Chapter

Medicinal Plants of the Peruvian Amazon: Bioactive Phytochemicals, Mechanisms of Action, and Biosynthetic Pathways

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Abstract

The objective of this book chapter is to provide consolidated and updated scientific information about the medicinal plants of the Peruvian Amazon, which has a great richness of plants; many of these are used in folkloric medicine to treat several diseases. Recently, investigations have reported that these medicinal plants possess bioactive phytochemicals against several diseases such as diabetes, cancer, inflammation, infectious diseases, and several other health problems, thus corroborating some ethnopharmacological reports. The mechanism of action for selected bioactive phytochemicals was demonstrated at the molecular level as well as the metabolic pathways involved in their biosynthesis were described. Due to the large gap in scientific information revealed in this review, we formulated a series of strategies to close these scientific knowledge gaps and achieve a sustainable exploitation of medicinal plants in the Peruvian Amazon.

Keywords: cancer, diabetes, ethnopharmacological survey, folkloric medicine

1. Introduction

Peru is cataloged as a megadiverse country due to its great diversity of species, particularly in plants [1, 2]. This diversity is attributed to the large number of eco-regions present in our territory [3], which were originated by their particular geologic evolution [4]. The Peruvian Amazon includes a large proportion of this richness in plant species, and several are endemic to this region [5, 6]. The diversity, however, remains underestimated because until now a complete and updated inventory of plant species is lacking, but some estimates suggest that more than 50% of plant species are unknown to science [7, 8].

Similarly, there are many gaps in the scientific knowledge of medicinal plants of the Peruvian Amazon. These gaps are evident at various knowledge levels from the inventory of medicinal plants and their taxonomic identification, the bioactive phytochemicals produced, the mechanisms of action of the bioactive phytochemicals, and the metabolic pathways involved in the biosynthesis of bioactive phytochemicals. In part, these gaps in the scientific knowledge can be attributed to several factors: (1) the ethnopharmaceutical information has been obtained from few ethnic groups (probably <10%); (2) the majority of ethnopharmaceutical surveys have been focused on plant species to treat protozoal diseases, with particular emphasis on malaria and leishmania [9–12]; and (3) the research centers in the Peruvian Amazon generally lack trained scientist, laboratory equipment, and standard methods to perform bioassays for the discovery of bioactive phytochemicals against diabetes, inflammation, hypertension, cancer, infectious diseases (viral, bacterial, and fungal), and other health problems. Consequently, it is fundamental to implement strategies to surpass these limitations and to close these large knowledge gaps.

Parts of the problems mentioned are addressed in this book chapter that consists of six topics. The first topic "The diversity of plants in the Peruvian Amazon" describes the diversity of species reported for the country and the Peruvian Amazon and are mentioned the possible factors involved in light of current knowledge. The second topic "Medicinal plants and indigenous people in the Peruvian Amazon" highlights information about medicinal plants and ethnic groups. Relevant information of the recently elaborated partial database of medicinal plants is also discussed. The third topic "Some bioactive phytochemicals identified in medicinal plants" presents structures of bioactive phytochemicals against cancer, inflammation, diarrhea, malaria, and diabetes. The fourth topic "Mechanism of action of select bioactive phytochemicals" explains the molecular bases of the mechanisms of action of well-characterized phytochemicals such as taspine, crofelemer, mitraphylline, quercetin, linalool, and bixin. The fifth topic "Biosynthetic pathways for relevant bioactive phytochemicals" describes and provides graphically key metabolic pathways involved in the biosynthesis of quercetin, linalool, and bixin. The final topic "Strategies for the sustainable use of medicinal plants" recommends the adoption of strategies to accelerate the generation of scientific knowledge that permits a sustainable exploitation of the medicinal plants in the Peruvian Amazon.

2. The diversity of plants in the Peruvian Amazon

The plant diversity in the Amazonian lowland rain forest is astounding. This diversity was recently demonstrated with a large-scale taxonomic inventory, which identified 14,003 species; 1788 genera; and 188 families of seed plants, in which 50% of these species can reach ≥10 cm stem diameter at breast height (DBH). More than 52% of seed plant species diversity in this region include shrubs, small trees, lianas, vines, and herbs [1]. The Peruvian Amazon includes ~39% (5401 species) of these species. Also, a previous study showed that a forest near to Iquitos is the most species-rich in the world, with ~300 species ≥10 cm in DBH [2]. In addition, it is estimated that ~17,143 plant species are circumscribed within the national boundaries [13], and approximately 13% of these plant species are endemic to the Peruvian Amazon [5, 6]. It is speculated, however, that only 60% of the Peruvian flora has been identified [7]. Consequently, Peru is considered to be one of the 17 megadiverse countries, a global center for species

richness of plants and other organisms [14]. This peculiarity is attributed to the most Holdridge life zones (containing 84 of the 107 eco-regions of the world) that possess our country [3], which was determined for their particular geologic evolution [4].

3. Medicinal plants and indigenous people in the Peruvian Amazon

The Amazon lowland rain forest provides multiple benefits to its inhabitants [15]. According to Schultes [16], rain forests have an incalculable value as an untapped emporium of germplasm for new commercial plants. For example, to the inhabitants of Mishana (a community near Iquitos), the tropical forest provides timber resources (e.g., sawlogs and pulpwood) and several forest products such as edible fruits, oils, latex, fiber, and medicines. The yield of these forest products is provided by 72 species (26.2%) that are sold in the Iquitos market [17]. In addition, it is estimated that ~4400 native plant species of the Peruvian flora are used by inhabitants for 49 different applications [18]. With reference to bioactive plants, it was reported that more than 1300 species are used by natives in the northwest Amazon as medicines, poisons, or narcotics [16]. To date, however, the list of medicinal plants useful for the discovery and development

