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The Dawn till Dusk of phytopharmaceuticals

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ABSTRACT

Herbal products and their formulations have a large market at the global level. A significant portion of the worldwide population relies upon herbal treatment. Their apparent non-toxic and cost-effective nature appeals to the population and drives researchers to pursue them for drug development. However, due to the lack of scientific evidence, their conventional preparation, poor regulation and control make these an unseen threat to the people. There has been a long-standing argument that allopathic medicines are better than herbal medicines due to their specificity and precision. To compete with modern medicines, a concept of science-based phytopharmaceutical drugs was introduced through a draft amendment notified to the Drugs and Cosmetics 1940 and Rules 1945. The amendment has introduced a definition for botanicals and their scientific evaluation for quality safety and efficacy by the Central Drugs Standard and Control Organization (CDSCO) office as a marketing authorization requirement. The present article discusses the advantages and challenges faced in the development of phytopharmaceuticals, and how they differ from dietary supplements and herbal drugs. It also gives consolidated information on Phytopharmaceuticals and their regulatory and Pharmacopoeial status with an exemplary PPI monograph – *Aegle marmelos*. The plant selection was done based on extensive research using the PRISMA approach. A detailed view of the opportunities and challenges provided by phytopharmaceuticals is explained in the present review.

1. Introduction

Plants are a great reservoir of various phytochemicals, exhibiting several therapeutic activities paramount for drug development industries. Human civilization has exploited this reservoir since prehistoric times for disease treatment and cure, preserved in traditional knowledge (Benzie et al., 2011; Bunalema et al., 2014; World Health Organization. Regional Office for South-East Asia., 1990). With time and the uprisal of modern medicines armed with science and technology, several scientifically proven synthetic drugs have overshadowed traditional knowledge (Singh, 2010).

These medicines are designed to act specifically, resulting in pharmacological actions that may lead to unavoidable adverse effects. The recent development of the inconsistent response of synthetic medicines stirred the interest of global pharmaceutical companies in natural and herbal products to rediscover their potential as the source of safer drug candidates (Joshi et al., 2011; Sen and Chakraborty, 2017).

India has recognized the Indian systems of Medicine, where six different types of medicinal systems are enlisted. These are *Ayurveda*, *Yoga*, *Unani*, *Siddha*, *Naturopathy* and *Homoeopathy* (Vaidya and Devasagayam, 2007). Since 1995, the Indian government has been regulating the above-mentioned medicinal systems, headed by the Department of Indian System of Medicine and Homoeopathy (ISM&H), later renamed as the Department of AYUSH in November 2003. In November 2014, a concrete step was taken by the government to revive the long-lost knowledge of the traditional medicines of India by creating the Ministry of AYUSH, ensuring its optimal development and propagation on the global platform. Several developed countries are also embracing herbal medicines as alternative & complementary drugs. The U.S. Pharmacopoeia has also recognized the Dietary Supplements monographs of botanicals and their ingredients. The exponential growth of the herbal drug market invariably shows the increase in consumption and demand for herbal products, mostly utilized by low and middle-income groups consolidating approximately 80 % of the global population. This also raises concerns about the proper regulation of herbal medicines in the market (Jain et al., n.d.; Patwardhan, 2014).

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The herbal & traditional medicine market in India is increasing exponentially, and the country is one of the biggest contributors to the global herbal medicine industry (Barkat et al., 2020). According to the World Health Organization reports, India has exported approximately 104,511 tonnes of AYUSH medicines between April 2021 – January 2022 (Salmerón-Manzano et al., 2020). Previously during 2020–21, India exported approximately US$ 540 million worth of herbal medicines. This is greatly recognized by the WHO as it has established the WHO Global Centre for Traditional Medicine in India(World Health Organization, 2022).

Though the initiative gives recognition to herbal formulations, herbal medicines are still lagging behind allopathic/modern synthetic medicines as their chemical characterization and therapeutic activity validation have not yet been scientifically proven. The sudden increase in the demand for herbal medicines also raises issues regarding their safety and efficacy, impeding their acceptability by Indian Medical Association (I.M.A.) and at the global level as mainstream medicines (Ekor, 2013; Katiyar, 2019). The global acceptability for herbal medicines can only be reached if these are developed scientifically. To fulfil this purpose, the Government of India has designed a new drug category called "Phytopharmaceutical drug." Phytopharmaceutical drugs include the purified fraction(s) of the medicinal plant or its part with scientifically proven bioactivity (Bhatt, 2016; Katiyar, 2019). The purified fractions of a plant or its part is considered a phytopharmaceutical drug if quantification and characterization of a minimum of four marker compounds are done. The chosen marker compounds should contain at least one bioactive marker with defined pharmacological activity (Katiyar, 2019). The present review provides consolidated information on phytopharmaceutical drug, outlining the current aspect at the global level.

