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Technology Readiness Level for the R&D Streaming of Phytomedicines: Proposal of a Framework for Nonclinical Stages

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Abstract

This study proposes the development of a system to classify phytomedicine projects by applying the technology readiness level (TRL). This strategy is gaining relevance in the field of health innovation because it promotes synergism between researchers and R&D managers working in this area. Nine TRLs were created for the development of herbal medicines by the authors, which is a group of experts in natural products, supported by pre-existing records on project management in the institutions to which they belong. The levels were determined by mirroring the bench-to-bedside development of synthetic drug pathways, in accordance with concepts of translational research. Each level was sectioned by disciplinary areas ruling pools of multiple activities, the achievements of which represent independent technologies. Short content deliveries (SCD) were empirically established at the end of each level as a requirement to enter the next technological stage. A TRL scale was constructed to classify the stages of phytomedicines development to reflect project maturity. Detailed descriptions of the first five nonclinical levels and their sublevels were provided. At the end of each level, the SCD served as an indicator of sufficiency to move on to the next stage. The TRL framework for developing phytomedicines provided an organized panel to clarify the independent technology generated in each stage. The integration of these technologies constitutes a valuable tool for institutions that foster pharmaceutical product development. The five initial levels of TRL considered here can contribute to accelerating innovation in R&D organizations dedicated to the development of plant-based products.

Keywords

Technology Readiness Level, Phytomedicines, Drug Development, Translational Research

1. Introduction

1.1. Background

The technological development of drugs and medicines encompasses a complex set of research activities occurring in multiple areas of knowledge, which must integrate their results and converge toward the designed product. The management of this multidisciplinary process has become a challenge for researchers involved in stages that concern their academic expertise but is often extrapolated to reach complementary methodologies from frontier fields. However, evaluating and controlling the project flow is even more difficult for R&D managers in organizations that assign them the responsibility of recommending changes in the project course or deciding whether it should continue to be funded or aborted [1] [2]. Therefore, there is a need for managerial tools to foster project institutional management by strengthening team awareness of the whole development process of any project and program in which they are involved.

In the case of phytomedicines (herbal medicines in general), this scenario assumes particularities that emanate from distinct paradigms than those governing drug development based on individualized chemical entities, being either synthetic or bio-originated molecules. The main distinctions lie at the more basic research levels and derive from the concept that multiple-compound plant extracts are active pharmaceutical ingredients [3] [4]. Moreover, there is widespread recognition of synergistic interactions between different plant ingredients, which eventually increase the efficacy and counterbalance toxicity [5]. Therefore, any tool applied to the management of phytomedicine development projects must first clarify the entire R&D process by considering the steps that support its specific technological flow. In this line, a previous theoretical frame on such a subject has been recently reported by our research group in Brazil [6]. The present study extends the construction of a semiempirical project management tool applied to the R&D of phytomedicines by combining the concepts of translational research [7] and the technology readiness level (TRL) [8] [9]. The former refers to ordering the distinct knowledge silos involved in the development of a medicinal product that frames the multidisciplinary panel and paves the way for translational research. The latter classifies the independent technology generated at each stage into an increasing scaling system, as depicted in Figure 1 and briefly contextualized below.

1.2. Translational Research & Drug Development

The integration of different scientific disciplines has been recognized as essential