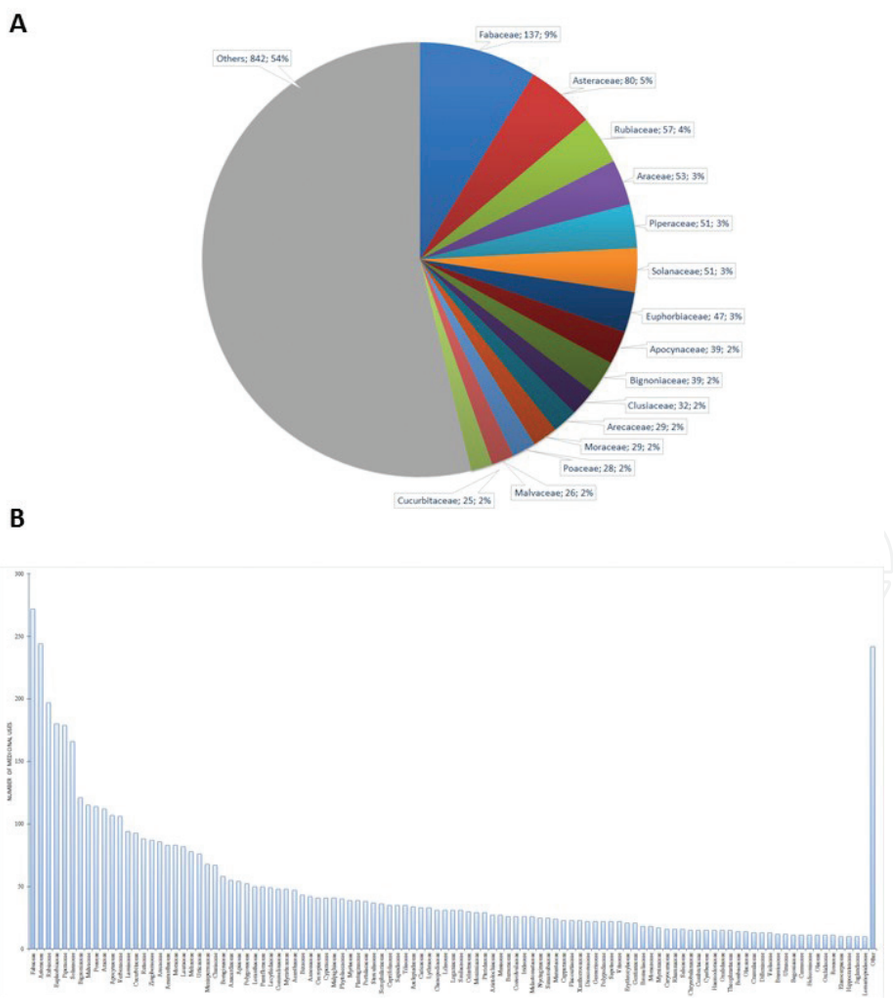

Figure 1.
Families of medicinal plants (A) and number of their uses (B) to treat diseases in the Peruvian Amazon.

Figure 2.
Selected ethnic groups from the Peruvian Amazon.

of drugs is fragmentary and incomplete, because the ethnopharmacological surveys conducted in the Peruvian Amazon are sporadic and scarce. Recently, we elaborated a partial database of medicinal plants of the Peruvian Amazon, which is based on the few available ethnobotanical studies [9–12, 19–25], one list of the Research Institute of The Peruvian Amazon (IIAP) and surveys carried out by our research group in the *Pasaje Paquito* (the main center for commercialization of medicinal plants in the Loreto region, Iquitos). The medicinal plant database includes 1410 species belonging to 157 plant families; these taxonomic assignations were verified with the Plant List database (http://www.theplantlist.org/). Of these, the top 10 families by number of medicinal plant species are Fabaceae (137), Asteraceae (80), Rubiaceae (57), Araceae (53), Piperaceae (51), Solanaceae (51), Euphorbiaceae (47), Apocynaceae (39), Bignoniaceae (39), and Clusiaceae (32). In addition, this database reveals that the plant families with the highest number of medicinal uses are Fabaceae (272), Asteraceae (244), Rubiaceae (197), Euphorbiaceae (180), Piperaceae (179), and Solanaceae with 166 medicinal uses (**Figure 1**).

It is paradoxical that only some ethnic groups were evaluated to date for ethnopharmacological surveys, given the Peruvian Amazon's ethnic diversity (**Figure 2**). According to a recent national census, the indigenous population of the Peruvian Amazon consists of 332,975 inhabitants that include 13 linguistic families that are grouped into 51 ethnic groups. Of the total number of communities registered, 21 are polyethnic [26, 27]. In all these ethnic groups, the millenary knowledge of medicinal plants used to combat common diseases is a fundamental component within the indigenous health systems, which has been maintained from generation to generation. However, due to the transculturation by modernization and globalization, this ancestral knowledge is being lost [15]. Consequently, it is necessary to implement strategies to preserve this invaluable knowledge for the benefit of humankind.

4. Some bioactive phytochemicals identified in medicinal plants

Presently, the list of medicinal plants of the Peruvian Amazon is partial; in consequence, only for the most known plants were identified a few bioactive phytochemicals (**Figure 3**). There is no way to estimate how many new biochemical structures, probably of great value to humankind, remain undiscovered in the Peruvian Amazon. Some of the phytochemicals isolated and with corroborated bioactivity against cancer [28], inflammation [29], diarrhea [30], malaria [31], diabetes [32], and several other diseases were determined [33].

