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Science means learning to say "I don't know." – Ashok D. B. Vaidya (2011)

1 INTRODUCTION

Morbus Parkinson, also known as Parkinson's disease (PD), is a progressive ailment of the central nervous system (CNS) in humans (Armstrong and Okun 2020). While there is no cure for this impairing disease to date, the pharmaceutical industry provides an array of synthetic drugs to ameliorate symptoms with efforts being made towards the development of disease-modifying treatments (DMT), thus obtaining a lasting clinical benefit (Morant et al. 2019; Lang and Espay 2018). More recently, surgical procedures to the brain have become part of the treatments offered by modern medicine, such as deep brain stimulation, amongst others (Kogan et al. 2019). However, therapy is expensive and thus is not accessible to many PD patients in the world (Fothergill-Misbah et al. 2020). Even those who can afford medical specialists, plus all the prescribed medication to manage disease symptoms, may – nonetheless – still not enjoy an acceptable quality of life because of the narrow scope of conventional antiparkinson medication (Bloem et al. 2021; Behari et al. 2005).

This current chapter reports an initially singular case of a PD patient in Germany who could not be treated with conventional PD medication and whose quality of life had deteriorated dramatically after diagnosis, including long episodes of psychoses. Following therapy with an Ayurvedic (botanical) preparation from the beans of *Mucuna pruriens* (MP) the patient´s fate was improved substantially at the time (Anonymised 1997, 2010). This compelling and – rather by fortune – well-documented case was pivotal to spreading the experience with MP within the European network of PD patients, mostly by word of mouth. The PD patient community and neurologists were supported by available online information around the medicinal plant, MP, and the bean´s active components, as well as an initial clinical study (HP-200 Study Group 1995) followed by a second one (Katzenschlager et al.) in 2004. Based on this first evidence, some neurologists were willing to support their patients with MP-based complementary therapy. As far as the authors are aware, from approximately 1997 until to date such cases were treated predominantly in Germany, Switzerland, Austria (GSA[1] countries), and The Netherlands. Clinical experience is mainly based on the feedback

1 GSA: acronym referring to countries whose main spoken language is German – in German they are also referred to by the acronym 'D-A-CH' or 'DACH'.

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from patients and volunteers pushing to understand the added value of MP and prompting the availability of a safe and effective natural medicinal product that can be prescribed to PD patients. Their findings constitute the basis of this chapter.

2 PARKINSON`S DISEASE

Worldwide, PD is the second most common neurodegenerative disorder after Alzheimer´s disease, affecting over six million people. Prevalence is expected to double to over 12 million by 2040 and has been described as an emerging pandemic (Bloem et al. 2021; Simon et al. 2020, Neurology Collaborators 2019, Dorsey et al. 2018, GBD 2016).

PD belongs to a group of neurological disorders called parkinsonism. Therein, PD is the most common form of so-called Parkinson's syndrome, characterised by shaking (rest tremor), slowness of movement (bradykinesia), stiffness (rigidity), and postural imbalance. These are referred to as the four main motor symptoms (i.e. relevant to skeletal muscles). The main *non*-motor symptoms include constipation due to impaired bowel movements, insomnia, low mood related to depression, or cognitive impairments partly related to dementia (Armstrong and Okun 2020; Nouws 2015).

2.1 Causes and typology of PD

The causes of PD are likely multi-factorial and linked to both non-genetic (environmental) and genetic factors (Chade et al. 2006; Lau and Breteler 2006). An increased incidence of PD is partly thought to be related to the ageing of the population, although young-onset and juvenile-onset PD are expected to be likewise on the rise (Dorsey et al. 2018, Reeve et al. 2014). More recently, it has been suspected that in the majority of PD cases the disease is caused actually much earlier – at least 20 years before motoric symptoms show – after toxic substances entered the body via the gut (food?) or the nose (air?). The characteristic deterioration of specific cells in the brain are affected only in a relatively late stage of the disease (Bloem et al. 2021: 64).

There are disease variants such as the 'diffuse malignant type' with fast progression and little response to medication. Approximately 50% of PD patients, however, belong to the 'motor-predominant type', characterised by milder symptoms and better response to medication such as levodopa (LD) or dopamine (DP) agonists (see Table 1). Typically, disease progression in this group is slower. Intermediate PD types exist as well (Armstrong and Okun 2020).

The pathophysiology of PD is complex. Simplistically put, it is related, amongst others, to the degeneration or death of the brain´s basal ganglia, a group of clustered neurons of the subcortex. More specifically, they belong to dopamine-secreting neurons of the mid-brain region called *substantia nigra* and within this region they are located in the portion called *pars compacta*. The progressive 'death' or malfunction of these cells, also in other regions of the brain, is a result of mechanisms not detailed here. They lead to a deficit of dopamine (DP), a crucial transmitter in the central nervous system CNS (Davie 2008).

2.2 PD: Drug treatments

Existing drugs treating PD are largely symptomatic and address a variety of disease signs and symptoms. Rascol et al. (2002) provide a practical overview of the spectrum of medication. It comprises treatments to increase so-called dopaminergic stimulation, directly or indirectly (see Table 1). A second group of drugs not listed here reduces mainly cholinergic/glutamatergic stimulation in relation to other neurotransmitter systems (Cersosimo and Micheli 2007).

Our focus on dopaminergic stimulation and related drug therapy here does not mean that other PD medication is less important. We focus on DP (and its molecular precursor, levodopa or l-dopa),

TABLE 1
Treatments that increase stimulation via dopamine or in a dopamine-agonistic manner, modified after Rascol et al. (2002) and updated (Luo et al. 2020). Pro drug: a medicinal ingredient that is converted to a pharmacologically active drug once entering the body; **MAO-B inhibitor**: monoamine oxidase inhibitor type B, a drug that inhibits the enzymatic breaking down of dopamine; inhibition of the enzyme in the CNS keeps dopamine levels high. **COMT inhibitor**: inhibits the catechol-O-methyltransferase, an enzyme which usually methylates levodopa during catabolism peripherally (i.e. not in the CNS); also here, inhibition of the enzyme keeps levodopa levels and thus dopamine levels high. **DDCI**: dopamine decarboxilase inhibitor. *Combining LD, carbidopa with entacapone as a peripherally active inhibitor in one tablet (e.g. Stalevo®) aims at improving stable plasma levels of LD.

Pro-drug to dopamine substitutes the lack of endogenous dopamine in the brain	**Dopamine-agonists** act on specific receptors in a similar way to DP	**MAO-B inhibitors** prolong the availability of dopamine by inhibiting its catabolism centrally	**COMT inhibitors** prolong L-dopa bioavailability peripherally
L-dopa (+ DDCI: benserazide or carbidopa)	Apomorphine Bromocriptine Cabergoline Dihydroergocriptine Lisuride Pergolide Piribedil Pramipexole Ropinirole Rotigotine	Selegiline Rasagiline	Entacapone* Opicapone

because a lack of DP has been the key factor to understanding and treating PD. DP substitution via LD is still considered the first choice ('gold standard') in PD therapy today, almost 50 years after the market introduction of LD-based Madopar® by Hoffmann-La Roche (LD + benserazide) and Sinemet® by Merck and Co. (today MSD; LD + carbidopa), revolutionising PD treatment as from 1973 (Paoletti et al. 2019, Hornykiewicz 2010, Amrein, 2004).

2.2.1 Biochemistry and pharmacology of LD and DP

At this point it seems pertinent to explain, although simplistically, the concept of a pro-drug and why combining LD either with benserazide or carbidopa was a major step in the pharmacotherapy of PD. This goes with the second question of why, if DP is lacking in the brain, is it not actually DP that is being given to the patient?

Physiologically, for a substance to get into the brain, it needs to pass what is called the 'blood-brain barrier'. This barrier protects the extra-vascular part of the brain and spinal marrow – where there is no blood – from the blood in their vessels, safeguarding the central nervous system against inappropriate messenger substances or from toxins and pathogens. This barrier is most efficient in protecting against large and hydrophilic molecules, often positively or negatively charged ones. DP, whilst being a tiny molecule, in the bodily fluids it would be positively charged due to its amino group ($–NH_3^+$) and not cross into the brain. Conversely, small, uncharged, lipophilic molecules are much better able to pass this protective barrier, as would be the case for an (amphiphilic) molecule

like LD, carrying both charges in one. This means, due to LD´s amino group, plus its carboxyl group ($–NH_3^+$; $–CO_2^-$), positive and negative charges neutralise one another within the molecule, making its net charge zero at physiologic pH and the molecule more lipophilic. Once in the brain, LD gets decarboxylated (i.e. stripped of its carboxyl group (–COOH)), and thus converted from pro-drug LD to drug DP as an active neurotransmitter. This reaction, however, is not exclusive to the CNS beyond its blood-brain barrier. It also happens peripherally (i.e. in the rest of the body). This means that much of LD would be converted to DP by decarboxylation before reaching the CNS. The blood-brain barrier will not let DP pass whilst causing adverse reactions in the body´s periphery. To avoid such unwanted decarboxylation from happening, the DDCIs, benserazide or carbidopa, are added to LD, thus improving efficacy in the CNS, resulting in a marked improvement of akinesia and rigidity, but with less effect on tremor (Potschka 2010; Müller 2007).

For a deeper understanding of the biochemistry of dopamine in the CNS it is pertinent to look at its biosynthetic pathways. Fig. 1 shows a simplified version of this pathway described by Meiser et al. (2013), first postulated by Blaschko in 1939. It starts with L-phenylalanine, an essential amino acid. As the name indicates, it can be viewed as L-alanine – a non-essential, proteinogenic amino acid – with a phenyl group on its terminal end. Phenylalanine is a non-polar, neutral (uncharged) and hydrophobic molecule. A hydroxylation step (–OH) in the para-position of the phenyl group leads to 4-hydroxyphenylalanine or L-tyrosine, a non-essential amino acid that has been added a polar side group; though considered a hydrophobic amino acid, it is still more hydrophilic than its precursor L-phenylalanine and is found naturally in many foods that are high in protein – in cheese amongst others – and it is believed to promote ‘deep thinking’ in humans (Colzato et al. 2014). A second hydroxylation step in the meta position leads to LD (Fig. 1). LD is a normal compound in the biology of humans, some animals and plants (Hornykiewicz 2010). Decarboxylation, a common metabolic reaction (removal of –COOH), leads to DP as described above. In humans, DP is synthesised in the kidney and brain (Aldred and Nutt 2010) and belongs chemically to two structural families called catechol (Fig. 2A) and phenylethylamine (PEA, Fig. 2B). DP´s basic structure is thus called ‘catecholamine’ (Fig. 2C). Catechol and its derivatives naturally occur in small amounts in fruits and vegetables and play a central role in the browning of cuts thereof, when exposed to atmospheric oxygen (Mezquita and Queiroz 2013). Mostly synthesised by chemical industry, isolated catechol is toxic and is primarily used for the synthesis of pesticides and fine chemicals like perfumes, aromas (e.g. vanillin) and pharmaceutical compounds (Fiege et al. 2000). PEA in turn is classified as a CNS stimulant and neurotransmitter in humans, produced naturally in many plant and animal species including fungi. Food supplements sold on the market claim an improvement of mood and a benefit in weight loss, although evidence is so far rather limited (Fernstrom and Fernstrom 2007, Ueda et al. 2017).

Further steps in the biosynthetic pathway via hydroxylation of the ethyl side chain lead to noradrenaline, additional N-methylation to adrenaline (Fig. 1). They both have a function as hormones and neurotransmitters. One of the important roles in humans and other animals lies within the so-called fight-or-flight response to perceived threats (Fernstrom and Fernstrom 2007). They also exist as synthetic medications.

We have explained the related biochemistry to elicit why a DP deficit in the brain is treated with the precursor LD, but ultimately also to show that the chemical structure of important and different bioactive molecules is closely related, which may be relevant for a systems approach to primary and secondary plant metabolites and ‘omic’ analytical technologies outlined in the next section and towards the end of this chapter.