2. One plant drug

Pharmaceutical industries have focused on plant-derived small molecules for drug development due to their vast pharmacological functions. Nearly 30 per cent of natural products and their derivatives, including natural botanical mixtures are approved by USFDA (Newman and Cragg, 2020). In Ayurveda and other traditional medicines, various plants are used to prepare concoctions (Parasuraman et al., 2014). These concoctions are so complex that one may be unable to categorize them for one particular pharmacological/biological function. Moreover, due to the involvement of several active ingredients in different concentrations, which vary from batch to batch, it is impossible to calculate the maximum dose. Hence, these formulations, even if exhibit pharmacological activities, are considered Complementary and Alternative medicines, diluting the importance of medicinal plants (Ness et al., 2005).

A single medicinal plant is known to contain several phytoconstituents about a variety of pharmacological effects. These phytoconstituents may have different mechanisms of action, due to which some may show synergistic action, and many may not synergize for a particular biological effect (Alamgir, 2018; BUTNARIU and BOCSO, 2022). Hence, a drug development out of a medicinal plant or its part is a complicated procedure in which the selection of phytocompounds is done on the basis of their probable biological effects. The isolation of principal bioactive compounds is recommended as these are mostly predominant phytoconstituents in the medicinal plant (Shrikumar et al., 2007).

With the uprisal of multi-drug resistant microorganisms as well as multifactorial diseases such as diabetes and cancer, the concept of "one disease, one drug, one target" has lost its popularity (Casas et al., 2019; Galan-Vasquez and Perez-Rueda, 2021). While single target approach might be useful in single gene disorders, most diseases and pathogens attack the host system at multiple targets (Talevi, 2015). Hence, nowadays combined drug therapy is popular. The combined drugs developed out of the synthesized chemical molecules, although successful, cause severe adverse effects on the patients (Banerjee et al., 2020). With time, the pathogens also develop resistance against these multiple drugs, which again leads to a dead end for the disease treatment (Catalano et al., 2022). In this context, plant-derived medicines have the advantage over the synthetic medicines (Dinic et al., 2015; Medina and Pieper, 2016). This is because of the naturally occurring chemical moieties have apparently better bioavailability and compatibility with the host system (Hu et al., 2023). Nowadays, several pharmaceutical companies manufacture the herbal products containing the semi-purified extracts or oleoresin derived from a single plant as complementary medicines with the metabolomics enabled plant extracts profiling (Sahoo and Manchikanti, 2013). By harnessing the high-resolution technologies such as LC-MS/MS, GC–MS and NMR, the metabolites profiling of the plants becomes easier (Benkeblia, 2023; Xiao et al., 2012). This provides a new regime of multi-component drug discovery from a single plant part. Through different chromatographic techniques hyphenated with the computer-aided drug discovery (CADD) and spectroscopy, the designing of multi-molecular combinations showing synergistic effects becomes possible (Ece, 2023). This modern drug development technology is helpful in the development of *Phytopharmaceuticals*. Phytopharmaceuticals are multi-molecular combinations which follow a combinatory treatment module which minimizes off-target toxicity by synergistic potency and improves outcomes by synergistic efficacy (Mukherjee et al., 2021). Combination synergy is a multi-dimensional concept where synergy can be observed from a network pharmacology perspective. Network pharmacology uses systems-level drug–response phenotypes from various 'omics' platforms. This network pharmacology with metabolomics has been proven effective in elucidating the mechanisms of action of medicinal plants and complex traditional formulations (Ece, 2023; Mukherjee et al., 2021).

3. Phytopharmaceutical drug

As explained above, to encourage the "one plant drug" concept and the promotion of the technology-driven plant-derived multi-molecular drug(s) development, the Government of India published a draft amendment to the Drugs and Cosmetics Act 1940 and Rules 1945 thereunder (D&C Act and Rules) on 24th October 2013. (Narayana and Katiyar, 2013) As per the notification under rule 2 subsection (eb), "Phytopharmaceutical drug includes processed or unprocessed standardized materials derived from plants or parts thereof or combination of parts of plants, extracts or fractions thereof in a dosage form for internal or external use of human beings or animals and intended to be used for diagnosis, treatment, mitigation or prevention of any disease or disorder in human beings or animals, but does not include administration by parenteral route". Later, the definition of phytopharmaceutical was amended in 2015 and 2019 for more clarity. According to the current definitions described as per the Gazette notification dated 19th March 2019, G.S.R. 227 (E), under Chapter I of Subsection (aa) of New Drugs and Clinical Trials Rules, 2018, "Phytopharmaceuticals drugs includes a purified and standardized fraction with defined minimum four bio-active or phytochemical compounds (qualitatively and quantitatively assessed), of an extract of a medicinal plant or its part, for internal or external use on human beings or animals, for diagnosis, treatment, mitigation or prevention of any disease or disorder but does not include drug administered through parenteral route." (Bhatt, 2016; Gazette of India Notification Number G.S.R.227(E), 2019; Katiyar, 2019).