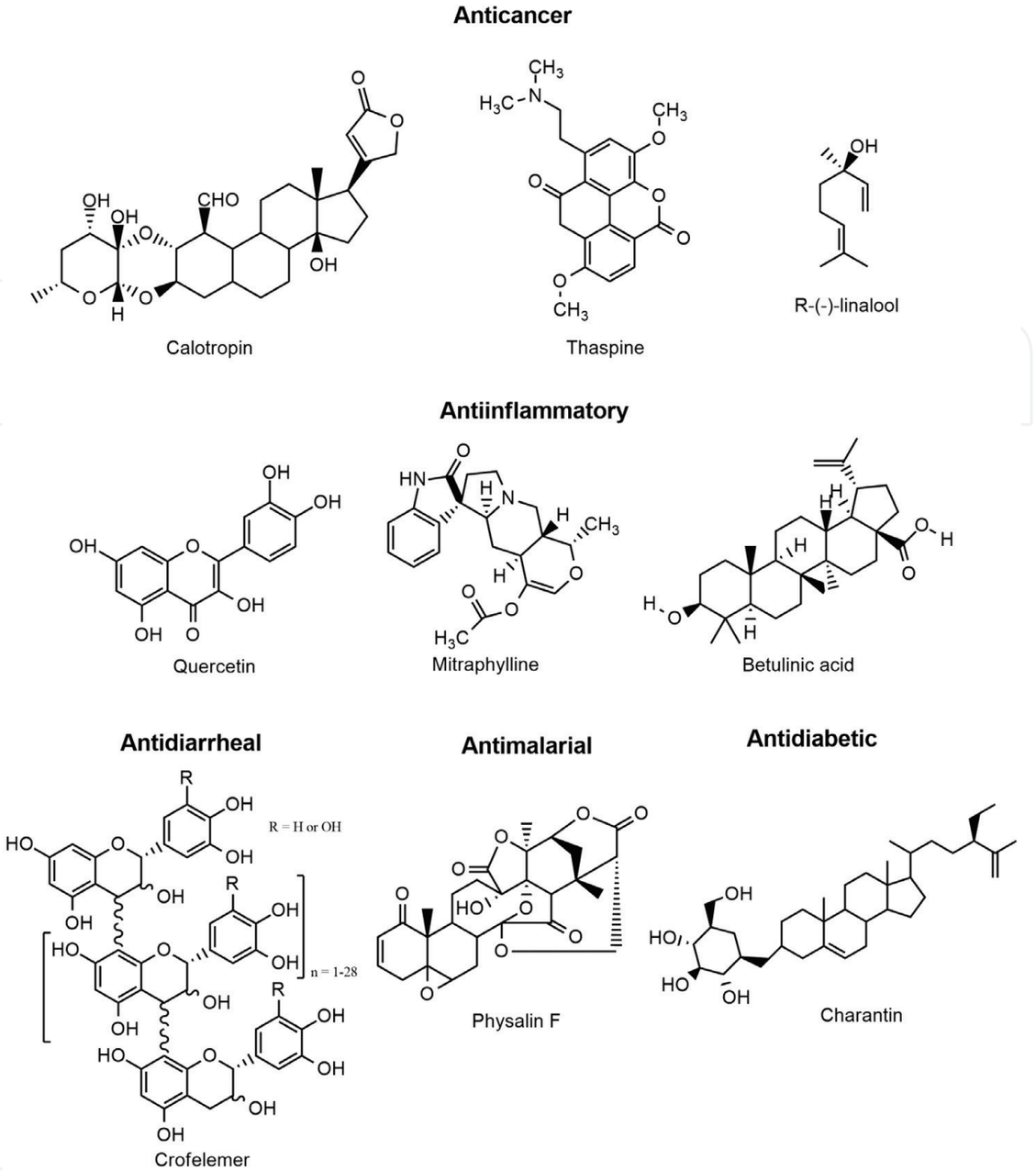

Figure 3.
A small selection of bioactive phytochemicals identified in medicinal plants of the Peruvian Amazon.

5. Mechanism of action of select bioactive phytochemicals

5.1 Bixin

Bixin constitutes the main pigment of the industrial annatto obtained from the seed coat of *Bixa orellana* [34]. This phytochemical belongs to the relatively small family of apocarotenoids; it was the first cis-carotenoid to be isolated from natural sources [35]. However, it was not until 1961 that its chemical structure and stereochemistry were determined through nuclear magnetic resonance spectroscopy studies [36].

This phytochemical compound shows pleiotropic bioactivities with health-promoting properties. It was recently demonstrated that bixin caused arrest of Hep3B cell line at G2/M checkpoint of the cell cycle and the molecular mechanism of action was demonstrated by a modeling study, which was based in the favorable

binding of bixin to domains of Bax BH3 and FasL proteins [37]. Consequently, bixin should be used for developing agents to combat human hepatocellular carcinoma. Bixin is also a potent activator of the transcription factor nuclear factor erythroid 2-related factor 2 (NRF2), which is the master regulator of the cellular antioxidant response protecting the skin against various environmental stressors including UV radiation and electrophilic pollutants [38–40]. The protective effects against solar UV-induced skin damage are due to the NRF2-dependence of bixin-induced antioxidant and anti-inflammatory effects [39]. In addition, bixin displays molecular activities as antioxidant, excited-state quencher, peroxisome proliferator-activated receptor α/γ agonist, and Toll-like receptor 4/nuclear factor kappa-light-chain-enhancer of activated B-cell antagonist. Together, these bioactivities may be important to the improvement of skin barrier function and environmental stress protection [40].

5.2 Crofelemer

Crofelemer previously known as SP-303 is a large proanthocyanidin oligomer isolated from the bark latex of the plant *Croton lechleri* Müll. Arg. [41]. Initial studies have demonstrated the immense antiviral activity of crofelemer against a gamma of DNA and RNA viruses such as respiratory syncytial virus, influenza A virus, parainfluenza virus, herpesvirus types 1 and 2, and hepatitis A and B viruses. The antiviral mechanism implies the direct interaction of crofelemer to components of the viral envelope, blocking both the viral attachment and the cell invasion [41]. More recently, crofelemer is used as a first-in-class antidiarrheal medication, and its efficacy has been investigated *in vivo* assays [42] and in patients with HIV-associated diarrhea, diarrhea of various infectious etiologies, as well as diarrhea-predominant irritable bowel syndrome [43]. Crofelemer was recently approved by the FDA to treat diarrhea in HIV/AIDS patients on antiretroviral therapy [44].