2.2.2 Disease biochemistry and DP metabolism

So-called disease modifying treatments (DMT) in PD treatment are opposed to a mere transient improvement of some of the symptoms. DMT are aimed at enduring benefit, slowing down

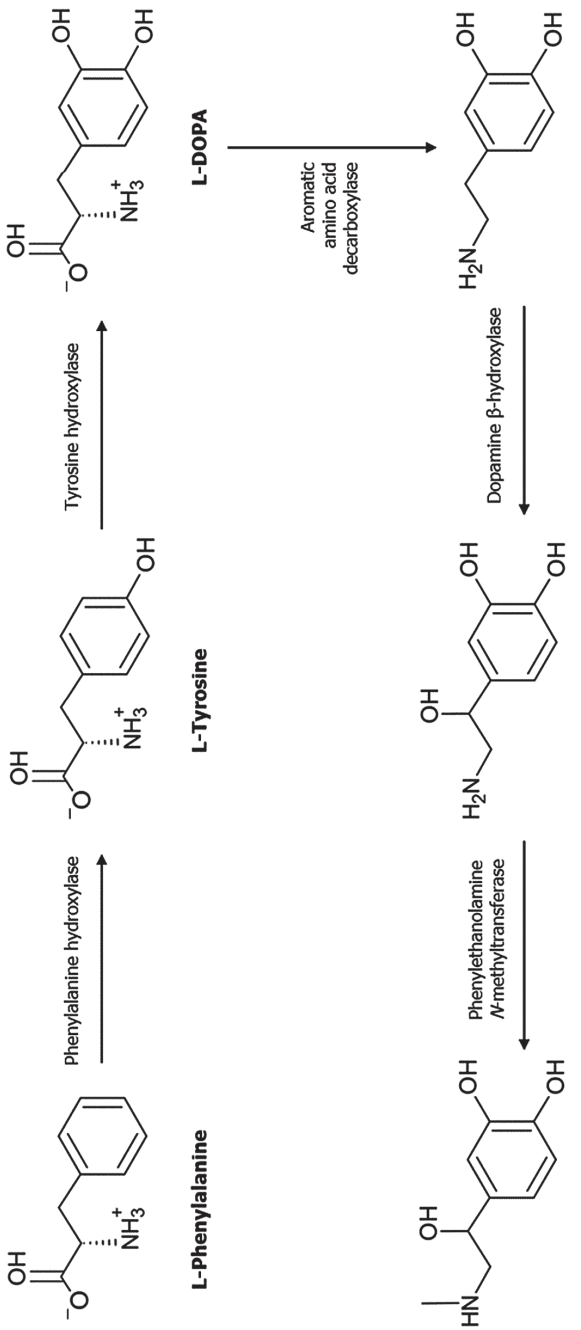

FIGURE 1 Biosynthetic pathways of dopamine synthesis and transformation (simplified after Meiser et al. (2013)); Graphics: Kiki Beekman/Advanced Chemistry Development Inc. (ACD/Labs).

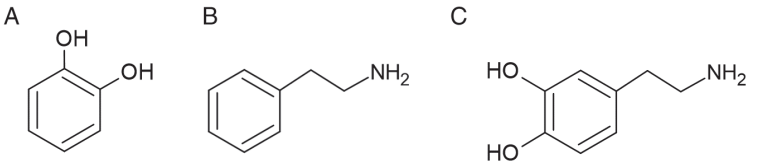

FIGURE 2 A. Catechol, a benzenediol known as 1,2-dihydroxybenzene or benzene-1,2-diol; B. Phenylethylamin (PEA): precursor L-phenylalanine. C. Dopamine, together with norepinephrine (noradrenalin) and epinephrine (adrenalin), belong to the family of catecholamines. Graphics: Kiki Beekman/(ACD/Labs).

progression and ideally at stopping or even reversing the neurodegenerative process, albeit that the latter seems far out of reach. Intensification of research is to be aimed at finding root causes and prevention strategies to PD (Bloem et al. 2021; McFarthing et al. 2020; Morant et al. 2019).

The loss of dopaminergic neurons (neurons related to dopamine) is considered to be related largely to oxidative stress in the *substantia nigra* (Meiser et al. 2013). Within the complexity of the catecholamine metabolism, catecholaminergic neurons are believed to represent an important source of so-called 'reactive oxygen species' (ROS: e.g. hydroxyl radical, hydrogen peroxide) promoting membrane lipid peroxidation, which in turn is considered critical for the survival of cells (Dexter et al. 1989; Fahn and Cohen, 1992).

The second contributing neurodegenerative factor is increased mitochondrial malfunction in ageing. Mitochondria are considered the 'power plants' in the cells. With adenosine triphosphate (ATP) as the 'energy token' in an organ – the brain – (requesting around 20% of the total body oxygen and glucose whilst constituting only 2% of the total body weight) metabolic imbalances related to the mitochondria might trigger detrimental processes (Park and Larsson 2011; Purdon et al. 2002).

To better understand the complexity of dopamine metabolism, Meiser et al. (2013) propose a systems approach on a metabolic level in the cell. Here, regulation takes place on the level of genome (DNA), transcriptome (RNA/mRNA), proteome (set of proteins) and the metabolome. The latter is defined as a set of small molecules in a biological sample, for example in the cell, that can be sugars, nucleotides, amino acids, lipids, vitamins, or even exogenous substances like drugs or toxins (Wishart 2007; Weckwerth 2003). Metabolome analysis entails making a snapshot of the cell biochemistry. This is challenging as such because of high turnover rates. Still, the antioxidant-reducing profile of a biological sample can allegedly be measured and helps to tailor potential antioxidant therapy through drugs or food supplements (Kohen and Nyska 2002).

While in the future, metabolomic approaches might have a lot more to offer in terms of fundamental understanding of the dynamics of live systems in general and PD pathophysiology and novel treatments in particular, we shall first revert to the classic DP-agonist treatments still used today (Table 1; Kraljevic et al. 2004; Cannon 1985).

2.2.3 DP agonists within R&D paradigms of pharmaceutical industry

Since Blaschko (1957) suggested dopamine to be a neurotransmitter, the principle of researching structure-activity relationships between semi-synthetic or synthetic molecules on the one hand and dopamine receptors in the human body on the other, became a major driver in pharmaceutical success stories for symptomatic PD treatments. With the advent of essential analytical methodologies, chemical industry was able to 'design' new molecules that were to be more or less as effective as their natural model – with tolerable side effects and at reasonable production costs. Based on fundamental molecular structures, such derivatives could exhibit better absorption properties following oral administration and improved distribution in the body, especially regarding the passage through

the blood-brain barrier towards their site of action. Much of this type of PD-related biomimetic research was performed in the 1970s (Cannon 1985; Tolosa et al. 1998). The research principle of finding structure-activity relationships in new molecules constituted a key factor for novelty and required patentability, thus representing the very basis of the pharmaceutical industry´s business models to grant returns-on-investment (ROI) at the time and still being of high relevance today (Munos 2009).

2.3 Alternative PD treatment with *Mucuna pruriens* (MP)

Moving away from more or less nature-based synthetic molecules and the pharma industries' IPR[2]-based business model, we now turn to an entirely natural treatment for PD; that is, to preparations made from *Mucuna pruriens* (MP) beans that contain LD naturally from a legume growing in most tropical and some subtropical parts of the world.

While considerable research has shown the effectiveness of MP in different ways, we first focus on an anecdotal report from a pharmacy in southeast Germany whose experience was pivotal in bringing an MP preparation from India into Europe ('Patient No. 1'). This report will be followed by a series of other PD patients' feedbacks in the context of more than 20 years of compelling and mostly unpaid, voluntary engagement to encourage, flank, and support research towards an EU-authorised medicinal product based on MP.

2.3.1 *Mucuna pruriens* L. (DC), its botany, diversity, and uses

MP is an annual climbing liana or shrub from the family of *Fabaceae* within the order of *Fabales*. The name of its genus *Mucuna* (Adans.) is derived from the Brazilian Tupi-Guarani[3] vernacular name *mucunã* comprising up to 150 species that can be annual or perennial and grow mostly in tropical and subtropical climates (Hutchinson 1964; Buckles 1995). Latté (2008) searched ancient literature where MP is identified and described under a variety of other genus names, such as *Stilozobium p*., *Negretia p*., *Dolichos p*. or *Carbopogon p*. The IITA Genebank (1987) adds *Macaranthus cochinchinensis* to this list of MP synonyms. MP can be found in Asia, Africa, and in the West Indies, Central and South America but is believed to have originated in China, Malaysia, or India (Moura 2018; Quattrocchi 2000, Eilittä et al. 2002). Pantropical (worldwide) distribution was presumably fostered by seeds adapted to oceanic dispersal (Moura et al. 2016). The plant grows well in a variety of soils and thrives vigorously, 'like a weed', mostly below 1600m (Eilittä and Carsky 2003; Eilittä et al. 2002, Buckles et al. 1998).

Two varieties or subspecies of MP are often described but not always differentiated as such. One is *Mucuna pruriens var. pruriens* whose beans are known under the trivial name cowage or cowitch bean (derived from Hindi: *Kiwach;* Manyam 1990). The second one is *var. utilis* whose seed is commonly called velvet bean. Latté (2008) in his succinct review specifies the use of *var. pruriens* mainly as a "medicinal plant with dark purple flowers like hanging racemes and red-yellow or brownish S-shaped puffy pods covered with stinging hairs". Seeds are brown and their LD content is specified with 4.0 to 4.9% based on dry weight with higher values (5.3%) in the endocarp. Itching reactions by the stinging hairs of *var. pruriens* are caused by a pruritogenic proteinase called mucunain and can be a severe problem for collectors (Shelley and Arthur 1955; Broadbent 1953).

2 IPR = intellectual property rights, usually referring more specifically to patents on substances, indication and production technologies but also including data protection (Ger.: *Unterlagenschutz*) (Begeroff et al. 2019).

3 Tupi-Guarani is referred to as a group of numerous indigenous languages from South America (Katzner 1996).

FIGURE 3 A: Seed pods of MP, source: *Herbario Alfredo Marín*, Etnoflora Yucatense, Autonomous University of Yucatan UADY, Mérida, Mexico. Cultivated and collected in 1988 near Valladolid, Yucatan, cat. No. 05123. Figure 3B: Different variants of cultivated MP seeds from Yucatan, Mexico, between approx. 13 and 17 mm in length. Photos: I. N. Fiebrig.

Var. utilis in turn is used primarily as fodder and green manure. Flowers are smaller and either of lighter purple colour or whitish. Seed pods are covered with felt-like hairs that do not sting (Fig. 3A). Seeds are of off-white or light orange colour or black, with some intermediately mottled variants (Fig. 3B). LD content is lower and given as between 3.1 and 4.9% based on dry weight.

Patil et al. (2016) nevertheless raise general doubts over the identification and authentic classification of MP, showing the wide diversity of *Mucuna* species and MP varieties using RAPD (Random Amplified Polymorphic DNA) as a PCR-based fingerprinting method. With regard to agronomic traits, like biomass production, fertility, and yield potential, Pugalenthi and Vadivel (2005), for example, characterised agrobiodiversity of 11 accessions of '*Mucuna pruriens* (L.) DC. *var. utilis* (Wall. ex Wight) Baker ex Burck' in four districts of South India alone. Sathyanarayana et al. (2011) used AFLP fingerprinting to assess the germplasm diversity of 25 *Mucuna* accessions belonging to five species, including *Mucuna pruriens* represented by its three sub-species *var. utilis*, *pruriens* and *hirsuta*, showing overall high genetic diversity, which is good for breeding programmes. High similarities between *var. pruriens* and *var. hirsuta* however, demanded merging under one name: *var. pruriens*. Another example is that of Ezeagu et al. (2003) who characterised physio-chemical properties of seeds from 12 accessions of *Mucuna* as well as the nutrient and anti-nutrient factors such as LD, trypsin-inhibitors, or tannins in the seeds. The authors conclude that differences in the chemical compositions of the various seeds are marginal once dehulled.

2.3.2 MP as part of ancient, traditional medicine

The medicinal use of MP in relation to PD goes back to the ancient, traditional medicine from India called *Ayurveda,* meaning 'knowledge of life' in Sanskrit[4], and is considered to be the oldest traditional medicine in the world. Its origins date back to the Vedic period[5] on the Indian subcontinent (Lampariello et al. 2012). Gourie-Devi et al. (1991) define *Ayurveda* as "…the quintessence of ancient systems of health care…" estimated to have already been practised in India much earlier, between 5,000 to 3,000 BCE. However, a completed treatise was not available until before 1,000 BCE (Dutt and King 2018). The conceptualisation of *Ayurveda* comprises three categories (humours): (1) *Dosha*, (2) *Dhatu,* and (3) *Mala*.

Dosha: In International Alphabet Sanskrit Transliteration (IAST), *doṣa* can be translated as 'fault', 'defect' or 'that which causes problems'. *Doshas* might offer the approach towards healing. The concept is divided into three types of substances: 'wind, bile and phlegm' (IAST: *vāta doṣa*, *pitta doṣa*, *kapha doṣa*), the so-called *Tridosha* system. It is believed to belong to three bio-entities controlling basic physiological functions. Each is divided into five sub-*Doshas*. The *Dosha* system is eventually embedded in the five classical elements or enduring qualities: (1) *Vayu* (air), (2) *Jala* (water), (3) *Aakash* (space or ether), (4) *Prithvi* (earth), and (5) *Teja* (fire) of which the entire universe is believed to be composed, thus making us part of it (Jaiswal and Williams 2017; Gouri-Devi et al. 1991).

The second abovementioned main system, *Dhatu*, in turn (Sanskrit: *Sapta Dhatus* or 'seven tissues') relates to human physiology and anatomy and is categorised as (1) *Rasa Dhatu* (lymph, tissue fluids, plasma), (2) *Rakta Dhatu* (blood), (3) *Mamsa Dhatu* (muscles) (4) *Meda Dhatu* (adipose fat and connective tissue), (5) *Ashti Dhatu* (bones), (6) *Majja Dhatu* (bone marrow and joint fluids), and (7) *Shukra Dhatu* (semen, reproductive system).

Ayurveda is finally rounded off by the third category, the *Mala* concept referring to three waste products of the body, also summarised as *Trimala,* to include (1) *Purisha* (faeces), (2) *Mutra* (urine), and (3) *Sweda* (sweat), including any excreta of eyes, ears, nose, nails, or hair (Jaiswal and Williams 2017; Jonas 2005).

This *Ayurvedic* structure was probably essential to build up a knowledge base and to transmit understandings about health and healthcare across the millennia from one generation to the next. While the underlying medicinal world view contributes to a holistic perspective of health, *Ayurveda* can give new momentum towards novel therapies in today´s sense of evidence-based medicine (EBM) where "the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients" is essential (Sackett et al. 1996).

