecular studies. New taxonomic developments are expected.

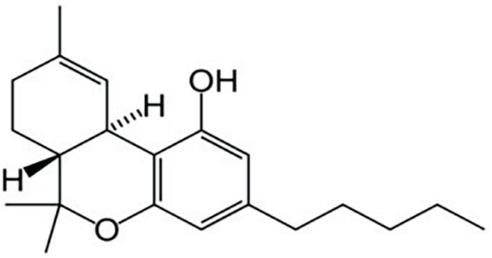
Cannabis sativa and *Cannabis indica* were recognized as distinct species within the *Cannabis* genus, with different morphological and chemical characteristics, and have different cannabinoid profiles and terpene compositions [34].

Classification of cannabis is a fundamental requirement for future research and medical applications. This approach is facilitated by obtaining an overview of the class and secondary metabolites with potentially therapeutic properties associated with each part of the plant.

Currently, researchers have attempted to discriminate and identify chemical differences between the categories of "Sativa" (narrow leaflet drug, NLD) and "Indica" (broad leaflet drug, WLD; [35]). The results of the chemotaxonomic separation of



Cannabidiol (CBD)



9-Δ-tetrahydrocannabinol (THC)

Figure 4.
THC and CBD are the more abundant markers of cannabis from a chemotaxonomic perspective.

"Sativa" and "Indica" were mixed, and the concentrations of THC and CBD seemed to have no differentiating value. However, specific terpenoids were more prominent in some varieties than others [25, 35].

An analysis of 81 marijuana samples and 43 hemp samples using single nucleotide polymorphisms (SNPs) revealed that marijuana and hemp were significantly different at the genome level, and that hemp was genetically more similar to the *Cannabis indica* type than to the *Cannabis sativa* [36].

Cannabis breeding has been actively pursued to develop varieties with specific characteristics, such as high cannabinoid content, improved terpene profiles, and resistance to pests and diseases [9].

These are exciting times for medical research into cannabis and its dozens of cannabinoids. After almost four millennia of its documented medical use in treating convulsive, spastic disorders and numerous severe syndromes, we are very close to obtaining conclusive proof of its effectiveness. We can foresee the era of evidence-based prescription of cannabis-based medicines in serious pathologies.

These examples show how plants are a source of variability, highlighting the importance of their control, from their production to handling of food or phytomedicine, to guarantee safety and quality in their use.

3. Genetic variability of the person

Talking about interindividual variability is a huge challenge, as it is a very vast topic, mainly because we are all different people from each other, and around 8 billion humans inhabit the planet.

The human genome is highly diverse, and genetic polymorphisms can influence how individuals metabolize and respond to medicinal plants.

The action of the plant on people who ingest it depends on variables ranging from ingestion to excretion and, above all, the metabolizer type.

The enzymes involved in the metabolism of medicinal plants and medicines, such as the enzymes that together constitute the so-called Cytochrome P450, can vary in terms of activity due to genetic differences, leading to variations in the way in which medicinal compounds are metabolized and resulting in its efficacy and toxicity.

In terms of pharmacogenomics, it is known that medicinal plants are metabolized by specific enzymes that metabolize drugs. This fact has several implications for its therapeutic efficacy. First, these enzymes are encoded by polymorphic genes that can affect how these compounds are metabolized. Variation in these respective genes results in variant enzymes exhibiting altered or abolished activity [37, 38].

Thus, in a population with individuals carrying a myriad of polymorphic drug-metabolizer genes, there is enormous variability in how individuals respond to herbal medicines. It is, therefore, necessary to consider the pharmacogenetic effects of these enzymes when medicinal plants and products derived from them are used as therapeutic means. In addition to being metabolized, herbal medicines can also affect the expression of some of this extensive group of enzymes through inhibition or induction [39, 40].

Notably, we can focus our attention on the detoxification systems of the human body, addressing Phase 0, I, II, and III systems, their variability, and their importance in the metabolization of herbal medicines and, consequently, their effectiveness and toxicity as well as possible interactions with other medicinal substances, which are processed by the same enzymatic protein systems.

Phase 0 system consists of membrane receptors (ex., OATs, OATPs) that function as small entry openings for substances to be metabolized, that is, to become active or, on the contrary, to make them water-soluble so that they can be excreted and eliminated [41].