The mechanism of action as antidiarrheal of this proanthocyanidin oligomer consists in the dual inhibitory action on two structurally unrelated prosecretory intestinal Cl− channels, which are responsible for chloride secretion and subsequent luminal hydration. The first target is an extracellular site of the cystic fibrosis transmembrane regulator (CFTR) Cl− channel (~60%, IC50 ~ 7 μM), which produces a voltage-independent block with stabilization of the channel closed state. The second target is the intestinal calcium-activated Cl− channel (CaCC) by a voltage-independent inhibition mechanism (>90%, IC50 ~ 6.5 μM) [45].

5.3 Linalool

An abundant (~90%) essential oil of the leaves of *Aniba rosaeodora* [46, 47] that is used in the traditional medicine of the Peruvian and Brazilian Amazon for its effects on the central nervous system, such as sedative, anticonvulsant, and antidepressant [19, 47, 48]. Additionally, linalool has anti-inflammatory [49], anticancer [50–52], antihyperlipidemic, antinociceptive, analgesic, anxiolytic, and neuroprotective properties [53]. Several studies have demonstrated a gamma of anti-infectious activity like antiviral [54], antibacterial [55–57], antifungal [58, 59], and antileishmanial [55, 60, 61].

The anticancer mechanisms of action of linalool in hepatocellular carcinoma (HCC) HepG2 cells were recently revealed by Rodenak-Kladniew et al. [50] (**Figure 4**). According to these researchers, linalool in a dose-dependently blocked cell proliferation by inducing G0/G1 cell cycle arrest, through Cdk4 and cyclin A downregulation, p21 and p27 upregulation, and apoptosis, characterized by

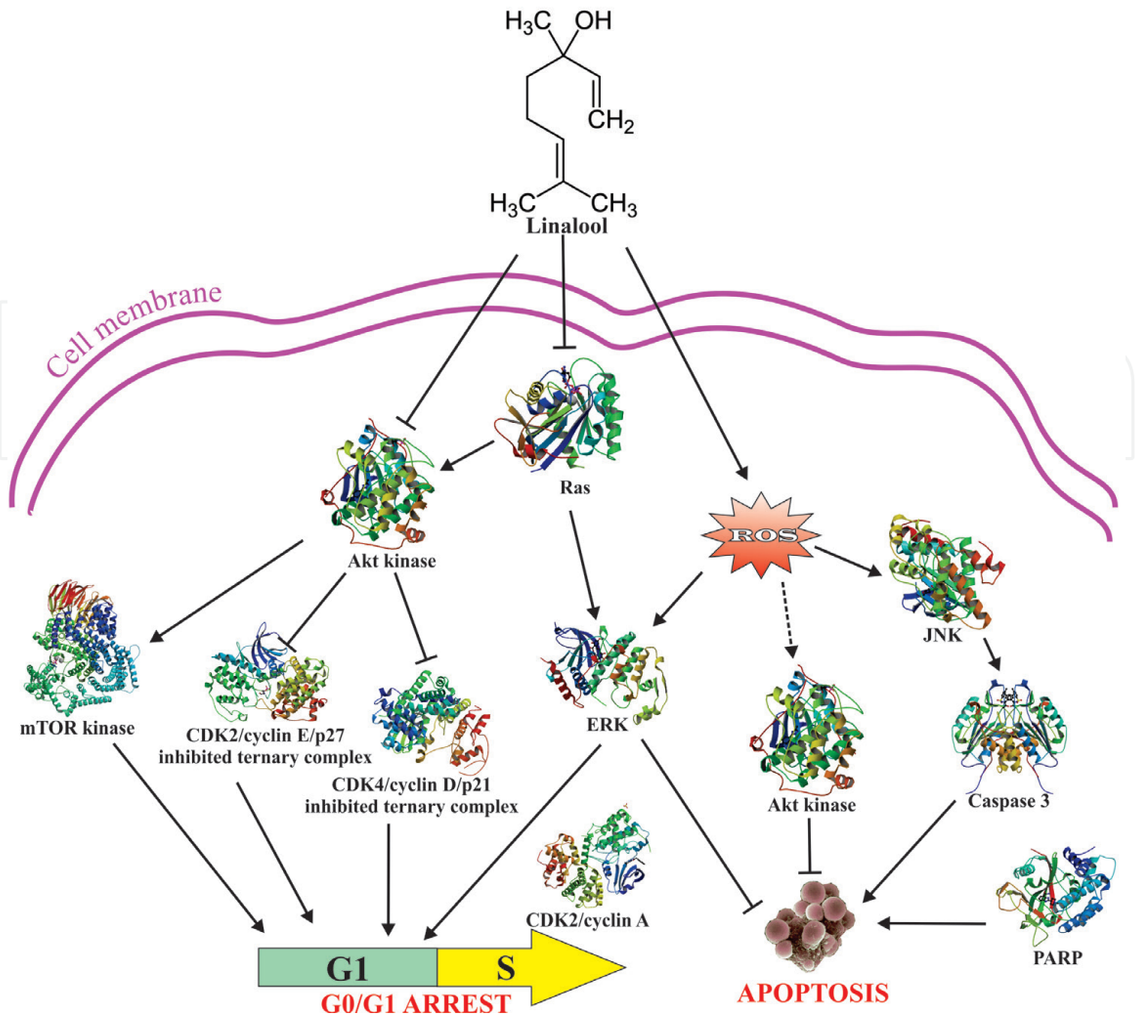

Figure 4.
Anticancer mechanisms of action of linalool in hepatocellular carcinoma (HCC) HepG2 cells.

mitochondrial membrane potential loss, caspase-3 activation, poly(ADP-ribose) polymerase cleavage, and DNA fragmentation

5.4 Mitraphylline

A pentacyclic oxindolic alkaloid that was isolated from the alkaloid fraction of the dried inner bark of *Uncaria tomentosa* (Willd. ex Schult.) DC; it represents the most abundant phytochemical (40%) of the alkaloid fraction [62]. Several investigations have demonstrated the immunoregulatory activity of this compound or the pentacyclic oxindolic alkaloid-enriched fraction [63–67].