Still today, *Ayurveda* can be seen as a system that aids improving the balance between mind, body, and spirit, thus promoting health and preventing disease but not fighting it (Miller 2016). Not all that is traditionally offered by *Ayurveda* can be practised the same way in other healthcare systems outside of India, such as those of the EU, for regulatory issues. Advice on appropriate diets, massage therapies, yoga, meditation, breathing and relaxation techniques, or bowel cleansing measures are accepted as complementary medicine here (Niemi and Ståhle 2016; Lad, 2012). The cost of such treatments may not be covered by the usual public, non-private insurance systems. This goes also for specific herbal medicinal preparations or dietary supplements, which may have additional import restrictions related to applicable medicinal product acts.

In *Ayurvedic* literature, a condition called *Kampavata* can be put on a par with 'shaking palsy'. First described by James Parkinson in 1817 (Parkinson 2016), it was coined with its current term Morbus Parkinson or PD by French neurologist Jean-Martin Charcot around 60 years later (Manyam, 1990; Critchley 1955). The '*Vata'* in *Kampavata* relates to the first aforementioned *Dosha,* whilst

4 Sanskrit: sacred language of Hinduism and language of Hindu philosophy amongst others, belonging to the old Indo-Aryan branch of Indo-European languages (Woodard 2008).

5 Vedic period: approx. 1,500 to 500 BCE, i.e., late Bronze Age to early Iron Age (McClish and Olivelle 2012).

'*Kampa*' means tremor. *Vata* is responsible for mental and physical movements in and of the body. Ancient *Ayurvedic* texts give details of *Kampavata* as an illness that can be related to PD, with typical symptoms such as rigidity and stiffness, slowness of movement, tremor as well as associated depression, somnolence, stammering speech, or salivating and drooling (Manyam 1990). This indicates that in these ancient times, PD was already known to be a condition requiring treatment, although decoding *Ayurvedic* concepts and translating them into the concepts of modern medicine is hardly possible (Ovalath and Deepa 2013). On the assumption that environmental toxins are also responsible for the manifestation of PD, this may not only comprise toxins from modern synthetic chemistry, such as pesticides or organic solvents, but might also include toxic substances from less polluted, more pristine environments according to Manyam (1990), or support theories of endogenous causes of neurotoxicity by isoquinoline derivatives (Storch et al. 2002).

Apart from the evidence that ancient *Ayurveda* not only had knowledge of *Kampavata* as a neurological condition, equivalent to today´s PD, it also knew of preparations containing MP – *Atmagupta* in Sanskrit – that would have been used to treat PD patients (Blonder 2018; Ovalath and Deepa 2013). Examples of documented ayurvedic preparations are *Chyavanprasha avalcha* or *Abhayamalaki avaleha* (Manyam 1990).

The isolation of LD in plants had first been reported by Torquati, having extracted an azotic (nitrogenous) substance from *Vicia faba* seeds in 1913 (Torquati 1913). Shortly afterwards, this led to the establishment of the chemical structure by Guggenheim, a young chemist working at the pharmaceutical company F. Hoffmann-La Roche (1913), who followed-up on Torquati´s work. Research culminated years later in the abovementioned launch of Madopar (synthetic LD; Hornykiewicz 2010; Amrein 2004). Researchers from India in turn had isolated LD from *Atmagupta* seeds in 1937. Its effectiveness in the treatment of PD was not appreciated by modern medicine at the time.

2.3.3 Clinical trial preparation made from MP bean powder

In 1995, a customer entered a village pharmacy[6] in South Eastern Germany and handed a scientific paper – and not a prescription as would be usual – over to the pharmacist. The copy of the paper with the title '*An Alternative Medicine Treatment for Parkinson´s Disease: Results of a Multicenter Clinical Trial – HP-200 in Parkinson´s Disease Study Group*' described a clinical study administering a treatment from beans of the medicinal plant MP (HP-200 Study Group 1995). The customer asked to procure what seemed to be clinical trial medication under the code name HP-200. The natural preparation was needed for her husband who suffered from severe Parkinson´s disease and whose standard medication had failed to alleviate symptoms.

Following an enquiry to the pharmacy´s distributing wholesaler, the only available product on the German market was a homeopathic preparation from the hairy, itchy pods of *Mucuna pruriens* to treat skin disorders (itching, Herpes Zoster) and liver ailments. Neither the herbal drug (whole MP beans) nor any allopathic herbal preparations were available.

It is the very structure of Germany´s mostly owner-operated pharmacies and non-limited shop concessions that encourages the procurement of non-standard medicinal products, and with it, the development of advisory expertise. Within this favourable framework, the pharmacist in charge (i.e. the lead author of this chapter) used his personal network of professionals to find the enterprise that had produced the clinical study medication, at the time already marketed in India as Ayurvedic medicine by Zandu Pharmaceutical Works Ltd (Zandu; see bean powder in Fig. 4). Overall, it took roughly six months to find the supplier of HP-200 and to solve all the related logistical and regulatory challenges that are unfamiliar to the average pharmacy. Amongst others, this entailed getting a pertinent medical prescription that had to be issued by the treating neurologist. HP-200 was liable to be defined as 'medicinal product without marketing authorisation in the EU' by German customs

6 Names of places and persons remain undisclosed or are altered in order to protect the privacy of individuals as well as business interests whilst complying with statutory requirements.

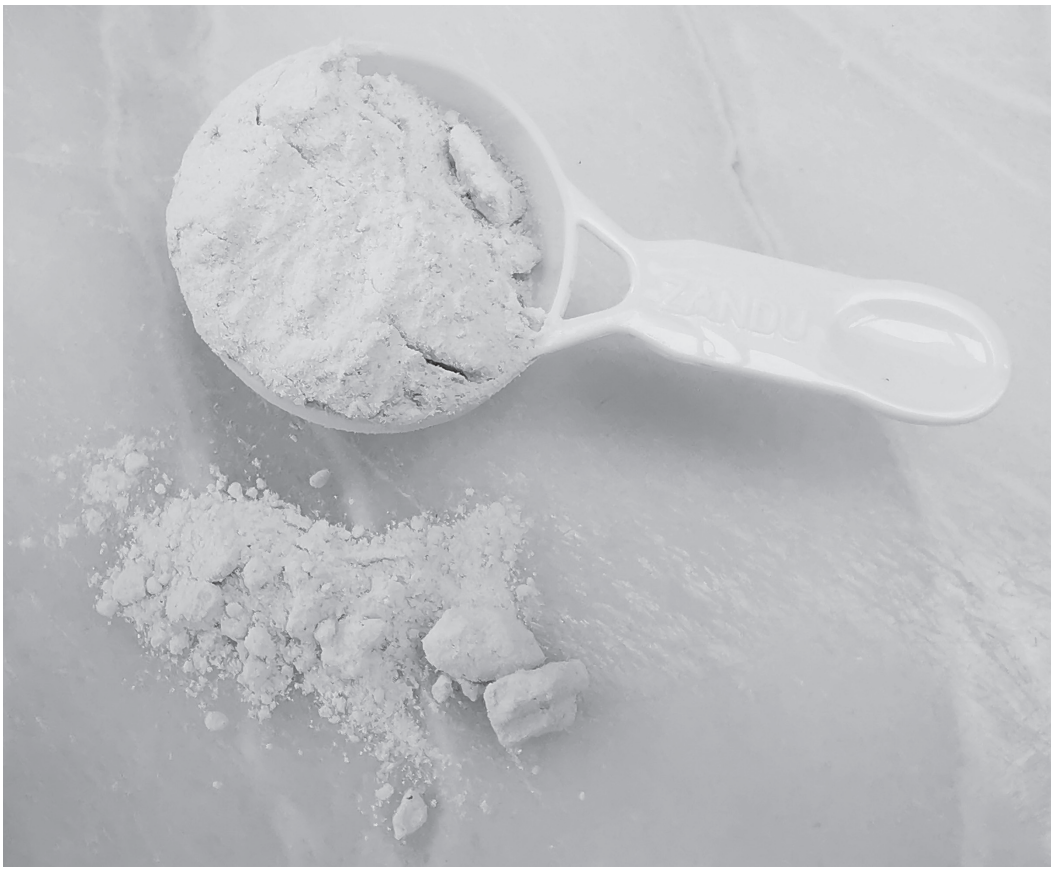

FIGURE 4 MP bean powder Zandopa by Zandu. Photo: I. N. Fiebrig.

authorities and would then have to comply with the German drug law and its general ban on the introduction of unauthorised medicinal products (Deutscher Bundestag 1976, p. 123: *Verbringungsverbot* §73(3)1.). The first pot of 600g of HP-200 – later to be renamed 'Zandopa' by Zandu – sufficient for one month´s treatment, was handed over to the patient´s wife together with dosage and application instructions. At the time the patient had been unable to leave his home.

2.3.4 Patient No. 1: The personal diary

The following details are taken from a case documented by the patient´s wife, who was a nurse by profession as well as the main caregiver at home. The documentation was provided to the pharmacist spontaneously with the explicit consent from the wife and the patient to use it for research purposes. In the following, we reproduce a summarised version of this case documentation so as to prevent redundancies, to ease readability, and to grant anonymity, whilst taking care to be unbiased as to all relevant information related to this case.

Patient demographics are summarised as follows: born 1936, male, Caucasian, German national. Profession as stated: "worked for many years in a window factory with direct exposure to nitrocellulose paint". First Parkinson symptoms showed aged 57 (1993) as slight tremor in right hand and pain as well as rigidity in left elbow. Belief system of the patient: a distinctive dislike for consulting medics and taking medication. For 57 years, he would only take medicinal herbs when feeling ill whilst believing strongly in his self-healing abilities. The wife

urged her husband to have a series of medical examinations performed. At their conclusion, the diagnosis of Morbus Parkinson had been established by a neurologist. The doctor prescribed various standard drugs to treat PD whilst continuously attempting to adjust medication appropriately. Four months later the patient had become a "wreckage" [sic!]. The wife describes his condition as follows: […] *He seemed collapsed, aged, constantly tired, weak, feeble. He developed depression and within a short period of time his condition worsened considerably. PD symptoms became worse and more frequent, such as difficulties swallowing, slurred speech, monotone voice, massive saliva production, plaques on the scalp, and the tremor had become even stronger. There was also the usual rigour, but only in the right arm.*

The doctor tried this drug and that drug, but everything only got worse – until he [patient] *suffered a psychosis. I stopped all medication and took care of him myself, without consulting the neurologist again.*

It took many months for my husband to become viable again, although I tried my best setting up a treatment programme for him to cope with the mental health problems without taking medication and without any external help.

Normally, in our society, it takes the help of neurological clinics and the use of psychotropic drugs to get out of such a serious condition. I had to look after him around the clock because he was a danger to himself and to us as family members. Above all, he was afraid of noises, such as the ticking of a clock, the passing of a car or other everyday noise.

Often, he could neither hear nor see me, he had a look on his face that seemed to go through everything. For weeks he couldn't sleep a minute, neither during the day nor at night. He was unable to take care of himself, he didn't know if he was hungry or thirsty or when he had to go to the toilet. The sense of personal hygiene seemed to be completely missing. It had become unthinkable for him to go out with people, to go shopping or the like, in other words, everything that would seem normal no longer functioned. [...and further psychiatric symptoms described] *Like a child, I led him by the hand and helped him to literally relearn everything. The therapeutic programme I had specially created for him included music therapy, massages, stroking, gradually more and more extended walks to deserted places* […plus spa treatment, movement exercises, speech therapy described in detail]. *Through my intensive and persistent training, patience and love, he regained more and more independence and self-confidence until he was restored. Now that he was no longer taking medication, he also became physically more stable and mobile, had a normal speech pattern again and felt generally better.* […the continued spa treatment also had a positive effect].

In August 1995 we moved to… [another place]. *My husband was no longer able to work and received an early retirement pension. As a result, we could no longer afford the spa treatment. This had a negative impact on his illness.*

He started to feel exactly the same pain in his right knee joint that he had once felt in his right elbow at the beginning of the disease symptomatology. After that, the whole right leg stiffened more and more. He audibly dragged it across the floor and stumbled more and more often. [The nurse describes details on changes in posture and gait pattern typical for PD – the patient was taken to another specialised clinic in April 1996 and diagnosed with PD for a second time. The patient was prescribed levodopa/benserazide 100/25 mg (1-0-1).]

After a short time, more negative symptoms set in again, and not one positive sign. The dose was immediately reduced. Levodopa/benserazide 50/12.5 with slowly increasing intake and up to 3 x daily one capsule. A few weeks later, I recognised renewed symptoms of psychosis. Levodopa was discontinued, but it already seemed too late. My husband had become mentally ill again. The doctor treating him told me that no one could help him [there] *now, that instead he had to be taken to…* [name of a city] *to the mental hospital.*

[She describes that instead of taking her husband to the psychiatric hospital, she did as she had done before, treating him at home by herself and giving him lots of sleep using a tranquiliser, because he had had many weeks of sleep deficit.]

Again, I did the training that had done him so much good before. Step by step, it's all very slow, but every hour is a small, almost imperceptible progress. This time, my husband had already made it after about three weeks.

[She describes his mental state and improvements towards a self-determined life in detail]

His frequent depressive phases often caused him to sink into negative feelings and think of suicide. He was driven by an inner restlessness, was dissatisfied, shouted at his family for no reason, always found a reason to get upset and then could no longer find anything positive about life.