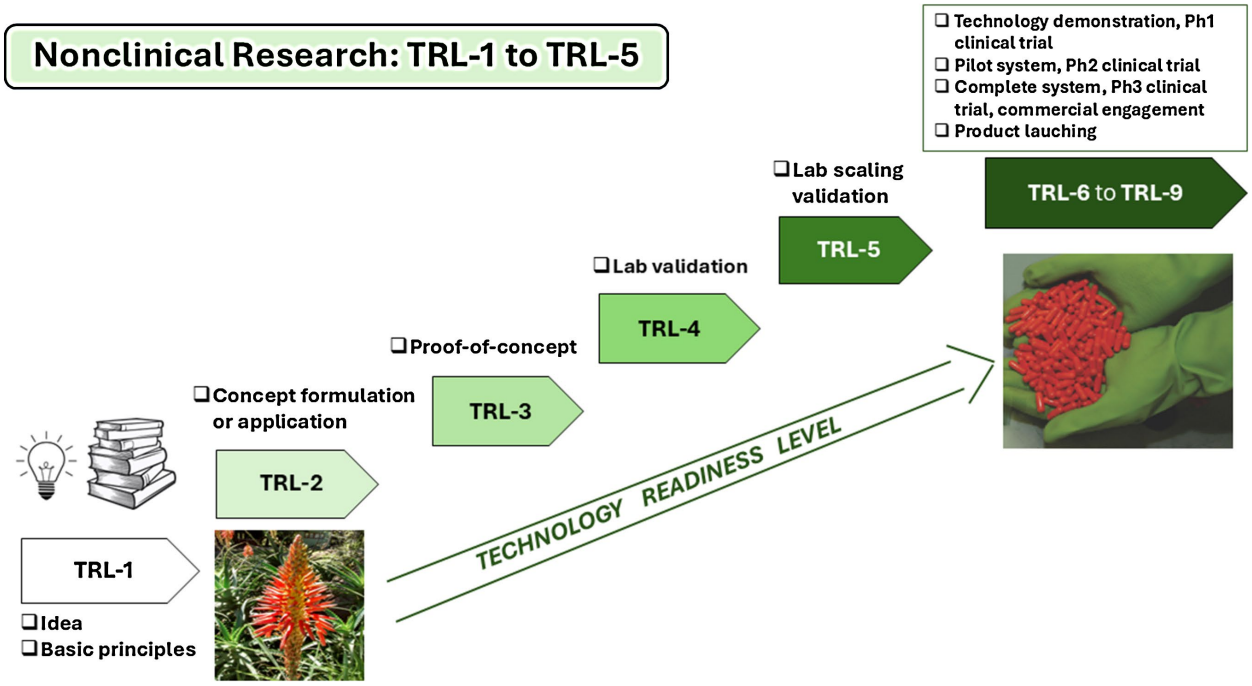

Figure 1. Schematic representation of technology readiness levels for phytomedicines.

for accelerating discoveries and developing health products in recent decades. The consolidation of this paradigm was fostered by the National Institute of Health (NIH) when it launched a roadmap based on the concept of translational medicine [10]. In such a system, which is generally embedded in translational research, the route "from bench to bedside" [11] was rationalized early through the idea of translational blocks comprehending basic biomedical research and clinical science and knowledge [12]. The first comprises nonclinical research thoroughly and represents the translation from basic science to human studies. The second has been better identified as Translational Science in Medicine [13]. The conceptual evolution of translational research converged, more recently, to detailed roadmaps for developing new drugs and medicines from either small or biooriginated molecules [14]. However, while the landscape for synthetic drugs has gradually evolved over time [7], a specific roadmap to phytomedicine development is not currently available. In short, the development of phytomedicines encompasses the scientific validation of the bioactive content of plants. In the chemistry silo, this is usually achieved by a selected method of extracting the metabolites of interest followed by standardization and technological transformation [15]. The proof of concept and pharmaceutical formulations also differ from the synthetic drug route. For instance, the impact of the quality of the plant raw material and the adequacy of analytical methods for standardization, as well as for monitoring complex mixtures of components during the technological transformation processes [4], will depend on different protocols. However, the regulatory matrix of some countries (including Brazil) is currently adjusted for the commercialization of herbal drugs (marketed as dry and shredded herbs), plant derivatives (extracts, tinctures or

similar, from defined parts of the plant), and phytomedicines (which aggregates a denser set of technologies) [16]. Considering this scenario, a putative roadmap for phytomedicines would only converge with the synthetic drug template regarding the more mature levels of development, e.g., those related to clinical efficacy and pharmaceutical production to meet the commercial scale. This partial convergence with the NIH roadmap is the main reason why the present study focused on the nonclinical stages and the ordering of the respective knowledge silos according to the translational perspective.