The mechanism of action as immunoregulator of mitraphylline consists in both to protect cells against oxidative stress and to elicit a response via an NF-kβ-dependent mechanism. The first mechanism is based on the inhibition of the inducible nitric oxide synthase gene expression; consequently, nitrite formation and programmed cell death are avoided. Finally, in the second mechanism, the inhibition of NF-kβ signaling permits the abrogation of the release of pro-inflammatory cytokines such as TNFα, IL-6, IL-1 α, IL-1β, IL-4, IL-17, and IFN-α [63–67].

5.5 Quercetin

A polyphenol categorized as a flavonol, one of the five subclasses of flavonoid compounds. This bioactive phytochemical is biosynthesized and accumulated in

tissues and organs of several medicinal plants of the Peruvian Amazon such as *Annona montana*, *Bauhinia longifolia*, *Bertholletia excelsa*, *Genipa americana*, *Inga edulis*, *Mauritia flexuosa*, *Myrciaria dubia*, *Oenocarpus bataua*, *Solanum sessiliflorum*, *Theobroma bicolor*, *T. cacao*, and *T. grandiflorum* [68–70]. Quercetin exhibits multifaceted therapeutic applications for multiplicity of unrelated acute and chronic human ailments like allergy, arthritis, asthma, bacterial and viral infections, cancer, cardiovascular diseases, inflammation, obesity, diabetes, mood disorders, neuropathologies, and other health problems [71–76].

This multiple health beneficial properties of quercetin are attributed to their particular mechanism of action based on inhibition of several key proteins and enzymes (**Figure 5**). For example, a recent research showed that this compound is a potent inhibitor of 25 human serine/threonine kinases [77]. The multitarget inhibitor explains its beneficial pleiotropic effects on humans. This flavonoid-type inhibitor is effective against xanthine oxidase, appropriate for the treatment of hyperuricemia, gout, and inflammatory disease states. The inhibitory mechanism is based on the favorable steric complementarity of the conjugated three-ring structure of quercetin with the active site of xanthine oxidase. The enzyme-quercetin binary complex is stabilized by van der Waals forces and hydrogen-bonding interactions with both binding and catalytic amino acid residues, respectively [78, 79]. Recently, Hamilton et al. [80] have demonstrated that quercetin is a competitive inhibitor of glucose uptake by GLUT1. These researchers showed that the inhibitory effect is simply by binding of quercetin to the surface of GLUT1 [80]. Finally, several structural studies by X-ray diffraction have corroborated the inhibitory complex of quercetin with several human protein kinases [81–83].

5.6 Taspine

An alkaloid isolated for the first time by Vaisberg et al. [84] from the bark latex of the plant species *Croton lechleri* Müll. Arg. Previous *in vitro* and *in vivo* investigations have demonstrated that taspine promotes early phases of wound healing in a dose-dependent manner [84, 85]. Taspine was also demonstrated to activate the pro-apoptotic cascade, which oligomerizes Bak/Bax into pores that result in the release of cytochrome c and consequently apoptosis in HCT116 colon carcinoma cells [86]. Similar results were reported for an *in vivo* study conducted with ZR-75-30 human breast cancer xenografts in athymic mice [87].

The mechanism of action of taspine as a topoisomerase inhibitor was revealed recently. Initially, using *in vitro* assays, Fayad et al. [86] observed the inhibition of both topoisomerases I and II by taspine. Castelli et al. [88] corroborated the

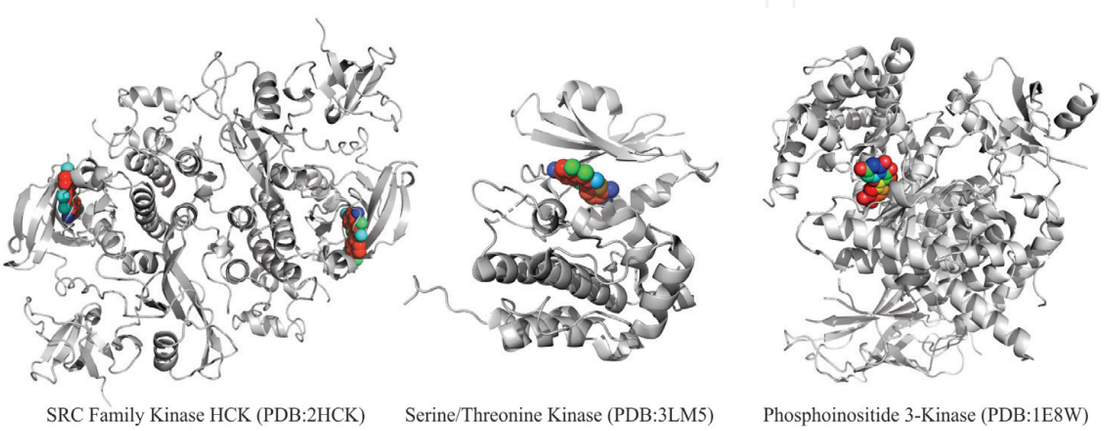

Figure 5.
Inhibitory complex of quercetin with selected human kinase targets.

inhibitory action of taspine on purified topoisomerase I and provided the molecular details of the inhibitory action. These researchers showed that taspine inhibits the catalytic process (cleavage and religation), and molecular docking simulations showed that the formation of the complex enzyme-taspine is accomplished by the interaction in the proximity of the active site preventing the cleavage reaction. While, that the religation inhibition is explained by DNA intercalation of the inhibitor with the enzyme-DNA-binary complex.