Phase I system consists of a set of enzymatic proteins called Cytochromes (CYPs), known, as a whole, as CYP 450 that involves an enzyme superfamily that, to date, has 18 different families and 44 subfamilies of enzymes [42]. Approximately 50–80 genes support these families, which encode all the necessary enzyme structures that makeup Citrochrome P450. Cytochrome P450 enzymes are called "CYP," a term that means proteins linked to heme, a prosthetic group, formed by around 500 amino acids [42] and composed of 57 isoenzymes, grouped into families and subfamilies. The identification of CYPs is presented with the prefix "CYP," followed by a number that represents the family, a letter that indicates the subfamily, and, finally, a number that indicates the isoform: CYP 1 (family) A (subfamily) 2 (isoform).

These hemic proteins contain the chemical element iron in their constitution, linked to a heme group. In addition to the animal kingdom, they exist in bacteria, fungi, and plants [42].

The name was adopted because this structure has an optical absorption capacity of around 450 nanometers when complexed with carbon monoxide [43]. This characteristic is due to the ferrous content of the constituent hemoproteins. CYT P450 proteins are widely disseminated in body tissues, with high concentrations in tissues such as the liver and small intestine [42]. They are anchored explicitly beyond the endoplasmic reticulum and in mitochondria membranes, predominantly in liver and bowel cells [42].

In addition to interacting with membranes, CYT P450 proteins interact with each other and other proteins, such as NADPH-cytochrome P450 reductase and cytochrome b5, which may contribute to controlling the detoxification process [44].

Cytochrome P450 enzymes are involved in around 95% of the redox reactions [45, 46] of the chemicals they metabolize, performing mainly in Phase I metabolism, essential functions. In this phase, the functions of detoxification/deactivation of xenobiotics (any substance foreign to the body, namely drugs, toxicants) predominate, with the most prominent CYP enzymes for these functions being those belonging to families 1–3 [42], being responsible by the metabolism of around 80% of medications, and contributing approximately 50% of the work of CYPs [47].

CYPs are responsible for several reactions, with monooxygenation [43] being the predominant chemical reaction, which is why they are also called enzymes with "monooxygenase" activity [48]. CYPs are directly involved in metabolic pathways that process not only endogenous substances (steroids, fatty acids, vitamins, etc.) but also exogenous substances (drug medicines, environmental pollutants, and carcinogens), making the molecules of these compounds more soluble in water and facilitating its excretion on the one hand, or promoting its activation, as is the case with some drugs or carcinogenic substances [47].

At a cellular level and as an example with a liver cell where much of the metabolism takes place, variability begins in the protein transporters responsible for the entry of the substance into the cell (Phase 0) then, in the variability of the enzymes responsible for the chemical modification of the ingredient to be detoxified (Phase I), predominantly in the endoplasmic reticulum, then in the enzymes involved in the conjugation process (Phase II) in the cytosol and, finally, the variability in the membrane transporters ABC, ATP-binding cassette transport (Phase III), responsible for forwarding the products already metabolically transformed, for the body's excretory pathways, mainly urinary and intestinal.

Considering Phase 0, it is essential to highlight that uptake transporters deemed specific to the liver, such as OATP1B1 and 1B3, as well as OATP2B1 and 1A2, were also found to be expressed in the intestine [49]. Grapefruit juice can inhibit the OATP1A2 transporter and thus compete with the bioavailability of certain medications [49].

Regarding CYPs (Phase I), there are different drug response phenotypes, which include poor metabolizers, extensive metabolizers, and ultra-rapid metabolizers, which influence the physiological effects of medications [50]. Particularizing and considering a Phase I enzymatic protein, CYP 2D6, for example, some people are ultra-fast, extensive, intermediate, and slow metabolizers depending on the active and inactive genes they possess, resulting from the phenotype of the person in question. Genetic variations and individual differences can affect the excretion rate of metabolites and influence the response to medications and other substances, including medicinal plants, and determine their possible side effects.

Regarding Phase II, there is also variability in interindividual enzymatic activity, which can condition changes in the metabolism of endogenous and exogenous substances with consequent repercussions on individual health.