About four weeks after the last psychosis, I made a final attempt to try levodopa/benserazide 50/12.5 mg again, but only at a lower dose (1-1-0). He never seemed to be in balance again, which made living together difficult in the long run and weakened the harmony [as it would happen] *even in the strongest family.*

His right hand was still shaking, now continuously, very badly, except when he was asleep. But the mobility was somewhat better. He was perpetually tired and powerless. But he also stumbled less and so we stayed with this setting of levodopa for the time being.

Dr. [general practitioner] *told me about a bean that produces dopamine*[7] *and grows in India. The only side effect is possibly flatulence*[8]*, but it is not yet on the market in Germany.*

For me, this meant finally getting my hands on something that would prevent my husband's psyche from getting into disarray and also prevent the devastating side effects from occurring altogether. This meant a real step forward in our case! [the last two sentences include a retrospective look after three years' use of HP-200]

You know yourself how I got hold of HP-200, and my gratefulness knows no bounds!!!

[At the end of January 1997] *my husband took HP-200 for the first time and as follows: 0-0-1 HP-200 in combination with levodopa/benserazide 50/12.5 mg 1-1-0.*

What follows is a patient diary. Only changes to the previous day are described. Day 1 and 2 showed no changes. Day 3: slightly increased symptoms of fatigue. Day 4: exhaustion and such fatigue that he fell over his own legs. Day 5: still extreme fatigue although less than previous day. Day 6: a little fitter with deep and restful sleep at night. Day 7: as day 6 and good mood. Day 8: medication changed to levodopa/carbidopa 50/12.5 1-1-0 and HP-2000-0-1-1. Day 10: calm and balanced, but not tired. Day 18: restless, nervous, little sleep, but probably caused by a family tragedy that had occurred. Day 19: slightly better than previous day. Day 20: slept well but very nervous. Day 22: excited, restless, nervous, hardly slept, still affected by the terrible event that directly affected us. Day 23: Strong tremor, sometimes involuntarily drops objects from his hand. He is very distressed by this observation. Day 25: slept well, noticeable dragging of the right leg, slightly less uncontrolled dropping of objects. Day 26: slept well, calmer, less trembling of the right hand. Day 27: levodopa/carbidopa 50/12.5 mg reduced to 1-0-0-0; HP-200 increased to 0-1-1-1. Day 30: deep, restful sleep, no tremor at times, positive mood. Day 31: barely noticeable tremor, no depression, good sleep. Day 33: he feels more energy, positive mood. Day 34: greater mobility of the hand, everything else positive. Day 36: the whole right side is so soft and mobile that it almost reaches a normal state. Day 38: stronger tremor, dragging of the right leg. Day 39: more or less trembling of the hand with good mobility, less tiredness and more stamina, clean speech, not slurred and no longer monotonous, no visible coatings on the scalp and since then no more depressions and no negative psychological changes.

This sums up the account up until day 52. Since day 50 he no longer takes levodopa[/benzerazide], *only HP-200 as follows: 1-1-1-1 at 1.5 g per taking* [1.5 g 4 times a day].

As has been shown so far, I can only confirm that HP-200 has had a very positive effect. It is almost as if my husband had regained his physical and mental abilities. I can say with certainty that

7 This is not quite correct as you will find in more detail below. Instead MP 'contains' levodopa naturally.

8 This is not according to the side effects stated by the pharmaceutical manufacturer. MP powder does have side effects similar to those of synthetic levodopa. However, the overall side effect profile is believed to be gentler and is being tolerated much better. Flatulence as a side effect is typical of a bean meal and to be expected in a bean powder.

my husband has become more resilient. However, I think that the effect of HP-200 will only really become apparent with time. I have given you all the background information so that you can better understand the problem we were dealing with and recognise the changes brought about by the new drug. [the wife apologises for the brevity of the report and expresses her hope that it may be of help].

This report is further corroborated by the fact that the PD patient himself came to the pharmacy to pick up a second pot of HP-200 at the end of the first month´s treatment. Neither his gait nor posture or other symptoms made it noticeable that he suffered from PD. The patient became a regular customer for HP-200 prescriptions. At the same time, it was probably word of mouth that led to prescriptions from other patients and other doctors. A survey as part of regular customer care allowed a spatial representation of anonymised prescriptions in over 12 years in DACH countries which ceased in 2010 (Fig. 5). Here, we show the spread of patients and prescribing doctors within DACH countries, although sporadically prescriptions came from other European and non-European countries as well.

At this point, it is necessary to note that HP-200 was being considered by some customs authorities at German borders to be a 'medicinal product' without marketing authorisation in the EU. This was due to product presentation making it look like a medicinal product and additionally due to levodopa as an active ingredient, regardless of its natural provenance. Thus, not only individual prescription was, and still is, mandatory for procurement activities, as already noted above, but also any kind of advertising is illegal (Medicinal Products Advertising Act, HWG n. d.). On the other hand, the geographical spread suggests that the urge for improved medication in PD patients is such that the impetus for self-initiatives from patients and their families is strong, possibly through networking within self-help groups.

Within this follow-up, the nurse of patient No. 1 was contacted and asked if she wanted to give some more information on her husband's health in 2010. At the same time, she gave her consent to publicise these writings in anonymised form.

She goes on to explain: [as from March 1997] *my husband took the HP-200 powder independently, regularly and on time. I asked him what flavour it had, as the grey-beige colour did not look exactly appetising. He said it was relatively tasteless. It did not give him flatulence as a possible side effect and even if it had done so, it could have been easily remedied and* [as a side effect] *it would not have been in any proportion to the benefits my husband had received from* [HP-200]. *The fact is that HP-200 made my husband increasingly better in all aspects of life. He no longer suffered from psychoses, became stable, had a much better and safer mobility and was able to do small daily tasks at home again* [the wife goes on to explain in more detail what practical activities of daily life he was able to perform, including socialising with neighbours]. *It was a time of breathing and relaxation for all involved.*

After a little over a year, significant physical deterioration appeared again. He became stiffer, stumbled more easily and began to tremble increasingly, no longer only on the right side of his body, but now on both sides and his head was also shaking. So, the dose of HP-200 was slowly increased until the positive condition was achieved again.

He and the whole family had had the best experience with this natural product HP-200 until 21.12.1999, i.e., for three years. It was three years of regained quality of life. Peace had returned, freed from the burden of the recurring psychoses. Then, shortly before Christmas Eve, my husband fell and was diagnosed with a fractured neck of the femur in hospital.

[The wife gives details about the hospitalisation including the husband falling into coma, suffering from pneumonia, losing his swallowing reflex after regaining consciousness and returning home with a gastric tube]. *But I wanted him to keep getting HP-200 and not all the medicines he had already tried and had had such negative experiences with. Doctors from all over Germany were consulted. They said my behaviour was irresponsible because at this stage HP-200 would no longer be able to help, and he was considered untreatable. On the other hand, the doctors did not believe me about how he would react to any of the other medication, i.e., going from one psychosis to*

FIGURE 5 Spatial representation of HP200/Zandopa prescriptions during more than 12 years in DACH countries. Mostly prescribers and their corresponding PD patients were not very distant from one another. In some cases, prescribers may have used the product for themselves or for treating close relatives, especially where no patients can be identified nearby. Graphics: Zoran Laufer/Lila Publishing e.K.

another. My husband was unable to voice his wishes and from today´s perspective I believe I was too tired to continue fighting on my own and to carry all the responsibility by myself. I let them medicate him with conventional dopamine drugs. His fracture of the thigh was then operated on with spinal anaesthesia. He could never walk again. Neither could he eat nor drink by himself. He received his

medication and food through a stomach tube. [Details about the husband having to be transferred to a nursing home as a result.] *My husband got psychoses all the time since he could no longer take HP-200. He no longer recognised the children, was in a wheelchair and degraded more and more. At times, for brief moments, he recognised me, but only rarely. He spent the last two years of his life in bed, full of contractures, unable to speak, without me being able to find any meaning in this way of life. He often opened his eyes in terror and with clenched fists pressed towards the ceiling as far as he could. (I thought: now he is seeing the horror images again that had tormented him countless times!)* [the patient died several months later and his wife writes in her last sentence]: *Everyone who is affected by this disease and reads my report should do what he/she thinks is right and even if the whole world may be against it, I wish them the courage and strength to go different, new ways* [signed by the wife of a PD patient].

Within the roughly 12 years that the pharmacy imported HP-200, later to become Zandopa and then to be licensed to Emami Ltd, patients were referred to doctors, and doctors in turn received all available and pertinent information related to the application of MP powder from the pharmacy. Feedback is summarised in the next section. With increased e-commerce in the pharmaceutical sector from abroad, customs authorities became progressively zealous, retaining Zandopa for unacceptable lengths of time before releasing it to the pharmacy and thus to the patient in need, making chronic therapy unviable, regardless of ethical aspects. At the same time, other e-commerce routes within Europe may have become more practical for PD patients – yet possibly without helpful advice from experienced doctors and pharmacists.

2.3.5 Feedback from 10 years of pharmaceutical advice to PD patients

The selected patient experiences presented herein are related to >300 PD patients who were supplied with HP-200/Zandopa® by one pharmacy in Germany, and who received at least one prescription up to ongoing prescriptions over a period of three years or less until the end of 2011 (Table 2, patients 2 to 6 and 8). Feedback from patient No. 7 (Table 2) is from the Netherlands, where Zandopa had been defined as food supplement at the time and was available from a Dutch Ayurvedic preparations supplier and with medical prescription only. Feedback had been received between 2007 and 2012.

Our argumentation towards improved management for at least some PD patients is largely based on our own notes, observations, and spontaneous as well as prompted patient feedback in our professional roles as pharmacist or herbalist and privately as caregiver to PD patients.

Such spontaneous feedback widens the knowledge of the pharmacist regarding the practical use of a specific medication which can direct further pharmaceutical advice to medical professionals and patients.

Table 2 summarises such feedback in a structured manner and shows a series of patient feedbacks that give clear indication as to a perceived benefit in quality of life (QOL) from taking HP-200/Zandopa mostly in the form of a supplement to conventional, guideline-compliant PD medication. This led to a reduction of perceived side-effects concomitant with the reduction of PD medication other than MP preparations. One case also indicates a benefit in QOL from MP in RLS, which is often treated with synthetic LD. Patient No. 7, from the Netherlands, claimed in his self-report that after taking his first medication of the day, synthetic medication only worked after a latency period of half an hour, whereas with MP powder the effect became apparent almost immediately, with the limbs and joints also appearing to work much more smoothly. Interestingly, the patient did a model calculation of the cost of his former synthetic PD medication (€ 3,700.00 p. a.) versus the cost of HP-200 as substitute medication (€ 890.00 p. a.), claiming exemplary annual net savings of € 2,810.00 to the insurance. Regardless of these effective savings, the patient´s insurer did not agree to make an exception to their rules and refused to reimburse the cost of the prescribed MP powder at the time.

TABLE 2
/d: per day; CG: caregiver giving feedback; N. d.: no date but within the given timeframe 1998–2011. ['text xyz'] = feedback summarised by editor; […] = redundancies removed from original statements by editor.

No.	Date and patient demography	Medication and treatment	Feedback
2	Male, PD	Levodopa/benserazide 100/25 tablets 3-4/d HP-200: 17–20 g powder first doses: 8.00 to 9.00 a.m.; last doses at 8.00 p.m.; plus selegiline in the morning.	2004, CG [The addition of HP-200 to levodopa/benserazide meant a reduction of side effects, tremor was minimised, no more spasms and no more feelings of pressure in the head. Taking entacapone could be stopped.]
	CG: „[…] *This combination* [levodopa/benserazide/HP-200] *has improved his condition a lot and he has also become much, much more agile and he can walk again very nicely. And his skin has now become completely normal, it no longer has the greasy sheen it had before. Swallowing has also got a lot better. Now he can again drink water from the glass in such a way that he holds the glass in his hand and drinks that way. In general, his whole condition has got much, much better and other people have already noticed that* [...]		
3	Female, PD at age 46 as a result of severe surgery, five months in wheelchair	Zandopa	2008, Pat: [Many different drugs to treat PD were tried. Through personal contacts at a self-help group she got to know about Zandopa. Four weeks after taking it, patient was much better and could leave the wheelchair, learnt to walk again.]
	"[…] *My tremors and cramps were visibly better. I just became a different person. My zest for life has grown again and I learned to be a happy person again! I am overjoyed that this Zandopa exists and that I have such great success with it. Unfortunately, my husband died [year], but my children share my happiness with me! Thank you for me becoming human again and thank you for your great help!*]"		
4	Male, PD symptoms since 1990	Withdrawal of lorazepam in spring 2009 MP capsules (3-5/d.) Metaldetox (ayurvedic) Ashwagandha capsules, 3/d. vegetarian diet, therapeutic massage, steam sauna	2010, CG: [mood improved during withdrawal, the last two weeks the patient had been in high spirits before his death in late 2009. Eating a (non-vegetarian) sausage in August 2009 as an exception had caused three days of spasms and extreme Parkinson symptoms.]
5	Male, age 71, PD 1999	Pramipexole, amantidine, rasagiline, HP-200	2011, Pat.: [Improvement by addition of MP preparation achieved: reduced tremor, facial expression more open, better gait, reduction of all PD symptoms, patient states to be living a relatively normal life since.]
6	Male, PD since 1998	4 scoops of Zandopa powder at night; Levodopa/carbidopa and cabergoline tablets during the day	N. d.; Pat.: see below.
	"*Taking Zandopa means a rest from the side effects of my PD tablets. […] I wake up after a restful sleep with no muscle or back pain. […] After taking the tablets, back pain, muscle twitching etc. start again.* "		
7	Male, age 65, PD since age 50	25 to 30 g HP-200 per day at maximum combined with LD + carbidopa and pramipexole	2008; after 14 years plus 1 year of HP-200. Gradual reduction of LD + carbidopa possible until half the original dosage with radically reduced side effects, improved sleep, faster and longer ON time; body more flexible in the morning and calmer mood.