6. Biosynthetic pathways for relevant bioactive phytochemicals

6.1 Bixin biosynthesis

The biosynthesis of the apocarotenoid ester bixin from lycopene requires four enzymatic reactions (**Figure 6**). The first enzymatic reaction of bixin biosynthesis is the 5-6/5′-6′ oxidative cleavage of lycopene catalyzed by lycopene cleavage oxygenase to produce two sulcatone and one bixin aldehyde molecule. The second enzymatic reaction is the oxidative conversion of aldehyde into carboxylic acid groups in bixin aldehyde to produce norbixin by bixin aldehyde dehydrogenase. The third enzymatic reaction is the methylation of one norbixin carboxyl group to produce bixin by norbixin methyltransferase. This enzyme utilizes *S*-adenosyl-L-methionine as a methyl-group donor. Finally, the last biochemical reaction is the methylation of one bixin carboxyl group to produce bixin dimethyl ester by bixin methyltransferase, using *S*-adenosyl-L-methionine as methyl-group donor [89–91].

6.2 Linalool biosynthesis

The fundamental building blocks in plants for terpenoid production, i.e., isopentenyl diphosphate (IPP) and dimethylallyl diphosphate (DMAPP), are generated via two independent pathways, namely, 2-C-methyl-D-erythritol 4-phosphate (MEP) pathway and the mevalonate acid (MVA) pathway [92, 93]. The plastid terpenes are formed exclusively via the MEP pathway; however, sterols are biosynthesized via MVA pathway in the cytoplasm and mitochondria [94, 95]. Radiolabeling studies in the early 1970s showed that in *Cinnamomum camphora* the biosynthesis of linalool is accomplished via the MVA pathway [96]. Nevertheless, recent transcriptome analysis of leaves in two chemotypes of *C. camphora* showed that both pathways provide the biosynthetic precursors IPP and DMAPP for the main monoterpenes (i.e., linalool and borneol) synthesis [97]. The balance of IPP/DMAPP is controlled by type 1 and type 2 isopentenyl diphosphate:dimethylallyl diphosphate isomerase, which reversibly converts IPP to DMAPP [98, 99]. Further, IPP and DMAPP are condensed by geranyl diphosphate synthase and isopentenyl diphosphate to produce geranyl diphosphate by geranyl diphosphate synthase. Finally, geranyl diphosphate is transformed in linalool by the action of linalool synthase (**Figure 7**).

6.3 Quercetin biosynthesis

A bioactive phytochemical that is biosynthesized through the phenylpropanoid pathway [100]. The initial reactions transform phenylalanine into 4-coumaroyl-CoA, which enters into the flavonoid biosynthesis pathway (**Figure 8**). The first committed enzyme in the flavonoid pathway, chalcone synthase, uses malonyl-CoA and 4-coumaroyl-CoA as substrates to produce naringenin chalcone. This metabolic

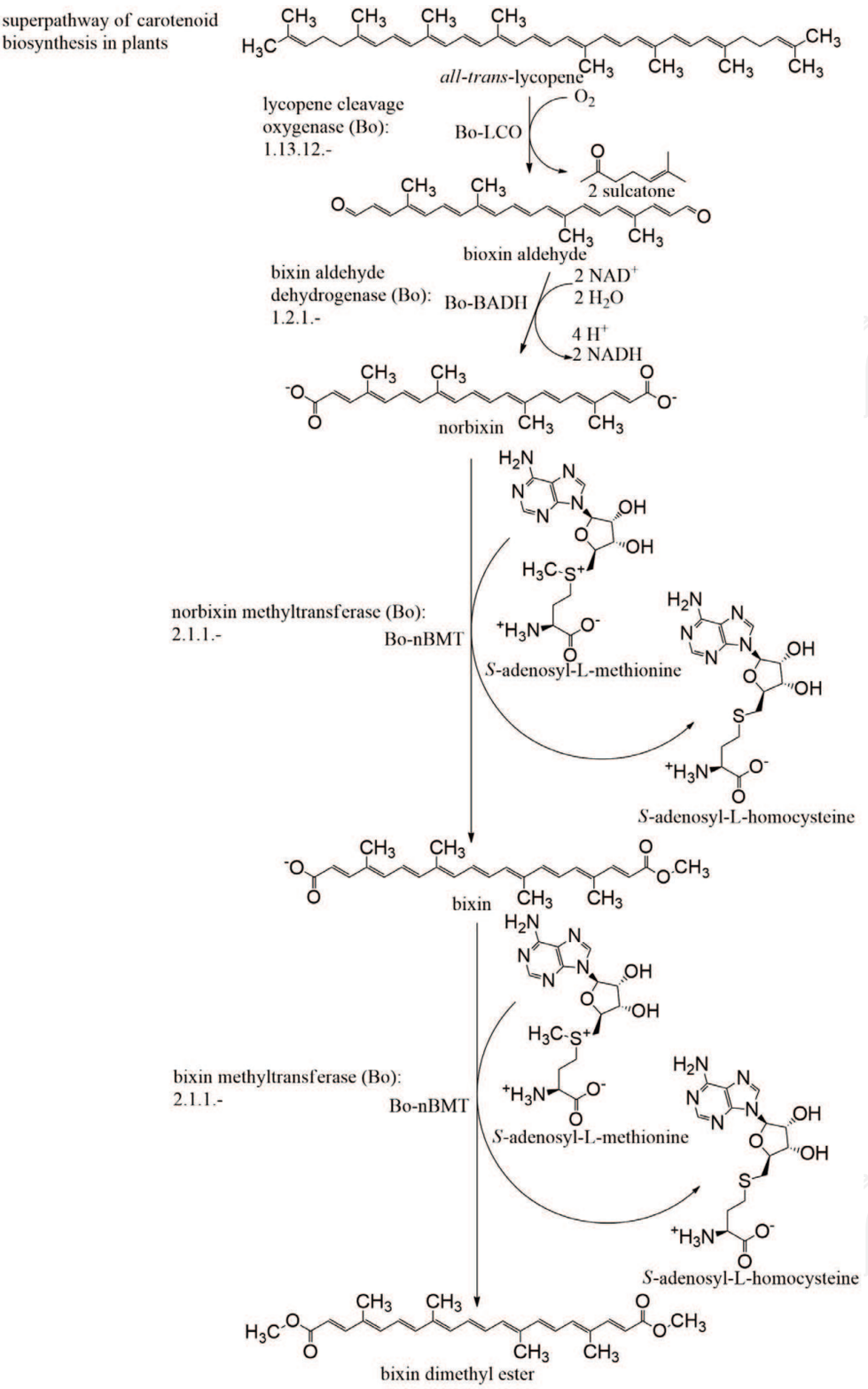

Figure 6.
Biosynthetic pathway for bixin.