For example, catechol O-methyltransferase (COMT) is an essential enzyme in Phase II of metabolism, deactivating endogenous or exogenous catechols, such as catecholamines and catechol estrogens, as well as in the metabolism of some medications. The catechol O-methyltransferase transfers a methyl group from SAM (S-adenosylmethionine) to a catechol-containing substrate molecule. A Val158Met genetic variant in the COMT gene leads to a several-fold decrease in enzymatic activity, accumulating potentially carcinogenic endogenous catechol estrogens and their reactive intermediates, thus increasing the risk of carcinogenesis [51]. The variation in COMT activity can also explain the effect of certain medicinal plants, such as green tea (**Figure 5**).

3.1 The case for green tea (*Camellia sinensis* (L.) Kuntze)

Although from herbal medicine perspective, *Camellia sinensis* (L.) Kuntze, *non fermentatum folium*, has been recognized in Europe as a traditional herbal medicinal product for the relief of fatigue and the sensation of weakness [52]; some studies have highlighted the antineoplastic potential of green tea polyphenols, quercetin, fisetin, or luteolin. These are common phytochemicals that can be markedly altered (either decreased or increased) by COMT-mediated O-methylation of these exogenous

Figure 5.
Green tea (Camellia sinensis (L.) Kuntze). Source: Jardim Botânico UTAD, Flora Digital de Portugal.

substrates; flavonoids can also behave as potent inhibitor compounds of the COMT enzyme, delaying the detoxification of endogenous catechol estrogens, potentially carcinogenic [51].

The human COMT gene contains a functional polymorphism, with a G → A substitution in nucleotide 1947 of exon 4 (COMTG1947A) altering the amino acid codon at position 108 (Val → Met) in the COMT protein, which is associated with a variation in the activity of COMT enzyme. Individuals with the G/G genotype have three to four times greater COMT enzyme activity than those with the A/A genotype, while heterozygotes have intermediate enzyme activity [53].

Green tea, a traditional drink in Asian countries such as Japan and China, is also rich in polyphenols such as catechins and gallocatechins, including epigallocatechin-3 gallate (EGCG), which have also been shown to exhibit antiproliferative and antiangiogenic effects in breast cancer cell lines. However, this protective effect of green tea is observed mainly among women with the genotype of low catechol-O-methyltransferase COMT activity. The inverse association between tea intake and breast cancer risk was observed only among individuals with at least one low-activity COMT allele [54].

Similarly, it was found that green tea consumers with the highest activity of the COMT genotype, in which polyphenols are effectively excluded, will obtain less protective benefits against the development of lung cancer [55].

Another Phase II metabolism enzyme is arylamine N-acetyltransferase 2 (NAT2), which is involved in physiological responses to xenobiotics, including medicines and exogenous chemicals in the diet and the environment.

The extensive polymorphism in NAT2 gives rise to wide interindividual variation in acetylation capacity, influencing individual susceptibility to various drug-induced adverse reactions [56] and even the risk of malignant neoplasms [57].

As mentioned, interindividual variability also occurs in Phase III transport proteins. There are several families of ABC genes and multiple encoded proteins, each with different specificities.

Genetic variation influences the effects of plant-medicine interactions, demonstrating pharmacogenomic studies that this influence may involve pharmacokinetic and pharmacodynamic pathways, with this knowledge being essential in contributing to the safe use of herbal medicines in clinical practice [58].

Thus, the dosage of herbal-based supplements can be adjusted to improve efficacy and reduce toxicity according to pharmacogenetic knowledge whose development leads to the discovery and identification of the targets/mechanisms of pharmacological effects and therapeutic responses of natural products effectively and efficiently at the complete genome level, allowing the rational development of herbal medicine as part of an accurate, practical medicine [59].

Plants and vegetable foods such as turmeric, thistle, apple, and green tea, in addition to grapefruit and broccoli, can interfere with the metabolization processes by activating or inhibiting the enzymes of the different phases, with interindividual variability.

Many plants are CYP activators, such as cruciferous vegetables (broccoli, brussels sprouts, cabbage, cauliflower, radish, and watercress) and St. John wort, which activate CYP 1A2; others are inhibitors, such as grapefruit, coffee (caffeine), and echinacea with CYP 1A2 inhibitor properties. Equivalently, grapefruit inhibits and St. John's wort activates the CYP 3A4.