1.3. The Technology Readiness Level and the Biomedical Sector

The concept of the Technology Readiness Level (TRL) emerged from the North American aeronautical engineering in the second half of the 1960s, reflecting the need to review technologies under development and understand to what extent they would be "ready" within a system directed to the production of aircraft [17] [18]. This strategy strongly allowed the USA Aeronautical sector to enhance the understanding between researchers and managers of projects and programs. In recent decades, the TRL scale has been consolidated as a system with nine levels, constituting a template that quickly spread to many other technological sectors. This nine-level system works as a metric to manage multidisciplinary R&D processes, considering that the independent technology developed at each stage (generally governed by methodologies from a specific knowledge silo) must be sufficiently ready (mature) to support the subsequent stages [9] [19]. In the current system configuration, lower levels of TRL1 and TRL2 are associated with basic research, while TRL9 denotes commercial-ready technology. TRL3 and TRL4 are related to research feasibility verification, and TRL3 to TRL6 are related to technological development. TRL5 to TRL7 intersect the system to encompass the technology demonstration; TRL6 to TRL8 refer to systems (whole project) and subsystems (project stages) development; and TRL8 and TRL9 refer to system testing, launch and operation [20]. Thus, in managerial practice, assessing technology readiness presupposes taking up the technological process into the nine serial stages, starting by defining each macroactivity level as reliably as possible, followed by describing the specific technologies they embrace, always considering the system on an ongoing basis [21]. Each level operates with specific indicators that subsidize accessing the requirements that support the technology conveyance through the process flow, although the steps are not always linearly arranged or even sufficiently clear as to their downstream or upstream boundaries. Being crucial to promoting maximum reliability to the system (whole process) [8], integration of the independent technologies (generated in each stage) will reflect how reasonably realistic (ready) they behave in a simulated environment during development [22] [23].

In the biomedical field, universally accepted steps, presented in a generic way, have been summarized on diverse websites, portals [24] and reports elsewhere [23] [25]. Inspired by the paradigms of the first TRL scale published by NASA in

1974, an incursion into the biomedical area was proposed by Savoini and Tronchin, who summarized the scales for evaluating the technologies involved in the drug development process has been reported [22]. As a rule, the TRL metric for the R&D of pharmaceutical products reveals the application of a uniform language, although it has been adapted to research lines targeting very distinct goals [23]. This approach has been universalized since the NIH release of the first version of the roadmap for translational medicine [12] to recent versions aimed at developing new drugs and medicines from either small molecules or biological origin [26] [27]. By crossing the ordering of technologies using the TRL metric applied to a semiempirical roadmap for developing phytomedicines [6], the present study proposes to build a suitable tool to manage projects in this area, with emphasis on the nonclinical stages.

2. Methods

The present study was developed by designing four main informational blocks: (1) Macro scenarios are based on the most updated NIH roadmap for product development in the biomedical area via translational research [26]; (2) Description of the TRLs for biomedical and pharmaceutical products from the Technology Innovation Agency of South Africa [24]; (3) The proposal for the systematic ordering of technologies, which incorporates TRL into translational research as a way of accelerating technological innovation [28]; (4) Modeling of the phytomedicines R&D project framework, aligned with previous theoretical proposition [6], and taking into the descriptions by Savoini and Tronchin [22]. These four information sources guided constructing the TRL scale specifically for the R&D of phytomedicines. Once the nine TRLs were defined, descriptions of the technological activities at each level were elaborated by expert (the authors) long-term consensus, with the incorporation of summarized delivery goals for each stage. However, considerations on the TRL scale for the development and production of phytomedicines are here exclusively described for the first five levels, which are those that incorporate the most relevant differences from the descriptions published elsewhere for other R&D sectors. For instance, proper descriptions for TRL-6 to TRL-9 may be correlated with those displayed in the Technological Innovation Agency of South Africa portal [24] and adapted to herbal products [6], as briefly indicated at the end of **Table 1**.