intermediary is converted to (+)-dihydrokaempferol by the action of two enzymes, one isomerase and one dioxygenase, respectively. Next, (+)-dihydrokaempferol quercetin is biosynthesized by two alternative and consecutive enzymatic reactions: first, enzymes (+)-dihydrokaempferol 3′-hydroxylase and quercetin synthase produce (+)-taxifolin as a metabolic intermediary, and, second, enzymes dihydrokaempferol synthase and kaempferol monooxygenase produce kaempferol as a metabolic intermediary [101].

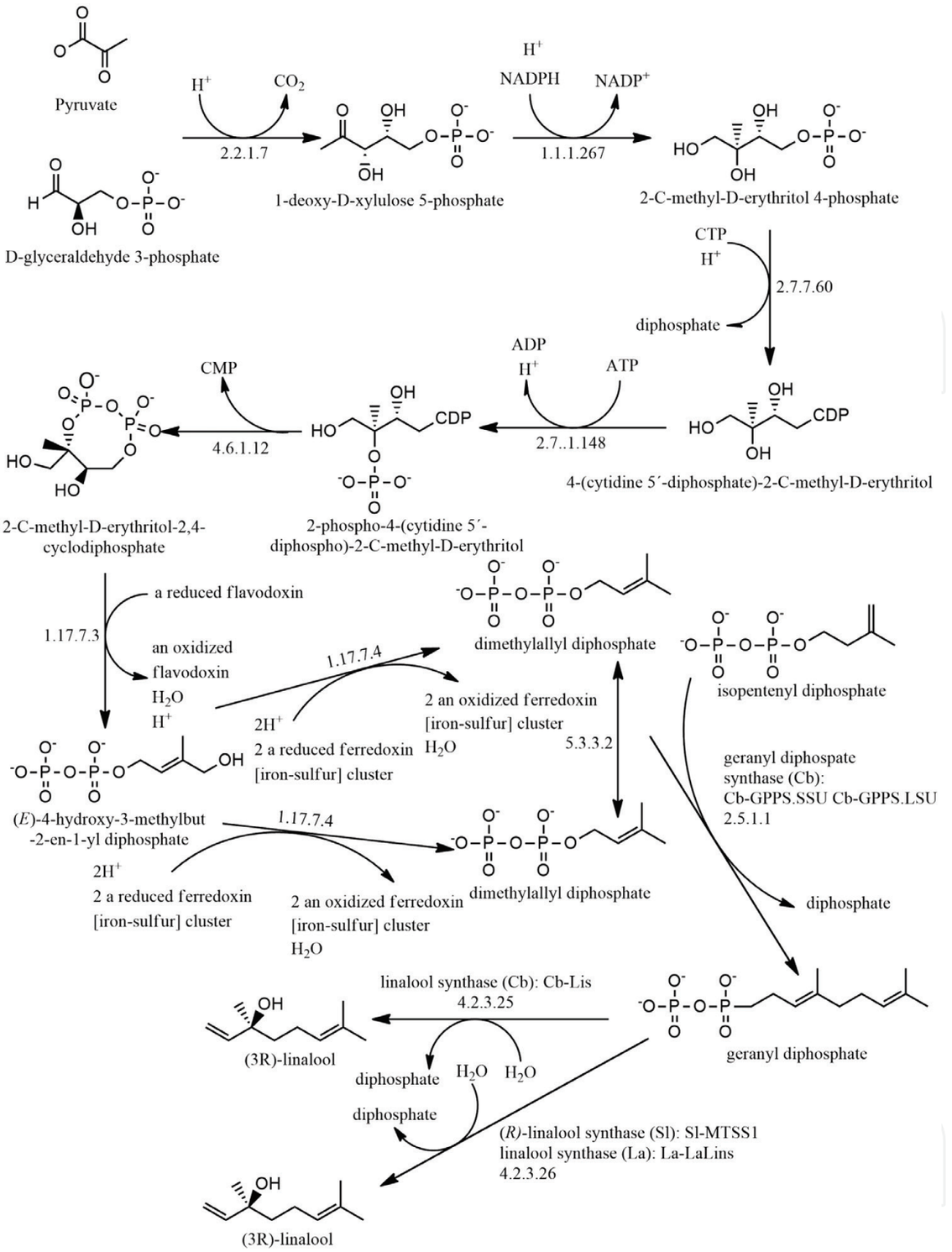

Figure 7.
Biosynthetic pathway for linalool through the MEP pathway.