Echinacea (**Figure 6**) root (*Echinacea purpurea* root), popularly used for conditions such as common cold, coughs, bronchitis, influenza, and inflammation of the

Figure 6.
Echinacea purpurea. Source: Jardim Botânico UTAD, Flora Digital de Portugal.

mouth and pharynx, reduces the oral clearance of CYP1A2 substrates and selectively modulates the catalytic activity of CYP3A in hepatic and intestinal sites. Care must be taken when co-administered with medications dependent on CYP3A or CYP1A2 for their elimination [60].

The intestine's high level of expression of CYP3A4 may condition CYP3A4 susceptibility to dietary modulation. Numerous food-drug interactions involving CYP1A2, CYP2E1, glucuronosyltransferases, and glutathione S-transferases have been documented, in addition to interactions involving transporters such as P-glycoprotein (ABC-transporter of Phase III) and organic anion transporting polypeptide [61].

The binding affinity and response to active compounds in medicinal plants are related to the variability of receptors and their expression; for example, variations in opioid receptors can influence an individual's response to analgesic plants, such as opium poppy.

The variability of response to medicinal plants is more complex regarding plants with psychotropic action. For example, considering cannabis, several factors seem to contribute to this variability, from purely genetic characteristics of the individual but also the cannabinoid profile, individual tolerance, route of administration, dose, mental state and physical environment of an individual, previous experience of consumption, one's health and metabolism, and age; all of them in addition to the purity and quality of the herbal material such as contaminants or impurities that can introduce unexpected or side effects. Its properties are mainly related to its chemical composition, which depends on the manufacturing method, hemp variety, and seeds used [22].

Another aspect of great importance in interindividual variability in metabolism concerns the intestinal microbiota. Gut microbial communities represent a source of human genetic and metabolic diversity. Gut microbiomes differ between people when viewed from the perspective of microbial lineage components, encoded metabolic functions, postnatal developmental stage, and environmental exposures [62].

Finally, it is also worth noting that, within the individual, variability also involves temporality. For example, human glucuronidation (Phase II metabolism) begins after birth and is scarce during fetal life. This fact may justify indirect hyperbilirubinemia in children in the neonatal period.

4. Anthropological variability

Anthropological factors such as diet, lifestyle, and exposure to environmental toxins can influence an individual's response to medicinal plants. For example, people from different regions may have different tolerances or sensitivities to specific herbal remedies based on their environmental exposures. Ethnic differences were found in the enzymatic activities of CYP3A4 enzymes [61] and in the pharmacodynamic response to cyclosporine between healthy African American men and White men [63].

However, it was noted that these differences could have resulted from non-genetic factors, such as diet or drug therapy, with the type of menu being another factor that adds to the variability of response to medicinal plants. There were found ethnic differences concerning CYP3A4 activity; however, these differences could be partially explained by different dietary patterns that can modulate this enzyme with a high level of expression in the intestine and specific for a wide range of substrates [61].

Ethnic aspects are to be considered. For example, *Moringa pteridosperms* and *Moringa oleifera* are widely used in sub-Saharan Africa, and polymorphisms in drug-metabolizing enzymes have been found to affect activities, with differences between racial and ethnic populations. An example of this is CYP2D6, where certain variants are found only in specific people; for instance, CYP2D6*17 among Black Africans, CYP2D6*10 among Asians, and CYP2D6*2 N reported in most populations but at different frequencies [64].

Ethnological variability is also associated with Phase II enzymes, for example, in the case of COMT and NAT2.

Regarding COMT, the frequency of the homozygous A/A genotype in the Fujian Han Chinese population was similar to that of the Kenyan, Japanese, Korean, and Taiwanese Han populations but much lower than in Caucasians and southwest Asians demonstrating differences and variability between groups—ethnicities in COMT enzyme activity [53].

The diverse functioning of COMT and its complex regulation by several genetic and environmental factors, including plant-based food ingredients, emphasizes the need to stratify further association studies between COMT genotype and cancer risk from product consumption containing catecho l [51].