The introduction of the "phytopharmaceutical" category of new drugs opens a new vista of Multi-Component Botanical Therapeutic (MCBT) discovery from rich bioresources of medicinal & aromatic plants (Rather et al., 2013). According to the above definition, the phytopharmaceutical drug formulation involves an extensive analysis of the mechanism of action, pharmacokinetics and pharmacodynamics study, and pharmacovigilance-based study of the purified fraction(s) from the medicinal plants. The Indian Pharmacopoeia Commission (IPC), an autonomous government body, regulates pharmaceutical drugs and their formulations, which is why this new class of drugs comes under this

body. IPC is currently working rigorously on the promotion of phytopharmaceutical monograph development. (Indian Pharmacopoeia Commission, 2022) Phytopharmaceutical drugs bridge the modern and traditional medicinal system with a touch of innovation designed using advanced technologies, delineating from conventional Ayurvedic medicines development (Bhatt, 2016; Sahoo and Manchikanti, 2013).

Apart from the government initiatives, several research institutes are rigorously working on developing phytopharmaceuticals, some in collaboration with the industries. Council of Scientific & Industrial Research – Central Drug Research Institute (CSIR-CDRI) is actively developing five phytopharmaceutical drugs viz., – Picroliv (for the treatment of non-alcoholic fatty liver disease), NMITLI – 118 AF1 (for stroke), NMITLI – 118 WFA (for bone health; co-development with industry partner), 4655/K09 (for hypertriglyceridemia), and Chebulinic acid enriched fraction (for benign prostatic hyperplasia). Out of the five, two are licensed products, and Picroliv is undergoing phase 3 trial, which will soon be out in the market if approved by the CDSCO (CSIR-CDRI, 2023).

Similarly, several pharmaceutical industries, such as Sunpharma, Phapros, etc., are encouraging the development of phytopharmaceuticals drug. This innovative medicinal class will bring a revolution in the pharmaceutical field. Nowadays, where disease pathogens are attaining resistance against pharmaceutical drugs, Indian scientists and intellectuals advocate the concept of a drug formulated out of one single plant (Catalano et al., 2022; Narayana and Katiyar, 2013).

It is important to note that the most basic requirement of phytopharmaceutical drug development is the characterization and quantification of a minimum of four phytocompounds in the purified fraction, which should be identified as bioactive or phytochemical markers. It is ideal if all of them are bioactive or support the principal bioactive compound in the pharmacological activity; hence, this is non-negotiable (Narayana and Katiyar, 2013). This can be achieved by adequately studying the chosen markers and their activities by conducting *in silico* and *in vitro* assays. Another reliable method for the isolation of bioactive fraction(s) is bioactivity-guided fractionation (BAGF), which involves the selection of the extracts and fractions showing bioactivity (Malviya and Malviya, 2017). After selecting the most active fraction(s), it can be subjected to compound(s) characterization and quantification of the identified bioactive markers. To ease the process, a targeted approach for biomarker(s) selection with the help of *in silico* drug discovery tools can be implemented (Danaboina et al., 2023; Tiwari, Mishra, Danaboina, et al., 2023) Most medicinal plants are being studied by researchers extensively; thereby, the plant metabolite profiles are readily available and can be exploited for phytopharmaceutical development purposes. (Kopka et al., 2004; Sharanya et al., 2020) A list of potential medicinal plants with high annual consumption, which can be pursued for phytopharmaceuticals development, is provided in Supplementary Table 1. IPC has developed several herbal monographs on medicinal plants and herbal products. A total of 183 herbal monographs are available in the IP-2022 (Tiwari, Mishra, Kumar, et al.. 2023) The selection of these medicinal plants was done not only on the basis of their high trade value, but also due to their extensive use in several ayurvedic and herbal medicinal products targeting various range of diseases which involves inflammation as one of the major symptoms.