(*continued*)

TABLE 2 (Continued)
/d: per day; CG: caregiver giving feedback; N. d.: no date but within the given timeframe 1998–2011. ['text xyz'] = feedback summarised by editor; […] = redundancies removed from original statements by editor.

No.	Date and patient demography	Medication and treatment	Feedback
			"[…] I got Parkinson's at the age of 50 and after about 15 years [taking] the number of about 25 pills per day consisting of the well-known [LD + carbidopa, LD + benserazide, LD + carbidopa + entacapone and entacapone]… and the [LD] agonists etc. [the pills] were no longer able to guarantee a whole day ON. The OFF periods continued to increase and became highly annoying. This phenomenon is well known and feared within our Parkinson's world. […] Now after a year of using HP-200, I am very satisfied with it and I hope that the long term will also be achieved. Every day you marvel at the fact that with HP-200 you can get out of bed after 10 minutes. […]"
8	Female, restless legs syndrome (RLS) for 40 years	HP-200/Zandopa	N. d.; Pat.: [Previously, during eight years only such drugs had been prescribed that the insurance would pay for. These medications had very strong side effects and the patient had to stop taking them. MP as alternative medication had produced significant relief "without side effects".]

2.3.6 MP, PD, and clinical experience

In Table 3 of this section, we give a summary of clinical experience with MP preparations based on a report commissioned by the Dutch Parkinson Association (Parkinson Vereniging; Stegeman et al. 2017), based on previous work of their 'Project Group *Mucuna pruriens*'. The report has been produced by Cochrane Netherlands, having reviewed the central question of the efficacy and safety of MP in PD patients based on pertinent publications. To this end, evidence of the following four claims about MP was researched: (1) inhibition of PD progression, (2) absorption enhancement of synthetic LD, (3) faster onset and stronger, as well as longer, effect with fewer side effects than synthetic LD/CD, and (4) inclusion of additional substances responsible for this improved effect. Our summary in Table 3 is completed with an added publication (Nagashayana et al. 2000) and updated with more recent data (Cilia et al. 2017, 2018, 2018b).

Collected evidence comprising three randomised controlled studies (RCT) and two uncontrolled cohort studies were evaluated using the GRADE[9] system (cf Schünemann et al. 2013). The first documented clinical experience in the Cochrane review was the study by Vaidya et al. (1978) showing comparable efficacy to synthetic LD with fewer adverse effects in 33 PD patients. Major weaknesses of the study design are lack of a control group and a lack of description for the varying measurement moments of the end point (effect). However, this study may have inspired and supported the design and execution of the trial conducted by the HP-200 Study Group (1995) carried out in three centres in Mumbai (formerly Bombay) and one centre in Chennai (formerly Madras), India. Out of the 60 idiopathic[10] PD patients, 34 were LD naïve, meaning they had not taken LD previously in any form, such as synthetic LD. In both groups, the treatment was effective, with fewer side effects in the LD naïve group. Due to the lack of a placebo group, technically, how the disease would have manifested without treatment could not be measured. However, it was this very MP preparation that, once

9 GRADE: Grading of Recommendations Assessment, Development and Evaluation.
10 idopathic PD refers to the unknown cause of PD in these patients

TABLE 3
Summary of clinical experience with MP preparations based on a report commissioned by the Dutch Parkinson Association (Parkinson Vereniging; Stegeman et al. 2017) and updated/amended accordingly.

Study type/end point	Patients	Preparation	Outcome	Ref.
Open label due to difficulties in matching the placebo to the powder, no control group, bioavailability of LD studied on 9 patients from plasma; NUDS and handwriting.	33 PD patients included, 10 patients dropped out after 3 weeks, 18 men, 5 women, powder taken 4 weeks up to 1 year	Powder made from whole bean of MP purchased from local market, up to 40-50g of powder per day containing 4.5 to 5.5% of LD.	23 patients treated on average for 20 weeks. Decreased incidence of adverse effects compared to synthetic LD that patients had received before entering trial. Powder was well tolerated; reduced bulk and improved taste and flavour were desired by patients. Significant absorption of LD, peak of blood plasma levels after 1 hour of admin. Significant therapeutic response, side effects infrequent and mild. Conventional side effects of LD not observed.	Vaidya et al. 1978
Open label study, no control group; UPDRS scores, Hoehn and Yahr stages measured at weeks 2, 4, 8 and 12.	60 idiopathic PD patients, 46 male, 14 female; 34 LD naïve, 12 weeks	HP-200*, powder formulation of MP endocarp in sachets, adjusted for LD content 3%; [taste correction with flavouring agent and sweetener for palatability but not defined]	Degree of adverse reactions defined as 'mild'; type of side effects similar to those when taking synthetic LD. "*…significant improvement in all the major components of parkinsonism…*"	HP-200 Study Group 1995; Manyam et al. 2004
Open label study, UPDRS rating	18 PD patients, on average approx. 60 years of age, Male/female ratio 5:4. All medication stopped 15 days prior to study initiation.	Mixture of cow´s milk, MP, *Hyoscyamus reticulatus* seeds, *Withania somnifera roots* and *Sida cordifolia* roots containing hyoscyamine, somniferin, ephedrine, amongst others.	Effect of LD contained in MP and to a lower extent in *H. reticulatus* and *W. somnifera* is confirmed. However, the study´s main conclusion lies on the benefit of *Ayurvedic* cleansing therapy ('*panchacarma*') before palliative medication.	Nagashayana et al. 2000

(*continued*)

TABLE 3 (Continued)
Summary of clinical experience with MP preparations based on a report commissioned by the Dutch Parkinson Association (Parkinson Vereniging; Stegeman et al. 2017) and updated/amended accordingly.

Study type/end point	Patients	Preparation	Outcome	Ref.
Randomised, controlled, double-blind crossover; 3 single dose challenges on different days; UPDRS and 'brain test' with AIMS and Goetz rating scale	9 idiopathic PD patients enrolled (QSBB criteria), 1 dropout (vomiting), 8 completed: 5 women, 4 men.	200 mg LD/50 mg CD vs. PTX-200**: sachets with powder standardised, dosed at 500 mg and 1,000 mg LD.	MP preparation led to considerably faster onset of effect, and approx. 22% longer effect. No significant differences in dyskinesias or tolerability were found.	Katzenschlager et al. 2004
Randomised, controlled, double-blind crossover; non-inferiority phase 2b study, monocentric in Santa Cruz, Bolivia by neurologist Janeth Laguna with experience in MP treatment for indigent patients; UPDRS III and AIMS.	18 advanced idiopathic PD patients on stable anti-parkinsonian therapy for at least 30 days	Single dose, 6 treatments: (1) 100/25 mg LD/DDCI 3,5 mg/kg; (2) high-dose MP powder at 17,51 mg/kg, (3) low-dose MP powder at 12.5 mg/kg, (4) LD without DDCI 17,5 mg/kg, (5) MP + DDCI 3,5 mg/kg, (6) placebo. MP powder from peeled and roasted seeds. Ground nuts/soluble coffee were used as MP placebo to mimic texture and flavour of MP powder.	In terms of efficacy, the treatment with MP low and high dose was not inferior ('non-inferiority') compared to LD/DDCI 90 and 180 min after intake in all outcome measures. No patients dropped out of the study and adverse events were reduced in MP high and low dose. MP seeds from 'Bolivian black ecotype' with 5.7% of LD were used in a form of 'no pharmacologic processing'. Overall efficacy of MP is in line with previous findings (Katzenschlager et al. 2004): "Shorter latency to ON, longer ON duration; reduced dyskinesias as compared to LD+DDCI".	Cilia et al. 2017 ClinicalTrials.gov identifier: NCT02680977.
Second part of the study by Cilia et al. 2017; open-label, non-inferiority, randomised, crossover, phase 2b pilot trial study; Quality of Life questionnaire, 39 items (PDQ-39)	14 randomised PD patients from the above group, Cilia et al. 2017. Study extension for patients having discontinued MP continued taking supernatant of aqueous suspension of MP powder instead, during between 2 and 48 weeks.	MP or commercial LD/CD; 2 dose adjustment periods before each treatment phase due to different ON times and dosing frequencies. 3.5-fold to 5-fold dose conversion factor LD/CD to LD in MP. Study extension with MP aqueous supernatant.	Proving non-inferiority of MP powder compared to LD/CD in terms of efficacy and safety over a period of 16 weeks. Efficacy of MP was similar to LD/CD. Tolerability issues of MP (gastrointestinal side effects and progressively worse motor performance)	Cilia et al. 2018; ClinicalTrials.gov identifier: NCT02680977.

			leading to dropouts, largely attributed to too short a switching process in the crossover design and advanced PD.	
Multicentre 52-week phase 2 prospective study in 3 Ghanaian hospitals; non-inferior change of Quality of Life as per PDQ-39, UPDRS I-IV, Hoehn and Yahr staging including postural instability and dysphagia.	26 LD naïve PD patients after three months, aim of study: 90 idiopathic PD patients.	MP powder from peeled and roasted seeds, 43 ± 6 g per day, suspended in water versus 620 ± 205 mg LD + DDCI.	MP was overall well tolerated; progressive shortening of ON time was seen after a few weeks in a few patients but no drop-out due to adverse events; some patients with long-standing untreated PD showed much improved postural stability due to MP powder. MP was successfully cultivated in a hospital´s garden and in the private gardens of 2 patients.	Cilia et al. 2018b Pan African Clinical Trial Registry, ID: PACTR201611 001882367. Study evaluation in progress (Cilia 2021)

Acronyms: AIMS, Abnormal Involuntary Movement Scale (Colosimo et al. 2010); CD: Carbidopa; NUDS: Northwestern University Disability Scale (Canter et al. 1961); PDQ: Parkinson´s Disease Questionnaire (Jenkinson et al. 1997); UPDRS: Unified Parkinson´s Disease Rating Scale I – III (UPDRS 2003; Goetz et al. 2007); QSBB: Queen Square Brain Bank criteria for PD diagnosis (Hughes et al. 1992); *HP-200: short term (48 h, female/male mice and albino rats) and long-term toxicology studies (52 w) with rats preceded the clinical studies to assure safety; **PTX-200: improved formulation compared to HP-200: stability, solubility, taste.

commercially available, was pivotal in the improvements of Patient No. 1 in Germany and many other patients who followed, some having provided the aforementioned patient feedbacks.

According to the late Dr. Krishnakant M. Parikh, who at the time was the owner of Zandu Pharmaceutical Works Ltd. (as per personal communication with the first author in 1997), HP-200 had been developed and was being marketed by Zandu to provide the Indian population with an affordable *Ayurvedic* alternative to comparatively expensive synthetic LD/CD preparations, which were unaffordable to many. It had also been Zandu´s aim to introduce the preparation as a nutraceutical or dietary supplement within Western medicine and to meet the local specifics of licensing regulations (in particular, the United States). This endeavour, however, did not materialise. The German start-up enterprise CMI AG (Centres for Medical Innovation AG), later to become Phytrix AG, had picked up the idea of developing an MP preparation, in order for it to attain regular marketing authorisation as a medicinal product in Europe and the United States at the beginning of the 21st century (Van der Giessen et al. 2004).

Meanwhile, Nagashayanas et al.´s (2000) study on 18 PD patients using an MP containing an *Ayurvedic* preparation added probably nothing of much relevance to the development of a modern herbal preparation outside of *Ayurveda*, whilst emphasising the complementary benefit of *Ayurvedic* cleansing or 'eliminative' therapy that included "[…] oleation, sudation, purgation, enema and errhines by administering prescribed *Ayurveda* drugs. […]". It is mentioned here for completeness.

The clinical trial by Katzenschlager et al. (2004) in turn is to be considered the first randomised, double-blind, crossover study on MP, according to the standards of EBM (cf Sackett et al. 1996) with trial medication PTX-200, similar to HP-200 (ground MP seeds), but produced according to GMP (Good Manufacturing Practice) medicinal product standards and with an improved pharmaceutical formulation to increase patient acceptance (taste, solvability, etc.). At the end of the trial with eight included patients and sponsored by CMI/Phytrix, the authors concluded: "The rapid onset of action and longer ON-time without concomitant increase in dyskinesias on *mucuna* seed powder formulation [PTX-200] suggest that this natural source of L-dopa might possess advantages over conventional L-dopa preparations in the long-term management of PD". Stegeman et al. (2007) critically concluded that the study showed no significant differences with regard to UPDRS scores between the three groups. Onset of effect in the MP treatment group, however, was roughly half an hour faster than in the LD/CD group (34.6 versus 68.5 min; $p = 0.021$) and lasted approximately 22% longer. The limited difference in UPDRS scores between groups may not come as a surprise due to the small cohort and the briefness of the interventions. The budgetary constraints of a start-up company may have put limits on a sizeable study in terms of the number of patients and duration of the study. Although speculative, the main intention of the clinical trial may rather have been to show sufficient effect of the herbal treatment with an improved, patent-protected formulation as part of the business model. This in turn may have been considered to be a strategic prerequisite to attract large investors able to finance the extensive clinical trials required until marketing authorisation was gained. Unfortunately, PTX-200 never reached the European market and Phytrix changed its research and business activities before the study was published.