The variation in the protective activity of green tea concerning cancer may have to do with variants in COMT activity between populations and the different distributions of phenotypic frequencies, being the result of the selection of phenotypes over the years, according to dietary patterns, which may have an impact and implications for the prevalence of the disease.

Regarding arylamine N-acetyltransferase 2 or NAT2, many questions remain about the evolutionary mechanisms that led to the high prevalence of NAT2 slow acetylators between humans. Recent research studies demonstrate some evidence about NAT2 gene variation, suggesting that slow-acting NAT2 variants may have become targets of a natural positive selection due to changing livelihoods and lifestyles in human populations over the past 10,000 years [65].

A higher prevalence of the slow acetylation phenotype was observed in populations that practice agriculture (45.4%) and herding (48.2%) as compared to people that rely primarily on hunting and gathering (22.4%) (P = 0.0007). This fact began to be seen in the frequency of the slow variant 590A, which occurred three times more frequently in food producers and farmers (25%) compared to hunter-gatherers (8%) [65].

These findings are consistent with the hypothesis that the Neolithic transition to subsistence economies based on agricultural and pastoral resources modified the selective regime that affects NAT2 in the acetylation pathway, with evidence of a correlation between the prevalence of slow acetylators in humans may have been a subsistence strategy adopted by past populations over time in the last 10,000 years; it appears that a slower rate of acetylation may represent a selective advantage in people that change from foraging and hunting-based food to pastoralism/agriculture in the Neolithic period [65].

Understanding how NAT2 genetic diversity is structured in humans is of anthropological importance and medical relevance for pharmacogenetics and epidemiological applications. Genetic heterogeneity is observed between populations from different parts of Asia and between people from Africa and America, and differences in allele frequencies between populations and individuals of different ethnic or geographic origins must be considered, as they may respond differently to acetylated drugs [65].

Impressive patterns of geographic differentiation were described for the slow acetylation variants of the NAT2 gene, suggesting that this genetic locus has been subject to the action of natural selection over time. The correlation of the allele associated with the enzyme's slow activity may have conferred a selective advantage in populations switching from food gathering to agricultural activities in the Neolithic period in an adaptive evolution of the NAT2 gene. The rs1799930 A allele has been associated with slower acetylation capacity in vivo and is much more frequent in farmers and pastoralists compared to hunter-gatherers, highlighting the functional importance of this polymorphism in human adaptation to environmental fluctuations in xenobiotics [66].

Another example related to gut microbiome variability is that Native Hawaiian and Pacific Islander (NHPI) populations demonstrate a disproportionately higher rate of diabetes mellitus type 2, a chronic disease that arises from metabolic dysfunction and is often associated with obesity and inflammation. Reversible lifestyle habits, such as diet, may protect against or contribute to the increased prevalence of health inequities in these populations through the gut microbiome-immunogenetic axis, i.e., the connection between diet, epigenetics, microbiome composition, immune function, and response to infections [67].

Different dietary patterns and eating habits have contributed to variability from an anthropological perspective and can condition different disease prevalences between other communities. A diet rich in fiber, found in whole grains and some fruits and vegetables, facilitates a favorable composition of the intestinal microbiome and increases the production of butyrate, acetate, and propionate, which are short-chain fatty acids that act in metabolic and immunological pathways, protecting against the metabolic syndrome and chronic inflammatory states associated with dysbiosis. Native Hawaiians and Pacific Islanders who once thrived on healthy traditional diets may be more sensitive than non-Indigenous peoples to the metabolic disruption of Westernized diets that affect the immunogenetic-gut microbiome axis [67].

Another example was pronounced differences in bacterial species assemblages and functional gene repertoires observed between individuals residing in the United States compared to other countries. These distinctive characteristics are evident in early childhood as well as adulthood. Furthermore, the similarity of fecal microbiomes between member families extends across cultures. These findings highlight the need to consider the microbiome when evaluating human development, nutritional deficiencies, physiological variations, and the impact of westernization, with sustainable agriculture policies and better nutrition having to be adapted to different cultural conditions but also to different intestinal microbiomes [62].

Anthropological factors can also influence medicinal plants' use in other health practices. For example, some individuals may combine herbal remedies with modern medicine, while others may rely solely on traditional herbal treatments. Among patients using conventional and traditional medicine systems, issues to be addressed include interactions between drug-drug, herb-drug, and herb-herb, and genetic polymorphisms in genes coding for drug-metabolizing enzymes [68].