3. Results and Discussion

The proposed TRL scale for the technologies involved in R&D and the production of phytomedicines is shown in **Table 1**. The basis for **Table 1** structuring is the panel of activities that make up the R&D stages in natural products and phytomedicines, as proposed elsewhere [29]. Descriptions of the technology-related TRL-1 to TRL-5 levels constitute the nonclinical stage of phytomedicine development, as they were empirically split in the present study. The descriptions established by the South African Technology Innovation Agency (TIA) for synthetic

Table 1. Proposal of TRL system related to phytomedicines development: descriptions of technologies and sectional delivery goals.

Technology Readiness Level (TRL)	Definition for the Natural Product Area	Description of the Technology	Delivery Goal
TRL-1 Basic research technology/exploratory research (No specific application)	Prior information	Pharmacobotanical and ethnobotanical/ethnopharmacological or pharmacological status (state of the art)	Report containing data on the plant: presence in pharmacopeia, memento, positive lists of regulatory agencies and governmental programs; relevance of registration by enough traditional use; popular usage; observed/reported biological activity; justification for the choice of plant species
		[a]Technological status of the plant species (state of the art)	Report with prospection of products and processes developed with the plant species (patented or commercialized)
		[a]Extensive literature review	Report containing chemical, biological, agronomic data, etc.
		Botanical characterization and occurrence of the species	Botanical description, including data on systematics, phenology and distribution in the territories
	Obtaining the plant for laboratory studies	Botanical identification	Exsiccate record and deposit number; additional data, if any
		Sector regulatory information	Proof of compliance with the requirements of environmental standards concerning the genetic access (georeferencing of collection, public x private x special areas), agricultural organs permissions (includes threat to the species), autochthonous culture-protecting regulators, health guidelines, and others
		Collection or acquisition from third parties	Extractivism *in situ*, *ex situ*, proven donation from a third party (institution, company or individual) or invoice from a supplier or succedaneum
		Origin from extractivism or regular cultivation	Supplier: organized production chain or Local Productive Arrangement (LPA)
Short Content Delivery (SCD) of TRL-1	*SCD: Principles (hypothesis, method, results) observed and reported that characterize evidence of biological activity of interest or new technology (e.g., published article)*		
TRL-2 Basic Research Technology/Concept Formulation (Practical application identified; required material/process confirmed; concept technology/hypothesis confirmed)	Primary processing of the plant (laboratory scale)	Manual screening (separation of undamaged plant organs of interest) and cleaning Drying Comminution	Justification for the chosen part of the plant; location and method (manual or mechanical) of separation (during or post-harvest); fresh or dry material Description of the method established for drying Description of the established fragmentation method, with possible experimental optimization
	Bioguided secondary processing of the plant (laboratory scale)	Extraction	Justification for the chosen biological model. Report with quantitative results of effectiveness on a specific target or related targets. Planning the