By contrast, a philanthropic approach seemed at the heart of research endeavours of the research group around Prof. Gianni Pezzoli, supported by the Italian non-profit foundation *Fondazione Grigioni per il Morbo di Parkinson*. They argued that while LD is the cheapest treatment in PD, in many low-income countries it is nevertheless neither available to, nor affordable for, many patients (Fothergill-Misbah et al. 2020). Thus, to start with, a low-cost preparation method based on MP beans was developed jointly in Italy, Bolivia, and Ghana (Cilia et al. 2011; Cassani et al. 2016). Beans of known LD content were roasted for ca. 15 minutes until the tegument popped. This would ensure microbial safety and ease the peeling. Subsequently, the beans were ground (e.g. with coffee grinders), sieved, and dosed as a powder in soup or water for intake. A subsequent two-part study was performed at *Clínica Niño Jesús*, a neurology clinic in Santa Cruz, Bolivia. The neurologist Janeth Laguna here had already had long-standing experience with indigent patients using MP.

The first part of the study included 18 PD patients on stable anti-parkinsonian therapy who were to receive six different single-dose treatments in varying sequence, depending on randomisation. The six groups comprised (1) LD+DDCI (3.5mg LD/kg) as reference, (2) MP high dose (17.5mg LD/kg), (3) MP low dose (12.5mg LD/kg), (4) MP reference dose (3.5mg LD/kg + DDCI), (5) LD without DDCI (17.5mg/kg), and (6) placebo. For the first time, this study explored the established treatment with synthetic LD and DDCI versus an adequate corresponding dose of LD in MP. This had been expected to be significantly higher due to the lack of DDCI in study preparations like HP-200 (Zandopa) or PTX-200 (by Phytrix) but were never systematically matched with synthetic LD plus DDCI, nor referenced additionally to the well-studied effect of synthetic LD without DDCI. It is proposed that MP preparations contain one or more natural substances with an activity similar to synthetic DDCIs, such as genistein and its precursor genistin (Cassani et al. 2016; Kasture et al. 2013; Hussain and Manyam 1997). MP was shown to be non-inferior to synthetic LD+DDCI and to be a potentially effective and safe alternative to marketed medication in indigent populations who cannot afford a regular medicinal product. The second part of the study on 14 of the 18 initial patients, however, points towards issues with gastrointestinal side effects (these are well known) and a reduction of ON time (tachyphylaxis) during the eight-week treatment period (Cilia et al. 2018). The authors conclude that a longer titration period (conversion phase) between one treatment and the next one and longer follow-up times (3–9 months) are needed to improve tolerability and plan a study on a larger population of PD patients. This planned 52-week follow-up trial with MP from home grown seeds vs. synthetic LD/DDCI in three Ghanaian hospitals has so far been presented as a conference poster with no peer-reviewed paper published, yet with data analysis being performed at the time of writing of this chapter (Cilia 2021; Cilia et al. 2018b).

The Cochrane team´s conclusion regarding the efficacy and safety of MP qualified the conducted research as 'limited' with low levels of evidence and very low levels of confidence in the effects found – based on the GRADE system (Stegeman et al. 2017). The Cochrane review did include the Bolivian trials, at the time unpublished, but the small number of additional patients may add little to their verdict of raising their emphasis on the need for curative or progression-inhibiting PD treatments. However, the patient feedbacks cited above in this chapter have shown MP preparations to be beneficial at least to a few patients who would either not accept some of the conventional medication or who would suffer too much from their side effects. It is possible that precisely these critical patients (e.g. suffering from cognitive impairment, psychotic symptoms, or other advanced symptoms and impairments) would have been typically ineligible for any of the clinical studies conducted so far, but conversely might have particularly benefitted from them, had they taken part (e.g. Cilia et al. 2017).

In addition, the hope of at least a reduction of disease progression is an important one, jointly with curative PD therapy. Thus, the neuroprotective activity of MP and a resulting reduction of oxidative stress in the brain, including oxidative stress caused by long-term therapy with synthetic LD, has been suggested by various authors, whilst remaining controversial and requiring further long-term clinical research (Tharakan et al. 2007, Radad et al. 2005, Berg et al. 2004).

2.4 Other medicinal uses and pharmacologic effects

MP has not only been a medicinal plant of particular interest for PD, including its neuroprotection through a presumed anti-oxidative effect. Latté (2008) lists numerous other indications from folk medicine, also comprising parts of the plant other than the beans, such as leaves or roots, with some research conducted on seed extracts regarding anti-diabetic, anti-venom, anti-microbial, or anti-tumor effects. A more recent review by Rai et al. (2020) evaluates research conducted into anti-ischemic, anti-inflammatory, anti-epileptic, or anti-hypertensive effects, pointing out the potential of MP in other neurodegenerative diseases such as Alzheimer´s and Huntington´s disease. Much of the research on indications other than PD has so far been conducted in *in vitro* or in animal models,

including probably the most popular indication, that of an aphrodisiac to enhance male virility, in rats (e.g. Suresh and Prakash 2012). It is likely that folk medicine claims around aphrodisiac properties of MP seeds have created an astonishing wealth of marketed dietary supplements (Google 2021). Whilst recent reviews on folk aphrodisiacs do not include MP, its aphrodisiac activity has been shown with MP seed powder in male rats and, although speculative, may find recommendation amongst males within electronic social networks (Ashidi et al. 2019; West and Krychman 2015; Sandroni 2001). Such dietary supplement preparations are usually made from MP extracts (as powder) and filled into capsules, as opposed to the whole ground MP bean preparations used in clinical trials (Table 3). We mention this here, because from spontaneous, as well as prompted, patient or caregiver feedback, we know that such extracts are factually being used by PD patients instead of clinically tested Zandopa for three main reasons: (1) lack of availability of Zandopa, as it is considered an unauthorised medicinal product by EU customs authorities; (2) ease of taking a capsule versus the bulk of powder suspended in a substantial amount of liquid; and (3) none of the gastrointestinal symptoms typical of a bean meal. Although such patient feedback has been too scarce to derive any level of clinical evidence, we grouped the feedback we gathered into three main categories for MP extract in capsules: (1) 'beneficial in combination with other PD medication to lower side effects of synthetic levodopa and other medication'; (2) 'no benefit' (because side effects are equal to taking synthetic LD); and (3) 'no effect'.

2.5 MP as food supplement

In the EU and other jurisdictions, food supplements fall under food-related laws and regulations. Legislation pertinent to medicinal products and their marketing authorisation does not apply (Anadón et al. 2021; Silano et al. 2011). Thus, quality standards in terms of active ingredients are not as strict as they would be under drug laws. In the case of MP, this concerns LD or other secondary plant metabolites thought to be responsible for the putative benefits of MP bean preparations as well as their extracts (Hussain and Manyam 1997; Latté 2008). Such extracts may not contain enough LD, lack other unidentified anti-parkinsonian compounds, or lack natural efficacy-enhancing adjuvants or side effect-reducing components because they were not extracted adequately (i.e. with the appropriate extraction process or such compounds were not determined by quantitative analysis during production or, even though extracted, these active compounds may not be stable enough over the shelf life of the product). For example, aqueous extraction of LD may lead to polymerisation and thus inactivation of the LD, whilst extraction of the putative neuroprotective, anti-oxidative components may rely on extraction with fewer polar solvents (Misra and Wagner 2007). In summary, food supplements from MP may have been more easily available to consumers and patients than Zandopa, but quality – including partial or total lack of natural active ingredients, the presence of toxic substances as well as illicit health claims, and 'prohibited endorsements' in advertising – present additional risks to PD patients (Muela-Molina et al. 2021, Jairoun et al. 2020, Low et al. 2017; Latté 2008). Furthermore, food supplements are not subject to the quality regulations laid down in pharmacopoeias or required by pharmaceutical production standards, such as GMP (Good Manufacturing Practice; Daue 2017) or GACP (Good Agricultural and Collection Practice; Nieber and Dohm 2013), while specific GMP standards of their own may apply (FSE n. d.).

Food supplements, however, do not require previous proof of efficacy and safety, and their declared ingredients including LD content are allowed to vary up to 50% in the actual product. Medicinal (pharmaceutical) products, in contrast, have set this margin of deviation to 5% (BVL n.d.)

2.6 MP as food

With the closeness of food supplements to food and food regulations, it is pertinent to mention that MP beans with their high protein content serve as a valuable legume to some ethnic groups

in tropical countries in South America (e.g. Brazil), Africa (e.g. Ghana, Nigeria, Malawi), or Asia (e.g. India, Philippines) (Pugalenthi 2005; Onweluzo and Eilittä 2003; Eilittä et al. 2002). However, LD in the seeds and other alkaloids, including hallucinogenic substances in various parts of the plant, are considered anti-nutritional (Pathania et al. 2020; Pugalenthi et al. 2005; Szabo 2003). MP beans consumed as food require the inactivation of LD and possibly other anti-nutritionals through cooking (wet heating) or fermentation (Eilittä et al. 2003).

In fact, it is LD, indolealkylamines, and the hallucinogenic potential of some components that have led to food supplements with 'MP extract' being considered 'novel food' in the category of "Part A – forbidden substances" according to an assessment commissioned by the German Ministry for Climate Protection, Environment, Agriculture, Nature and Consumer Protection of North Rhine-Westphalia (*Ministerium für Klimaschutz, Umwelt, Landwirtschaft, Natur- und Verbraucherschutz des Landes Nordrhein-Westfalen*; Clausen et al. 2011, p. 58). While MP beans as raw material are not considered a drug substance according to this report, MP extracts as a food supplement are viewed as a non-authorised novel food that cannot be legally traded in the EU. In principle, this would also apply to the whole unextracted bean if traded as foodstuff (NFL 2015). The European Food and Safety Authority (EFSA 2012) lists MP along the same lines (i.e. as a plant of possible concern regarding all parts of the plant and substances like LD, as well as indole alkaloids, therein). A further risk assessment report by the Spanish agency AECOSAN (2016) concludes: "due to the presence of L-Dopa, and other biologically active substances which may in turn have a synergic action, the voluntary intake of seeds of *Mucuna pruriens* in uncontrolled and unassessed conditions is a 'risk factor' to be considered for the health of consumers".

It seems prudent to position 'MP as medicinal plant material to treat PD patients', whether as raw material (beans), as semi-finished bulk (e.g. powder), or as part of ready-to-take preparation (e.g. capsules) within the realm of pharmaceutical business activity. This could be, for example, retail pharmacies that would warrant originality, quality, safety, and availability alongside qualified advice regarding the product. MP as food or food supplement on the shelves of supermarkets or drugstores in the EU would certainly not be the right distribution channel.

2.7 MP and agroecology

From our personal view, if a nomination existed for 'Plant of the Year' in Medicinal Agroecology, MP would qualify as one of the first nominees. Lampariello et al (2012) wrote their review on 'The Magic Velvet Bean' concentrating on medicinal properties and concluded: "*Mucuna pruriens* is an exceptional plant" both as a food – regarding the beans – and as medicine – regarding all parts of the plant. Eilittä and Carsky (2003), on the other hand, introduce MP from the agricultural perspective as being "an intriguing crop" and point out that MP has been viewed "as a potential miracle crop" to "alleviate decreasing soil fertility in tropical regions".

Beside its medicinal and nutritional properties for humans, MP also plays a functional role in agroecosystems such as through providing a livestock fodder rich in protein, carbohydrates, and fat, preventing soil erosion in arable systems and fertilising the soil through nitrogen fixation. There is extensive literature around the use of MP mostly in traditional and small-scale farming for subsistence (Eilittä et al. 2004; Eilittä and Carsky 2003). Here, we shall refer to a few selected examples for illustration only.

In view of climate change and the fragility of supply chains such as experienced as a result of the CoViD-19 pandemic crisis, it is worth noting that MP is fairly resistant to low soil fertility, drought, and soil acidity whilst being less tolerant to frost, water logging, and cold climate (Galanakis 2020; Pugalenthi et al. 2005). MP's use as fodder has been explored in monogastric animals such as fish, poultry, and swine. It is grown and used to feed ruminants like cattle with protein and amino acids on islands such as Mauritius or Madagascar, thus promoting self-sufficiency and decoupling from soybean-based corporate feed supplies (Pugalenthi et al. 2005, Muinga et al. 2003; Buckles 1995). It has also been studied as feed supplement in small ruminants like goats and sheep (Eilittä et al. 2003).

From the perspective of cultivation and the promotion of mixed cultures for improving agricultural sustainability, MP helps to suppress weeds. MP will also protect the soil from erosion by rainfall. In inter-row cropping systems, for example, it has been shown to benefit main crop yield, while in practice, MP should be sown well after the first crop, such as corn, to avoid overgrowth of the companion species (Buckles et al. 1998; Buckles 1995).