4.1 Plant/diet-drug interactions

P450 is a cytochrome with an essential role in metabolism, being susceptible to induction or inhibition caused by substances found in plants [47, 69–72] with consequent repercussions on the expected effects of drugs.

Patients should be trained to avoid certain plant-drug combinations that are clinically relevant [73].

Meta-analyses demonstrated a significant effect on CYP1A2 and glutathione S-transferase-alpha (GST-α), with Cruciferae consumption increasing the activities of these enzymes by 20–40% and 15–35% respectively, suggesting that patients undergoing pharmacotherapy with CYP1A2 or GST-α substrates may have altered drug exposure profiles if they concomitantly consume large quantities of cruciferous vegetables [74].

The interactions of grapefruit juice with cyclosporine and felodipine, St. John's wort with cyclosporine and indinavir, and red wine with cyclosporine have the potential to require dosage adjustment to maintain drug concentrations within their therapeutic windows [61].

There is still some controversy regarding the clinical significance of potential interactions between diet and medications. For example, regarding St. John's wort (*Hypericum perforatum*), some results suggest that it is unlikely to inhibit the activity of CYP 2D6 or CYP 3A4 when taken at doses recommended for depression [75].

Food-drug interactions involving Phase I CYP1A2, CYP2E1, and Phase II glucuronosyltransferases and glutathione S-transferases have also been reported. However, most of these interactions are modest in magnitude and clinically relevant only for drugs with a narrow therapeutic range. Recently, interactions involving drug transporters, including P-glycoprotein and organic anion-transporting polypeptide, have also been identified. More research is needed to determine the scope, clinical relevance, and magnitude of the effects of food on drug metabolism and transport.

Another aspect linked to variability in the use of medicinal plants is interference in pharmacodynamics, which is also a result of individual phenotypic variability. For example, cranberry (*Vaccinium macrocarpon*), commonly used as an aid in the treatment and prevention of urinary infections [76], can interfere with warfarin without altering the binding to plasma proteins of S- or R-warfarin. The interaction depends

on the VKORC1 1173 T > C polymorphism, an epoxide reductase essential for activating vitamin K, a cofactor of clotting factors. It was found that individuals with CT and TT genotypes of VKORC1 present a reduction in warfarin activity when administered with cranberry extract by 22% and 11%, respectively [77]. This case is an example of genetic polymorphisms in the pharmacodynamic pathway that may also be involved in plant-drug interactions.

Numerous interactions between plants and medicines have been described and explained by the pharmacodynamic and metabolization process [78–83] where CYP play a role (**Tables 1–3**).

Pharmacodynamics (PD) and pharmacokinetics (PK) are hard to predict in all patients, and best practice involves the use of standard dosing based on weight and therapeutic drug monitoring (TDM).

Pharmacodynamics (PD) and pharmacokinetics (PK) are hard to predict in all patients, and best practice involves the use of standard dosing based on weight and therapeutic drug monitoring (TDM). Pharmacogenetics (PG) is the use of genetic screening to predict metabolic responses to different drugs and enables more accurate predictions of PD and PK to be made. The biggest challenge in reducing metabolic

Pharmacodynamic and/or pharmacokinetic changes	Pharmacokinetic mechanism	Examples of influenced drugs	Probable outcome
Increased concentration of ARV*	Inhibition of CYP3A4 (intestinal)	Indinavir	Increased ADR risk**
	Inhibition of CYP2D6	Ritonavir	
		Cobicistat	
Concentration reduction	Alteration of GPP	Celiprolol	Therapeutic failure
Concentration reduction	Inhibition of CYP1A2	Antipsychotics and antidepressants	Therapeutic failure
Increased concentration	Unknown	Sulfasalazine	Increased ADR risk
Synergistic effect	Unknown	Warfarin	Increased hemorrhagic risk
Increased concentration	Unknown	Palbociclib	Increased ADR risk
		Capecitabine	
		Enzalutamide	
Concentration reduction		Talinolol	Therapeutic failure
Increased concentration	Inhibition of CYPA4/5	Tacrolimus	Increased ADR risk
Concentration reduction	Inhibition of GPP	Azatioprin, ciclosporin	Hepatotoxicity
Increased concentration	Inhibition of CYP3A4	Everolimus	Increased ADR risk
	Inhibition of GPP		
Reduced bioavailability (dose dependant)	Inhibition of GPP	Digoxin	Therapeutic failure