7. Strategies for the sustainable use of medicinal plants

To date, the research contributions of the Peruvian Amazon to ethnopharmacology have been very limited, and data are still fragmentary and dispersed. Consequently, to ensure a sustainable economic development, we need to obtain a competitive advantage based on our medicinal plant resources. To achieve these goals, we must formulate appropriate strategies based on solid scientific knowledge. First, we need to record the millenary knowledge of folk medicine practiced by the total ethnic groups of the Peruvian Amazon. Second, based on this information, we

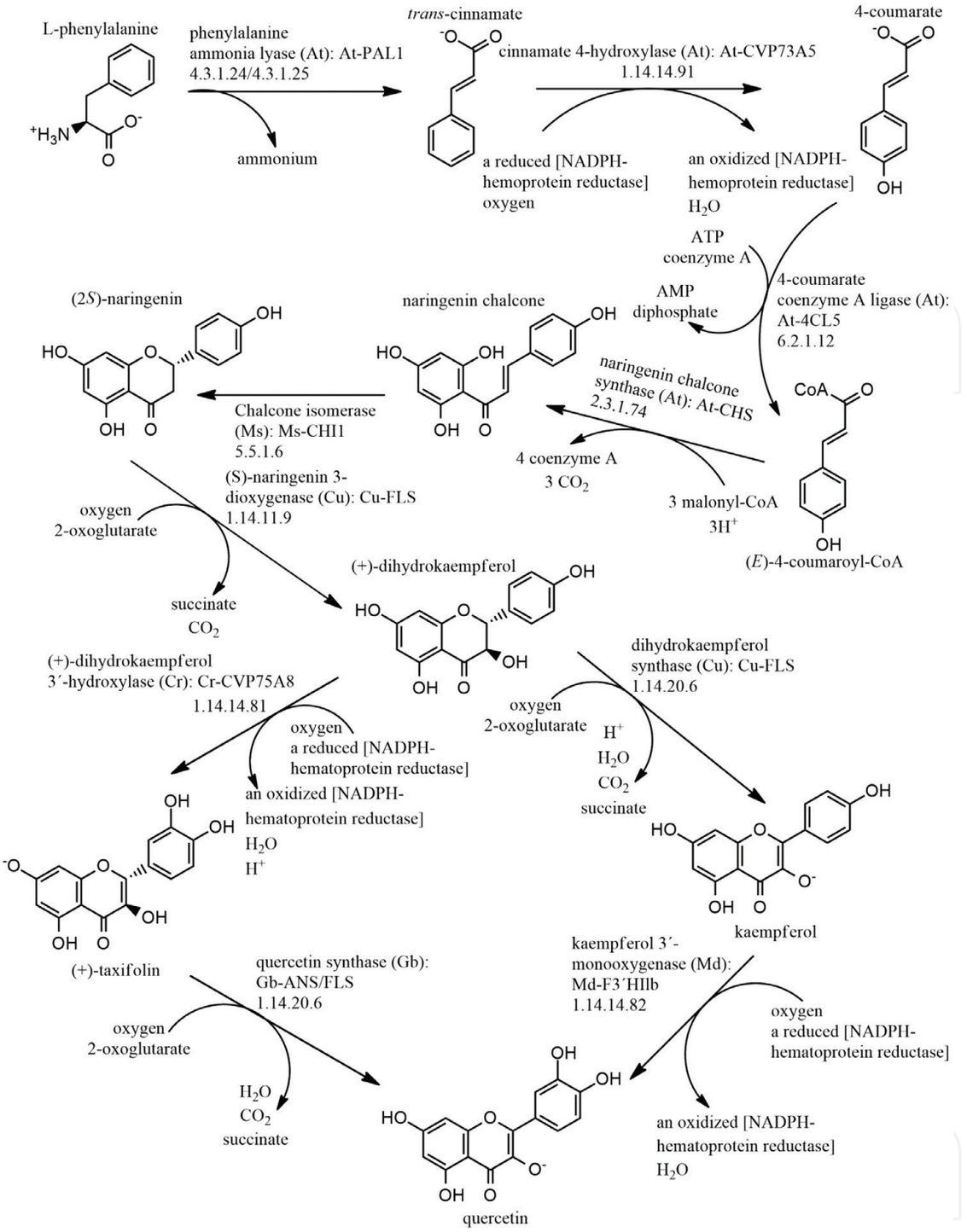

Figure 8.
Biosynthetic pathway for quercetin.

should construct a complete catalog of known medicinal plants with correct taxonomic identifications. Third, an enriched germplasm bank of medicinal plants should be established with accessions of several sites of the Peruvian Amazon. Fourth, the bioactivity of extracts/bio-guided isolated and purified phytochemicals with a battery of *in vitro* and *in vivo* standardized bioassays against multiple diseases (e.g., diabetes, cancer, bacterial infections, etc.) should be established. Fifth, multiomics approaches such as genomics, transcriptomics, proteomics, and metabolomics should be performed to identify key genes, enzymes, and metabolic pathways responsible for the biosynthesis of promising bioactive phytochemicals. Sixth, in the short term, a web-based computerized database to facilitate storage, management, transfer and

exchange, and analysis of the data by researchers, planners, and other interested users should be developed and made freely available. Finally, the availability of this basic scientific information could support the development of genetic improvement programs for medicinal plants and allow a boost of biotechnological applications, based on synthetic biology tools and using bacterial, microalgal, and several other cell-/tissue-based platforms for the production of phytochemical compounds of interest, thus preventing overexploitation and species extinction of medicinal plants.

8. Conclusions

The Peruvian Amazon houses multiple medicinal plants, but the species catalog is still incomplete, because ethnopharmaceutical studies are lacking in the great majority of ethnic groups. A select number of medicinal plant species, however, have been identified as a potentially useful source of bioactive phytochemical compounds to treat various diseases such as diabetes, cancer, inflammation, and infections caused by pathogens, among other health problems. Also, for some of these bioactive phytochemical compounds, the mechanisms of action are known, which are characterized by presenting a common pattern, their pleiotropic effects, which is attributable to act on multiple targets, consequently, affecting various cellular processes. In relation to the metabolic pathways responsible for biosynthesis of these molecules, only very few are known, but for the vast majority of phytochemicals, it remains a great mystery that needs to be clarified. Therefore, we formulated a series of strategies to close these scientific knowledge gaps and achieve a sustainable exploitation of medicinal plants in the Peruvian Amazon.

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Conflict of interest

The authors declare no conflict of interest.

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