			proof of concept
		Primary biological screening using validated models toward biological target: *in vitro*, ex-vivo, in silico efficacy tests	Description of the procedure established for fractionation and justification for its choice; chemical characterization of fractions by chromatography and physicochemical techniques in general
		Bioguided fractionation of the extract	Description of the procedure used to separate the constituents, evidencing the yields and purity levels of the isolates
		Isolation and purification of constituents	Report containing the methods used in the constituent's identification (physicochemical, spectrometric, comparison with references)
		[b]Identification of isolated constituents	Justification for the chosen biological model. Report with quantitative results of effectiveness on a specific target or related targets. Planning the proof of concept
	Chemical standardization of extract/fraction	Development of methods for qualitative studies: HPLC-DAD, HPLC-MS, GC-FID, GG-MS, CCD, CCD-MS; others	Chemical profile of the plant matrix (extract or fraction) established by the selected method
		Selection of constituent (or succedaneum) to act as a chemical marker	Justification for the substance chosen as a chemical marker and description of its characterization process; possibility of commercial acquisition
		Seasonal studies on the plant material	Studies of plant metabolic variation due to seasonality in cultivation or from extractivism
		[b]Validation of the analytical method	Full description of the method and its validation parameters; selectivity and/or specificity; repeatability etc.
		[b]Methods applied to quantitative studies: HPLC-DAD, HPLC-MS, GC-FID, GC-MS, TLC/densitometry; others	Qualitative/quantitative chemical profile of the extract/fraction, regarded to the selected marker or Chemical Reference Substance (CRS) chosen
	Active Pharmaceutical Ingredient (APIp) proposal and its formulation	Initial planning of the pharmaceutical form (dosage), indicating the intended Active Pharmaceutical Ingredient of plant origin (APIp)	Technical report with the characteristics of the proposed APIp (candidate), containing support for the possibilities that indicate the suggested pharmaceutical form and the form of administration of the finished phytomedicine
Short Content Delivery (SCD) of TRL-2	*Research plans and protocols developed, peer reviewed and approved (e.g., published article).*		
TRL-3 Research on feasibility/Establishment of the critical	Batch process scale-up at bench level (Chemically Uniform Batch, CUB): plant	Obtaining the PRM (plant or part of the plant) in the quantity necessary to the batch process scale-up at pre-pilot	Description of the means to bench scale up the quantity of the PRM as representative of the one to be used in the finished product, marking relevant issues related to the origin of the PRM, collection

function or proof of concept	raw material (PRM); extraction; fractionation; isolation of constituents	plant scale (CUB)	or acquisition, etc.
		Obtaining and optimizing the CUB, whose uniform quality will feed the downstream stages of the technological development chain at bench scale	Description of the bench batch optimization process, aiming at obtaining the Single Batch, explaining the methods (e.g., experimental planning), yields evaluation and description; proposal of APIp
		Bench batch quality applied to the CUB: application of validated methods to quantify extract and intermediates (APIp candidate); determination of residual solvents	Technical report with results of the application of the method already developed and validated to establish the quality of the input (extract, fraction, isolated); residual solvents in the extract or fraction (candidate for APIp) determined by recognized method
	Proof of concept	Confirmation of activity (efficacy) by validated biological *in vitro* and/or ex vivo models; in silico support	Justification of the chosen biological model. Report with quantitative results of effectiveness on a given target or related targets: extracts; fractions; isolated constituents
		In vivo pharmacological tests with test-substances in an animal model	Justification of the chosen model. Report with quantitative nonclinical efficacy on a given target: extracts; fractions; isolated constituents; protocols registered in the pertinent Registration in the pertinent Ethics Committees
		Cytotoxicity of compounds, tested according to protocols recommended by regulatory standards	Report with cytotoxicity levels (extracts; fractions; isolated constituents) defined for different cells, including average growth inhibition, lethality; data on selectivity and other parameters
	Admeasurement of characterization parameters for formulation	Pharmaceutical characterization of the candidate for APIp	Description of the results of the physicochemical analysis for APIp: melting/boiling range, solubility, stability, etc.
		cFormulation trials, and optimization of the pharmaceutical process for the APIp candidate	Description of development: pharmaceutical form and characterization; dissolution tests and protocol evaluations according to the nature of the product formulated with the APIp (solid, semi-solid, liquid, other)
		[c]Studies of specific formulations	Description, with justification, of the production and analysis of micro- or nanoparticles, methods and techniques employed. Measures of encapsulation efficiency and particle stability
Short Content Delivery (SCD) of TRL-3	*Candidates for phytomedicine development characterized in nonclinical studies*		
TRL-4 Technology Development/Validation in laboratory environment	Chemical standardization in laboratory environment	[d]Extraction and batch process scale-up (extract or fraction or isolated) in laboratory environment	Report with data from the scaled-up extraction, fractionation or isolation process, including yield and description of extract/fraction/compound characteristics
		Isolation of plant constituents	Report on the characterization of the isolated and