In her plea, van de Vijver emphasizes the potential of MP and medicinal plants in general from a socio-economic and ecological perspective (see Foreword One of this book). With a predicted growing need for accessible and affordable anti PD medication, the controlled cultivation of MP becomes urgent for PD patients in low- and middle-income countries. At the same time, producing medicinal plants for high value markets can provide an important source of income to smallholder farmer communities as part of an agro ecological farming system and a driver for farmers to transition from industrial to sustainable or regenerative agriculture (van de Vijver 2022).

3 DISCUSSION

We have traced a perspective of MP as a medicinal plant able to contribute to various aspects of health in humans and sketched to a lesser extent the role of MP in agroecosystems including animals, plants, and soil. Our emphasis lay on clinical experiences with PD patients. These comprised – some more, some less – controlled trials with relatively small numbers of patients, and short trial periods together with spontaneous or prompted patient feedback; the latter outside of the formality of clinical trial settings. As to its role in Traditional Medicine (TM), such as *Ayurveda*, MP falls under the scope of the latest World Health Organization Traditional Medicine Strategy (WHO 2014). The strategy paper aims at "…supporting Member States in harnessing the potential contribution of T&CM [Traditional and Complementary Medicine] to health, wellness and people-centred health care…".

We argue that while this strategy paper is indeed an important starting point, it may promote less in terms of manifesting the desired "safe and effective use of TM [Traditional Medicine] by regulating, researching and integrating TM products, practitioners and practice into health systems, where appropriate" (WHO 2014). We further argue that if national governments are comfortable leaving such changes mainly to market forces, too little shall happen in terms of 'appropriateness' and developments in the best interest of the patient. For MP, this may mean that research shall remain scattered over long periods of time, with clinical trials not being part of a coherent and sustained clinical development programme leading to marketing authorisation of a safe, effective, and affordable medicinal product. We propose various reasons why this may be so and how to overcome the challenges through the suppositional perspective of the industry and so-called 'market forces'.

3.1 Top global pharma companies

The top global pharmaceutical companies are generally active in the market of prescription ('Rx') drugs, with an R&D of their own typically feeding medicinal product innovation into a neurologic product portfolio. Such portfolio may comprise medicines to treat PD, some of them including LD (cf. Pharmaceutical Technology 2020).

Pros: Such multi-nationals are assumed to be in a financial position that would permit the long-term investments needed for clinical development towards marketing authorisation. For MP, this would ideally be an extract. Such an extract would need to present all the benefits of the admixture of active components in MP seeds and conform to the high-quality standards of the pharmaceutical industry in terms of pharmaceutical stability as well as clinical safety and efficacy. The lesser volume of extract would be more acceptable to patients, as opposed to bulky and unpalatable volumes of ground MP seed.

Cons: (1) A natural LD preparation within an existing portfolio of other businesswise successful synthetic LD-containing PD medications may represent undesired competition. It might position the MP product in a niche with too small an ROI. (2) Intellectual Property (IP) protection may be limited to patents on specifics of the extraction process or plant variety rights, if any. This stands in opposition to IP rights on a New Chemical Entity (NCE, new synthetic drug substance), more clearly defined and an essential part of well-established and lucrative pharma business models (cf. Saha and Bhattacharya 2011; Kartal 2007). (3) Aspects of equitable sharing of benefits arising from the use of genetic resources (cf. Nagoya Protocol 2011; Mishra 2005) may add to (4) the complexity of batch-to-batch quality assurance of the MP product, if not one active component, but rather a combination, is shown to be responsible for improved efficacy and neuroprotection as well as curbed side effects. The stability of all active components needs to be warranted on the one hand, whilst on the other, the quality of MP seeds will vary from harvest to harvest including climate and soil conditions, and depend on the accessions cultivated (Kroes 2014). (5) If these are not already enough imponderabilia, a new MP-based PD medication would need to show its benefits over pre-existing synthetic LD preparations, so as to be acceptable for reimbursement by health insurers (Gerber-Grote and Windeler 2014).

3.2 Herbal pharma companies

In Germany, pharmaceutical companies specialising in the production and marketing of herbal medicinal products have historically grown from small, family-owned enterprises such as small-scale manufacture in retail chemist shops, going back to a time before the rise of synthetic drugs in the last century (Kraft 2001). In 1976, there were around 78,000 herbal medicinal products available on the German market (Beer et al. 2013) while the second half of the last century has seen a rising public demand for herbal preparations as alternatives to synthetic medication in the Global North (Sewell and Rafieian-Kopaei 2014; Harrison, 1998), with Germany and France leading in Europe regarding total over-the-counter (OTC) sales (De Smet 2005; Steinhoff 1993). Nonetheless, amongst herbal medicines in Europe, there has probably never been any blockbuster, as there have been with synthetic molecules that bring significant profits.

Since 2004, new social legislation in Germany has severely restricted the reimbursement of OTC medication by public health insurance in order to cut public spending in health care. Continuous harmonisation of drug legislation and marketing authorisation requirements, which demand proof of safety and efficacy within the EU on the other hand, have made clinical investments towards the registration or authorisation of herbal medicines too risky and expensive for some products, with innovations becoming rare (Armbrüster 2016). By the end of 2015, only 1,613 single herbal preparations and 201 combination products were left on the national pharmaceutical market (Beer et al. 2013). Armbrüster and Roth-Ehrang (2021) analysed the legal situation in Germany and advocated for various improvements to make herbal medicines more attractive to investors, thus safeguarding therapeutic diversity in future.

Turning back to PD, LD treatment, whether herbal or not, requires medical supervision, making Rx status mandatory. Prescription drugs, however, is a market that herbal pharma companies do not customarily target. In 2015, more than 98% of all herbal medicines sold in German chemist shops were prescription free (Armbrüster 2016). An authorised MP preparation for treating PD would thus require additional marketing investments addressing prescribers instead, and not patients. One such successful example of a herbal medicinal product is Laif® 900, a highly dosed dry extract of St. John´s wort (*Hypericum perforatum*) authorised for the treatment of moderate depression. It received Rx status once it had proven its efficacy for the stated indication and is being reimbursed by health insurers (Uebelhack et al. 2004). Laif 900 is currently marketed by Bayer Vital GmbH, part of global player, Bayer AG, which acquired a typical German family-owned herbal pharma company, Steigerwald Arzneimittelwerk GmbH, in 2013, to help widen Bayer´s OTC portfolio

(Communications Bayer AG 2013). Acquisitions of this kind can make one preparation a herbal 'cash cow', whilst the loss of other, less profitable herbal preparations may in turn be 'accepted with approval'. The resulting (strategic) 'death' of a pre-existing diverse herbal product portfolio usually happens 'silently' and to the detriment of individualised patient care.

3.3 Current and future trends

Where does all of this take us? In present times, on the one hand, the WHO publishes an updated list of essential medicines defined as "those [medicines] that satisfy the priority health care needs of a population…" and includes evidence regarding efficacy, safety and comparative cost-effectiveness (WHO 2021). The model list contains medicines to treat conditions posing the greatest threat to public health; it contains more than 2,000 unique medicines for 137 member countries (Persaud et al. 2019).

The list contains some plant-derived molecules, such as atropine (e.g. *Atropa belladonna*), caffeine (e.g. *Coffea arabica, Thea sinensis, Ilex paraguariensis*), codeine and morphine (e.g. *Papaver somniferum*), paclitaxel (e.g. *Taxus brevifolia* or via a precursor from *Taxus baccata* or biotechnologically from *Taxus* cell cultures), pilocarpine (e.g. *Pilocarpus jaborandi*), and quinine (*Cinchona* species). Herbal preparations are the exception, such as podophyllum resin (from e.g. *Podophyllum peltatum*) or senna (from *Senna* species) as sennosides or 'traditional dosage forms'. Most of the essential medicines are mono-substances of semi-synthetic, synthetic, or biotechnological origin, sometimes in combination with up to three other active substances, not forgetting levodopa (+ carbidopa or benserazide). They can be considered mainstream (WHO 2021a). On the other hand, the 62nd World Health Assembly in its agenda item 12.4, 'Traditional Medicines', included TM to strengthen health systems whilst defining TM as covering a wide variety of therapies and practices, to include herbal medicines, thus being implied as complementary to WHO´s essential medicines list. The importance of plants and plant extracts and their medicinal value as part of TM is undisputed, with TM still being a mainstay of healthcare in some regions of the world (WHO 2009, 2014, 2021a). What changes are needed to get safe, efficacious, and affordable herbal medicinal innovations to the market swiftly and make them, if not deemed essential, at least to be considered highly desirable? How could such herbal medicine from MP become a fully integrated and affordable complementary therapy for the treatment of PD in both affluent and low-income countries? An important step forward on policy level is the initiative of the WHO in setting up an expert committee for an international herbal pharmacopoeia. Its aim is to create a harmonised compilation of entries from national (herbal) pharmacopoeias that ensure the quality and safety of herbs and herbal (medicinal) products in a global market (WHO 2020). In our view, this pharmacopoeia must also comprise GACP, including best agroecological practices to ensure freedom from pesticides within land regeneration processes that re-establish or maintain environmental integrity.

3.3.1 Pipeline of herbal treatments against PD

In their recent review, McFarthing et al. (2020) analysed trial data from the ClinicalTrials.gov database on 145 registered and, at the time, ongoing clinical trials (21 Jan 2020) targeting PD, either in a symptomatic (ST) or disease-modifying (DMT) manner. They assigned the trials to one of 14 groups and included one group called 'botanicals', referring to "agents derived from herbal extracts where the mechanism of action was unknown or unclear" and found in both the ST and the DMT category. Three out of the total of four studies were in clinical trial phase II (WIN-1001X, DA-9805, and SQJZ herbal mix), one in phase III (Lingzhi), with 'SQJZ herbal mix' belonging to the ST category, the others to the DMT category. The authors refer to the botanicals as follows: "[…] they are mixtures with a number of potential active agents and have attracted a lot of attention in the Parkinson´s community as a source of current and future medicines". A 2021 update on PD-related clinical trials by Prasad and Hung (2021), with a selection of 293 registered clinical trials as from

TABLE 4
Current herbal anti-Parkinson clinical trials registered on ClinicalTrials.gov, a registry run by the US National Library of Medicine at the National Institutes of Health, considered the world´s largest clinical database. Summaries have been drawn from McFarthing et al. (2020), Prasad and Hung (2021) or directly from ClinicalTrials.gov (accessed 03/11/2021) and the 'herbal' dimension includes fungi.

Botanicals'ID	Trial Phase	Treatment Category	Composition	ClinicalTrials.gov ID	Sponsor
WIN-1001X	II	DMT: anti-oxidant, improved autophagy and reduced neuro-inflammation	Herbal extract from *Angelica tenuissima Nakai, Dimocarpus longan (L.),* and *Polygala tenuifolia*	NCT04220762	Medihelpline Co., Ltd. (CRO), Seoul, Republic of Korea
DA-9805	II	DMT: anti-oxidant, anti-inflammatory	Three main herbal materials, not specified	NCT03189563	Dong-A ST Co., Ltd., pharmaceutical manufacturer, Seoul, Republic of Korea
SQJZ herbal mix	II	ST: anti-oxidant	Herbal mixture of 'Chinese herbs' containing extracts of *Rehmannia glutinosa Libosch, Astragalus membranaceus (Fisch.) Bunge* etc.		Dongzhimen Hospital, Beijing, China
Linghzhi (fungus!)	III	DMT: neuro-protective	*Ganoderma lucidum* extract	NCT03594656	Xuanwu Hospital, Beijing, China
Hypoestoxide	I/II	DMT: anti-oxidant, anti-inflammatory	Diterpene from *Hypoestes rosea,* dry powder	NCT04858074	Prof. Adesola Ogunniyi, University of Ibadan, Nigeria

2008 till 16 June 2021 from the same database, shows two active studies in relation to antioxidant botanical-based medication hypoestoxide (phase I/II) and the abovementioned WIN-1001X. Studies on botanicals from both publications are summarised in Table 4. It is striking that none of these studies seems to stem from Europe, but rather from countries with a long tradition of ethnomedicine (TM), such as China, Korea, or Nigeria.

The most recent addition to the ClinicalTrials.gov database regarding PD and herbal treatments is a clinical study sponsored by Hong Kong Baptist University (Identifyer: NCT05001217). Its aim is to compare conventional medication regimes, including LD, with conventional treatment *plus* Chinese herbal treatments – in four patient subgroups according to a Chinese medicinal pattern: (1) *Huanglian Wendan* decoction ('phlegm-heat stirring wind subgroup'); (2) *Jin Gui Shen Qi* pill ('spleen- and kidney-*Yang* subgroup'); (3) *Qi Ju Dihuang* pill plus *Zhen Gan Xi Feng* decoction ('deficiency of liver- and kidney-*Yin* subgroup'); and (4) *Bu Yang Huan Wu* decoction combined with *Chang Yuan Wendan* decoction ('*Qi* deficiency and stasis of blood subgroup'). Herbal drugs follow the instructions of the China pharmacopoeia. The trial start date was 1/12/2021 and the trial end date is estimated for 31/01/2023 for this single-blind (outcomes assessor), randomised study that exemplifies a combination of conventional medicine with a patient-centred, individualised, herbal add-on treatment.