*References: [78, 80–83, 87, 89, 94]. *ARV: antirretrovirals.*
***ADR: adverse drug reaction.*

Table 1.
Curcuma: approved use for dyspeptic problems [12]. Some studies show a potential role as an immune modulator and anti-inflammatory [73, 82].

Pharmacodynamic and/or pharmacokinetic changes	Pharmacokinetic mechanism	Examples of influenced drugs	Probable outcome
Increased bioavailability	Unknown	Antirretrovirals	Increased ADR risk**
		Tacrolimus, ciclosporin	Toxicity/ therapeutic failure
Increased AUC	Inhibition of GPP	Simvastatin	Increased ADR risk
Inhibition of folic acid absortion			
Antagonism	Unknown	Warfarin	Therapeutic failure
Increased AUC	Inhibition of OATP1A1 and OATP1A2	Beta-blockers	Increased ADR risk
		Fluoroquinolones	Increased ADR risk
		Statins	Increased ADR risk
Reduced bioavailability		Nadolol	Therapeutic failure
Decreased absorption	Inhibition of OATP1B1, OATP1B3	Atorvastatin	Increased ADR risk
Decreased absorption	Inhibition of MATE1, MATE 2	Atorvastatin	Increased ADR risk
	Inhibition of OCT1, OCT2* (when in interaction with Metformin)		
Antagonism	Unknown	Lisinopril	Therapeutic failure
Increased bioavailability	Inhibition of GPP	Tacrolimus, ciclosporin	Increased ADR risk
Decreased bioavailability	Inhibition of OATP1B1, OATP2B1, OATP1A2 (gut) Activation of OATP1B3	Rosuvastatin	Therapeutic failure

References: [78, 83, 85–91]. *OCT1, OCT2: organic cation influx transporters. They are responsible for the hepatic and renal transport of Metformin.*
** *ADR: adverse reaction to the drug.*

Table 2.
Green tea: approved use [52] to combat asthenia and also described as having anti-inflammatory, antibacterial, and antiviral potential [84].

instability arises when we face different crops, plant selection, preparation methods and dosage that can vary and contribute to variations in the effectiveness of herbal medicines.

Anthropological studies can help preserve, understand, and respect the cultural context of practices in the use of medicinal plants and understand aspects linked to the variability of responses associated with the environment, adaptability, and the evolution of the human species.

Pharmacodynamic and/or pharmacokinetic changes	Pharmacokinetic mechanism	Examples of influenced drugs	Probable outcome
Risk of increased viral load	Inhibition of CYP3A4	ARV*	Therapeutic failure
	Inhibition of CYP1A2, CYP2C9	Caffeinne, tolbutamid	ADR risk**
Concentration reduction	CYP3A4 induction	Midazolam	Therapeutic failure
		Warfarin	Therapeutic failure
Concentration reduction	Unknown	Imunossupressors	Therapeutic failure

*References: [80, 82, 83, 86, 87, 90, 91, 93]. *ARV: antirretrovirals.*
***ARD: adverse reaction to the drug.*

Table 3.
Echinacea-approved use for common cold and acne [92].

4.2 The anthropological case of cannabis

Cannabis has been used for various purposes across cultures and throughout history. It has been used not only for medicinal but also for recreational, spiritual, and industrial purposes.

Different cultures have developed unique traditions and practices related to cannabis consumption. Over time, and in different rules, cannabis has been used as an analgesic, for pain relief, as an anti-inflammatory, and to treat various medical conditions. Traditional knowledge about the properties and aspects linked to the uses of the plant has been observed to vary between different cultures, often linked to beliefs and practices that are not only cultural but also religious and spiritual. For example, Rastafarians use it as a sacrament and certain Native American tribes use it in sacred rituals. Industrial uses such as hemp fiber production are historically known for manufacturing textiles, ropes, paper, and other products [95]. However, recreational use for its psychoactive properties in many parts of the world, both historically and in contemporary times, is recognized as the "anthropological marker of cannabis," although different varieties and methods of consumption have emerged based on cultural preferences. The legal status and social acceptance of cannabis vary widely from one region to another. Some countries and states have legalized its recreational and medicinal use, while others maintain strict prohibitions [96].