		for characterization as a reference substance	purified chemical marker, including yield and complete molecular identification
		Application of the validated method to quantify the chemical marker in a GLP environment	Report containing the chemical standardization process of the candidate for APIp, with statistically treated analytical data
	Revalidation of the Proof of Concept	Pharmacological tests with the target compounds in animal model(s) or substitute model	Justification of the chosen model. Report with quantitative nonclinical efficacy of test substances (extracts; fractions; isolated constituents) on a given target
	[c,d]Toxicology in a GLP environment	Cytotoxicity of target compounds according to protocols recommended by regulatory standards	Report with cytotoxicity levels (extracts; fractions; isolated constituents) defined for different cells, pointing out average growth inhibition, lethality; data on selectivity and other relevant parameters
		Genotoxicity assays (AMES and micronucleus)	Report with AMES and micronucleus test results for the APIp candidate
		Single-dose and repeat-dose toxicity tests, local tolerance	Report with results of single-dose and repeat-dose toxicity tests of the candidate for APIp
		Carcinogenicity and pharmacological safety tests	Report on the carcinogenic potential of the APIp candidate and on the pharmacological safety (if necessary)
Short Content Delivery (SCD) of TRL-4	*Trials, surrogate markers, and outcomes identified as supporting information for nonclinical and clinical trials: assessment and characterization of candidates to the phytomedicine construct. Delivery of laboratory prototype.*		
TRL-5 Technology Development/Validation in relevant environment, pilot scale	Obtaining the APIp candidate on a pilot scale in a GMP environment	[d]Transposition of the process of obtaining the extract/fraction to pilot scale	Description of the results involved in obtaining the APIp on a pilot scale, containing the transposition parameters; yield evaluation
		Chemical qualification of the pilot lot of APIp (extract/fraction) by physicochemical and chromatographic methods	Evaluation of the reliability of the chemical profile and the physical-chemical characteristics of the pilot APIp, comparing with standards generated by the technological chain upstream (use of the validated method for the process)
	Pilot process scale for the pharmaceutical formulation in GMP environment	Pilot scale preparation of the formula developed for the APIp candidate	Report containing evaluation of methods, techniques used and results compared with the product optimized for APIp on the laboratory scale
	Proof of the effectiveness of APIp and the product formulated on the pilot scale	Comparison of the results from the proof of concept with the test validation in GLP environment	Report with comparative data on the effectiveness of the pilot APIp with those related, obtained upstream of the technological chain
	Planning the clinical trial	Technical data package containing pharmacology and nonclinical toxicology studies, proposed manufacturing information, and clinical	Dossier with nonclinical studies that will support studies in humans

	protocols suitable for Phase 1 clinical trials
Short Content Delivery (SCD) of TRL-5	*Drafting of the resulting documentation on technical data package content: data from non-clinical pharmacology and toxicology studies, proposed manufacturing information, and clinical protocols suitable for Phase 1 clinical trials. Delivery of the production prototype.*
TRL-6 Technology Demonstration	Integrated prototype system verified in the operating environment. See [6] and [24].
TRL-7 System commissioning	Integrated pilot system demonstrated in operational environment. See [6] and [24].
TRL-8 System commissioning	System incorporated in the commercial plan. See reference. See [6] and [24].
TRL-9 System operations	System attested and ready for full commercial use. See [6] and [24].

Indexes (a), (b), (c) and (d) indicate technological steps that can be interposed, carried out concomitantly, or eventually reverse the order of fulfillment, depending on the project design. SCD = short content delivery to comply with the respective TRL. CUB: Same material, qualified as chemically uniform, that must go upstream across all the technical activities toward the prototype. APIp: active pharmaceutical ingredient from plant origin. PRM: Plant Raw Material. HPLC-DAD: High-performance liquid chromatography coupled with diode array detection. HPLC-MS: High-performance liquid chromatography coupled with mass spectrometry. GC–FID: gas chromatography coupled to flame ionization detection. GC–MS: gas chromatography coupled to mass spectrometry. TLC: Thin layer chromatography. GLP: Good Laboratory Practice. GMP: Good Manufacturing Practice.