The scope for treating neurologic diseases seems to offer a lot of potential for research (a potential that currently does not seem to be recognised by 'Big Pharma') as expounded, for example, by Balkrishna and Misra (2017). Calling it 'The Herbal Hope', they had compiled 31 *Ayurvedic* medicinal herbs with traditional therapeutic answers to eight common brain disorders, including PD. The authors argue that, as opposed to the 'allopathic system', *Ayurveda* is in principle more focused on treating the cause of illness rather than the symptoms, whilst admitting that comparative studies are still needed to show this. In the wake of the CoViD-19 pandemic crisis an editorial in the *Journal of Ayurveda and Integrative Medicine*, Vaidya et al. (2020) emphasised the importance of integrated healthcare (IHC) within a synergic vision. It must combine modern allopathy with the medicine from traditional healers. The author lists 14 of the most important *Ayurvedic* drugs to be implemented urgently – with MP in PD being No. 1 on this list.

We conclude that future research should bring MP further, in whatever form, as a (co)treatment – a 'medicinal supplement' and not a food supplement – for PD patients around the globe, with the potential to help slow down progression and treat PD (cf. van de Vijver, Foreword One to this book).

3.4 What could be the future role of metabolomics?

Being focused on the European context, as is in this chapter, it seems worthwhile looking at what the European Medicines Agency (EMA) and its Committee on Herbal Medicinal Products (HMPC) have to say regarding the challenges of quantitative and qualitative analysis of (traditional) herbal medicinal products. Such challenges must be resolved in order to gain marketing authorisation. In HMPC´s reflection paper on markers used for quantitative and qualitative analysis, active substances in *herbal* medicinal products are defined as consisting of:

> "…complex mixtures of phytochemical constituents. […] further complicated when two or more herbal substances and/or herbal preparations are combined in a herbal medicinal product. A limited number of herbal substances and herbal preparations possess constituents which are generally accepted to contribute substantially to their therapeutic activity. These are defined as '*constituents with known therapeutic activity*'. However, for the majority of herbal substances and herbal preparations, the constituents or groups of constituents responsible for the therapeutic activity are not known. In some cases, certain constituents or groups of constituents may be generally accepted to contribute to the therapeutic activity but are not responsible for the full therapeutic effect. Such constituents or groups of constituents are useful for control purposes and are defined as '*active markers*'. *Analytical markers* are constituents or groups of constituents that serve solely for analytical purposes […]" (HMPC 2008).

For constituents with known therapeutic activity, this means that they need to be determined quantitatively. For MP bean preparations – as described above – their favourable efficacy and tolerance profile is strongly believed to be related to additional substances other than LD. Exactly which ones they are and what quantities are required for such beneficial profile remains largely speculative.

In this context, new analytical methods are hoped to "create a type of 'holistic' fingerprint", but HMPC`s related concept paper raises doubts over their usefulness in the quality control of herbal medicinal products and regards them as 'optional'. One of the examples given is hyphenated techniques (HPLC-MS or LC-NMR)[11], which couple two different analytical procedures, a separating technique and a detection technique (HMPC 2018). Hyphenated techniques, however, are said to have improved dimensional changes in a remarkable manner in natural product analysis with a 'systems approach' to biochemical profiling using metabolomics within the so-called 'omic techniques' (Wilson et al. 2021, Weckwerth 2003). Metabolomics allow a non-targeted

11 HPLC-MS: High Performance Liquid Chromatography coupled with Mass Spectrometry; LC-NMR: Liquid Chromatography coupled with Nuclear Molecular Resonance.

identification and quantitation of small-molecular-weight metabolites and the determination of relationships among components of plant systems, thus supporting researchers by providing a fuller understanding of functional relationships of multi-component systems or 'biochemical networks'. Such 'metabolic fingerprinting' may lead to a better understanding of how exactly MP may have advantages over mono-substances like synthetic LD.

Mono-substances, be they for example pharmaceuticals – or pesticides – from synthetic organic chemistry and regardless of whether or not they produce any harmful effect, are *per se* xenobiotic to living systems, plants, and animals alike, including humans. Our evolutionary history of life on earth, from unicellular to multicellular life forms, is a historically complex mixture of components where no such thing as 'highly purified chemical entities' existed; they are alien to our evolutionary metabolisms. Animals have surely co-evolved with the plant kingdom, having had to deal with plant defence mechanisms all along. Today, all plants together are estimated to host more than 200,000 different metabolites (Mawalagedera et al. 2019; Weckwerth 2003). Although speculative, MP seeds may lend themselves particularly well to a starting point of a metabolomic approach of *Mucuna* species, not only because of the wondrously numerous medicinal aspects of the plant as such, but also because of seeds representing a metabolically 'frozen' or dormant state that is to kick-start plant metabolism once the seed starts germinating. With increased analytical reproducibility, we could gain insights regarding accession-to-accession and harvest-to-harvest variations as well as developing a better understanding of a metabolite-efficacy profile. Additionally, metabolomics may elucidate possible benefits of new accessions of MP or newly identified *Mucuna* species and their seeds; for example, the seeds of '*Mucuna sanjappae* Aitawade et Yadav' with a remarkable LD content allegedly in excess of 7% (Patil et al. 2015). The usefulness of metabolomic approaches is further supported by a recent study on various extracts from neuroactive medicinal herbs with sedative and anxiolytic effect. A correlation between comprehensive chemical fingerprints and their bioactivity was investigated and found to have commonalities for *Hypericum perforatum*, *Melissa officinalis*, *Passiflora incarnata,* and *Valeriana officinalis* (Gonulalan et al. 2020). Certainly, and more than ever, the future of herbal medicine requires a systems biology approach that looks at the complex interactions of components and their synergistic or antagonistic effects, as argued in a review including relevant experimental approaches (Williamson, 2001).

4 CONCLUSIONS

The CoViD-19 pandemic has shown the world to what astonishing degree pharmaceutical development can be speeded up, in terms of time to market, by financial interests and obviously by pressing medical need. Where profits are expected to soar, while multiple patents secure the investments sufficiently long term, the underlying technology of one of the first vaccines had been developed almost entirely through public and philanthropic funding (The Lancet 2020). Herbal and traditional (ethno)medicine, so far, can only dream of such copious financial support (Laird 2013). Large investments are much more likely to go into gaining IPR for so-called biologicals – such as vaccines or antibodies – or 'advanced therapies', such as medicines for gene therapy, somatic cell therapy, or tissue-engineered medicines. They fit the paradigms of high-tech IPR, so-called evidence-based medicine (EBM), and the imperative of statistical significance much better. For successful business models this is primordial, not least because mostly, health insurers and national healthcare systems, for reasons of their own, have a tendency to reimburse nothing less than EBM treatments – with evidence meaning 'statistical significance' regarding end points within a defined clinical trial population when the aim should *also and not least* be "improved quality of life for the world´s (over 6 million) different individual Parkinson cases" (Bloem et al. 2021).

The current R&D mechanisms, however, tend to lend themselves to grant first and foremost corporate ROI and speculation within global financial markets (Pandharinath 2011). In their opinion paper, Jureidini and McHenry (2022) argue that EBM has created an illusion from "[evidence]

corrupted by corporate interests, failed regulation, and commercialisation of academia" (cf. Jureidini and McHenry 2020). We believe, as such, that the underlying mindset will hardly support UN Sustainable Development Goals (SDG), especially SDG 3 'Good Health and Wellbeing' and SDG 10 'Reduced Inequalities' "*[ensuring] healthy lives and [promoting] well-being for all at all ages"* (UN 2021; WHO 2015). Current inequalities in health and wellbeing between the Global North and the Global South are largely related to colonial mindsets from the past, maintained and replicated in our current R&D systems and the protection of knowledge, technologies, and markets. This mindset is very much blocking R&D and business development for a sound herbal medicine sector in line with and supportive to SDGs 3 and 10. For this to happen, local and international R&D and market players in the herbal medicine sector are to collaborate on eye level. The negative impact of the current system shows the dramatic decrease of available herbal medicinal preparations in a country like Germany, once referred to as the 'Pharmacy of the World', in the limited freedom of choice for patients as well as in the current inadequacy of public health systems in low- and middle-income countries.

What is overlooked greatly by those promoting herbal medicine as a crucial healthcare strategy for low- and middle-income countries is the availability of the right quality of herbal material, collected from the wild in a sustainable manner or produced with appropriate inputs and training for domestication and cultivation. Only by creating short and transparent supply chains can the quality and safety of the herbal material be guaranteed (see also Chapter 9 of this book). In addition, the provision of the right quality planting material, appropriate and low-cost methods to analyse the spectrum and amount of important secondary metabolites as well as identifying potential toxic substances or contaminants has to be secured. Ecosystem degradation and biodiversity depletion is already undermining wild sources of medicinal plants. At the same time, the majority of governments are not supporting the domestication nor promoting the sustainable cultivation of the same. In addition, the capacity to process and produce herbal medicinal products according to internationally approved standards is generally lacking in the countries of origin of the herbal raw material. This increases the loss of quality and favours adulteration.

Therefore, we advocate for a more patient- and nature-centred approach in herbal medicine R&D that should include supportive policies backed by public funding and investments, whilst collaborating with pharmaceutical industries where fruitful. The idea is to integrate herbal medicine within allopathic treatment approaches as a *medicinal* supplement and not as a food supplement.

Delivery bottlenecks of allopathic, synthetic medicines in Germany, due to repeated 'healthcare reforms', with spending cuts by the insurance system have been described by Weidenauer (2020). The author compares the detrimental effects on the medicines market with the López effect[12] in the automotive industries. Weidenauer suggests a new model of healthcare based on a not-for-profit foundation that acts in the interest of the public in general and patients in particular. This could make use of the local small-scale production infrastructure of chemist shops that is commonplace not only in Germany (*formula magistralis, formula officinalis*) and would benefit from strengthening the pharmacist's role in individual patient care to start with. Such an R&D model should run under the umbrella of a trans-national organisation like WHO, seeking to implement R&D models in different countries, suitable to their specific cultural, structural, and economic realities. It should include open-source production protocols and be linked to generic marketing authorisation protocols, including proof measures for environmental protection to avoid the ruthless exploitation of resources.

4.1 Mucuna pruriens and medicinal sovereignty

We believe that this chapter is emblematic of an emergent field of research in a quest for what we call 'medicinal sovereignty', where peoples and populations of the world are granted the human right of

12 López effect: synonymous with cheap and often faulty components related to López de Arriortúa, a former executive in the automotive industries and his negotiation methods with suppliers, considered to have been ruthless (Bergmann 1998).

easy access to quality healthcare that incorporates traditional, regional, ethnobotanical medicine, and herbal medicinal products whose ingredients are sourced regeneratively, whilst taking into account all pertinent dimensions of sustainability. The idea of medicinal sovereignty has been inspired by the concept of 'food sovereignty' (www.foodfirst.org) and could translate to the right of peoples to (1) define their traditional herbal medicines by (2) promoting regulatory frameworks supporting marketing authorisation of such medicines in line with (3) a quality that assures therapeutic benefit and safety whilst (4) being sufficiently pragmatic and flexible to accommodate the idiosyncrasies of a specific health tradition (*Ayurveda*, TCM, etc.) and finally taking into account (5) aspects of a holistic sustainability and regeneration in agriculture and forestry comprising ecological, economic, and social integrity. This is in fact already being piloted by *Solidaridad* (solidaridadnetwork.org) in India through a collaborative effort of government, science, civil society, businesses, and farmer organisations (cf. van de Vijver, 2022).

For that matter, MP has not only been an *Ayurvedic* medicinal plant, but it has also been food for humans, fodder for animals, and a functional crop in agroecological systems. Ironically, amongst other environmental and genetic factors, the cause of PD has been linked to the ever-increasing exposure to and the chronic uptake of pesticides used by workers in conventional agriculture and passed on mainly through fruits, vegetables, and processed food or through private use of pesticides at home (cf. Epilogue One of this book, Leu and Shiva 2014; Keikotlhaile 2010; Dick 2006; Stephenson 2000). The link between occupational pesticide use and the cause of PD has been studied in various countries (Narayan et al. 2017). Furthermore, PD is now being recognised as an occupational disease in France, a country claimed to use 80,000 tonnes of pesticides per year and thus being the third largest pesticide user in the world (Giorgio 2018).

All of the above contributes to our plea for holistic research approaches as well as inclusive and regenerative business models. We would expect them to take us beyond concepts of reductionist singular components and towards increased knowledge of effective component systems, intrinsically more in tune with human physiology. With this in mind, we find it pertinent to cite Schwabl and van der Valk (2019) who challenge the notion of 'active substances' in biomedicines from Tibetan medical formulas altogether. They describe a flexibility in the herbal ingredients used as long as functional qualities are maintained. In Tibetan Traditional Medicine (TTM), medicinal plants from different plant species may be used interchangeably for the same formula, depending on their availability on local markets and as long as the Tibetan formula exhibits a comparable "[…] signature of action, especially when combined into multi-target 'network medicines' which mirror the complexity of chronic diseases". We believe it is important to get a better in-depth understanding of this functional complexity and of how it supports health and healing processes. Eventually, this may not only support TM and traditional therapies but also inform synthetic chemical ('allopathic'/conventional) pharmacology and overall clinical research. From patient experiences and research on MP it may be important for scientists to say "I don´t know…why MP seems to provide additional benefits to yet unmet medical needs", calling for increased and alternative, more holistic research approaches. For a final outlook, Epilogue Two in this book gives the reader a glimpse of the iconography and the idiosyncrasies of Tibetan (Buddhist) medicine.

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