Gathering data to develop medicinal cannabis use may lead to two types of products: herbal medicines based on padronized and/or quantified extracts on one side and medicines based on specific cannabinoids or combinations of the cannabinoids on the other. In any case, an integrated systematic approach shall consider the interindividual variability of their effects from a genetic and anthropological perspective (**Figure 7**).

Finally, high-quality evidence on the short- and long-term safety of medicinal cannabis is still lacking. Although there is no known level of cannabinoid ingestion that will result in a toxic or lethal dose in humans, it is reported that the median lethal dose of THC in animal models ranges from 800 to >9000 mg/kg (depending on the species). Thus, the estimates of a lethal dose of THC for a 70 kg human range up to >15 g, and for CBD, doses of ca. 1000 mg/kg have been tolerated in humans [97, 98].

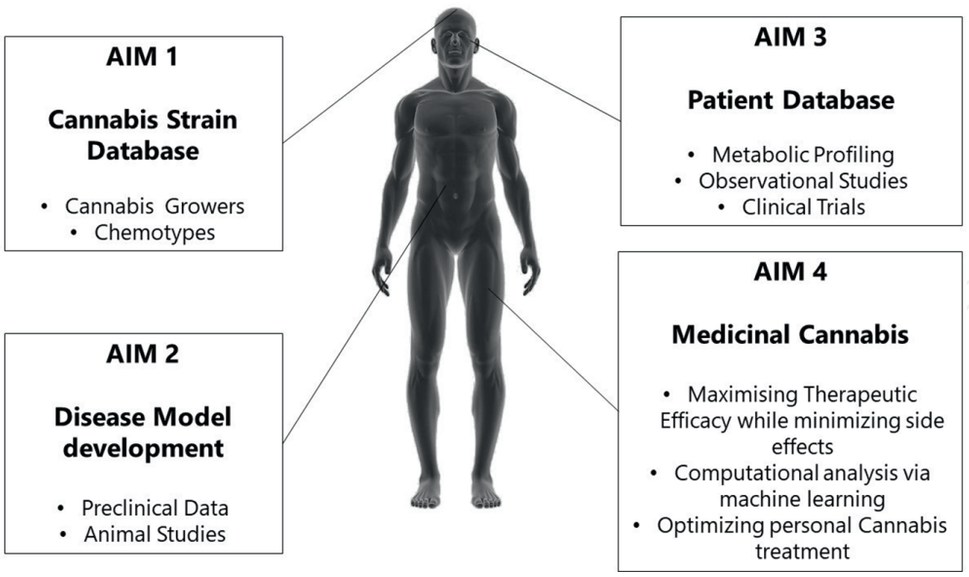


Figure 7.
Research on the therapeutical potential of specific cannabis strains.

5. Conclusions

In conclusion, understanding the interindividual variability of the effects of medicinal plants from a genetic and anthropological perspective is crucial to maximizing their benefits while minimizing potential risks. This approach can contribute to developing personalized and culturally sensitive herbal medicine practices based on nutrigenetics and ecogenetics aspects.

In the food supplements market, numerous plants are freely available for sale that people use, either by prescription or self-medication, intending to treat a health problem and often in combination with chemically synthesized medicines. Due to their multifactorial variability, this aspect denotes the concern and attention necessary to guarantee herbal supplements' standardization and quality control.

Furthermore, this guarantee is fundamental for the safety of consumers and healthcare providers, who already have the factor of interindividual variability to consider in responding to the use of medicinal plants and possible interactions with medications.

The domain of pharmacogenetics and pharmacogenomics, through the understanding of mechanisms of genetic variations and associations of differences in physiological actions of medicinal plants, allows us to understand how the interindividual variability, in part due to genetic composition, added to the genotypic biodiversity inherent to plants, can influence their physiological effects on the human body. This information can help personalize herbal remedies in a person-centered, holistic healthcare professional approach.

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