drugs were briefly provided from TRL-6 to TRL-9. The metric high levels refer to the stage of clinical studies, in combination with the preparation of robust and reproducible batches of the targeted product, already in manufacturing environments, and ending at its commercialization [24]. **Table 1** last column (results to deliver to the next stage) aligns conceptually with the TRL framework presented by the TIA Agency for Biomedical Projects, indicating the criteria (as key question for stage pass) to step forward to the next level. This artifice is quite useful in terms of presenting sectional scenarios, characterizing it as a staged process and identifying indicators for the evaluation by the managers of the independent technologies on development [8]. One can deduce, from the TRL scale panorama displayed in **Table 1**, that the broader possibility of innovation is conditioned to the first five levels, which coincides with a stronger R&D demand.

The TRL metric offers a suitable tool for organizing R&D projects in a way that brings advantages to organizations. Among the internal gains provided by the adoption of TRL are 1) the increased visibility of the organization about its own project portfolio, which contributes to strengthening the decision-making aptitude on the ongoing projects [21]; 2) clearer routes established for developing translational goals (currently usual in the biomedical and pharmaceutical fields); and 3) the enhanced awareness of the project teams involved in the translational research they carry out, into the perspective and alignment with the institutional mission. The TRL system provides semantic convergence toward a more precise and comfortable dialog between researchers and managers. Externally, organizing projects by TRL contributes to demonstrating to potential customers (e.g., industry,

other institutions, eventual partners of translational research) a portfolio characterized by differentiated offers based on the level of technology embedded in any ongoing project, prototype, or product. In summary, the TRL system allows speeding up the translation of projects, minimizing risks, optimizing cost-benefit solutions, and helping to incorporate results into the innovation system organizational practices.

Adopting TRL also contributes to the process of technology transfer by establishing canons [30] for negotiations between interested partners. As recommended and used in several initiatives to promote innovation [28], the TRL system is already routinely applied by different industrial sectors, despite being relatively ignored in the academic world [31]. In Brazil, there is a growing tendency for funding agencies to use the TRL scale as a criterion to evaluate projects' technological advancement and support decisions on R&D funding. Finally, several other metrics have been proposed to assess the readiness of certain processes occurring in diverse technological areas [19]. In particular, the level of readiness for innovation [32] and the level of readiness for the product [33] [34] have played relevant complementary functions in the assessment of maturity; this time, they are inserted in managerial domains closer to market and production regulation parameters [28]. Another important issue concerns the concept of institutional readiness, which was originally introduced as a parameter of effective fundraising [35] and later adapted to include values, resources, routines, and organizational practices [31].

4. Conclusion

This study presents a managerial framework built by crossing elements from translational research and the concept of the technology readiness level. The metric staged panel and the readiness level descriptions were semiempirically correlated to the phytomedicines scope from descriptions available for the synthetic drug roadmap. This TRL metric described here is currently being applied as a robust tool to manage the portfolio of projects in the Natural Products area, by the Project Management sector, in the Institute of Drug Technology of the Oswaldo Cruz Foundation, Brazil. The incorporation of summarized delivery goals at the end of each stage has been building a useful instrument that facilitates the understanding of the demands of project managers, by researchers who develop activities at each level of technology. As an initial proposal to make available a suitable tool for managing R&D projects of plant-originated pharmaceuticals, it should be subject to continuous improvement by practicing project management in this specific area. Its application can bring together researchers and managers toward the accomplishment of institutional goals as well as facilitate the academy-industry relationship at a time when the binomial Biodiversity & Health is gaining global prominence.

Conflict of Interest

The authors declare no conflict of interest regarding the publication of this article.

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List of Abbreviations

NASA	National Aeronautics and Space Administration
NIH	National Institute of Health; PRM: plant raw material
R&D	research and development; SCD: short content delivery
TIA	Technology Innovation Agency (South Africa)

Abbreviations used in Table 1 are displayed in its footnote.