4. Dietary supplements, botanical drugs, and phytopharmaceuticals

Dietary supplements, which is a broad category, include all or any herbal products which are intended to supplement the diet as herbals, vitamins, proteins, and metabolites. These are used worldwide for oral administration only (USFDA, 2024)). Moreover, these products are prohibited to include or add the chemical compounds approved as drugs or biologics, unless the compound was previously marketed as a dietary supplement or a food. As this category also includes herbal products, most of the conventional medicines are sold as dietary supplements. Since 1994, under the act of Dietary Supplement Health and Education Act (DSHEA) the U.S. Food and Drug Administration (FDA) is regulating the herbal products as supplements. Several natural extracts, sold as dietary supplements, have a long history of therapeutic activities ascribed in the folklore and ancient texts. These herbal extracts and products are available as the over-the-counter medicines, which are used by most of the urban populations in a free-flowing manner, encouraging poly-pharmacy at a global level. (Afolayan and Wintola, 2014); Lehman, n.d.; Singh et al., 2018) According to a survey, more than 50 per cent of the U.S. population uses dietary supplements on a regular basis. In Asian countries, this was noted to be 40 to 60 per cent, while approximately 30 per cent of the European population is reported for the regular use of these products. (Dwyer et al., 2018; Lordan, 2021) As the category mentions all the products as supplements, a belief of no adverse effect has also been created with time among the population. Hence, it is needed to acknowledge the herbal medicines as an interface between the supplement and the drug.

Apart from dietary supplements, the USFDA has defined one more category “Botanical Drugs”, which is controlled by the Center for Drug Evaluation and Research (CDER), FDA. This category includes the herbal products which are intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease in humans. These botanical drugs may be derived from plant materials, fungi, algae or their combination, which may be manufactured as oral or injectable products. These quality-controlled products are approved only after the clinical trials and may be available as over-the-counter medicines. (USFDA, 2023; Wu et al., 2020) The systematic approach for the development of botanical drugs is provided under the “Guidance to Industry for Botanicals as Drugs”, published by the USFDA in 2004. (Nooreen et al., 2018) To-date, two botanical drugs are given marketing authorization – *Veregen* and *Fulyzaq*. Veregen is an ointment for genital warts that is derived from green tea leaves (*Camellia sinensis* (L.) Kuntze), was standardized to sinecatechins. While, Fulyzaq is made from the red sap of the *Croton lechleri* Mull. Arg. plant, standardized to crofelemer is used in the treatment of diarrhoea in HIV/AIDS patients who are on antiretroviral therapy. (Narayana and Katiyar, 2013; Wu et al., 2020) The USFDA does not insist upon the principal active compounds characterization and quantification in developed botanical drugs, which differs from the phytopharmaceutical drug. (USFDA, 2023).

Phytopharmaceutical drug development involves standardization at three levels. First, the identification of the botanical substance used for the drug development at the species level along with the geographical variation. Second, extraction and purification of the raw herbs with a standardized procedure, focused on the enrichment and isolation of active phytochemical compounds. (Katiyar, 2019; Nooreen et al., 2018; Tiwari, Mishra, Kumar, et al.. 2023) And third, the characterization and quantification of at least four phytochemical compounds, including the principal bioactive markers, using advanced technologies. The biological activity of the developed phytopharmaceuticals will be assessed at the crude as well as the purified fraction level, supported with *in silico* predictions. These drugs will be under the regulation of Central Drugs Standard Control Organization (CDSCO), Ministry of Health & Family Welfare, Government of India. This will specify the therapeutic activity of the fraction with the maximum dose limit and the probable adverse effects due to the toxic phytochemical compounds (with define limit), hence can be prescribed as any other pharmaceutical drugs for the treatment of diseases. (Directorate of Printing, 2023) The salient features and basic difference between dietary supplements, botanical drugs, and phytopharmaceuticals are briefly elucidated in Table 1 and global aspects of Phytopharmaceuticals pertaining Table 2.

5. Phytopharmaceutical clinical trials

Phytopharmaceutical medicines are obtained from purified fractions of at least four bioactive or phytochemical compounds (assessed qualitatively and quantitatively) of an extract of a medicinal plant or part

Table 1
Salient features of dietary supplements, botanical drugs, and phytopharmaceuticals.

Salient features	**Dietary** supplements	**Botanical drugs**	**Phytopharmaceutical drugs**
Definition	Involves any substance which provides a supplement to the diet	Herbal purified extracts	Includes standardized purified fraction(s) derived from natural (plant or animal) products
Regulated by	DHSEA, USFDA	CDER, USFDA	CDSCO, GoI
Purpose	Add nutritious value to the daily diet	Treat, cure, or prevent the disease	Treat, cure, or prevent the disease
Criteria	No chemical substance is defined; the addition of chemical products licensed as drugs is prohibited.	Chemical substance or the total phytoconstituents content is defined; licensed as a drug.	A minimum of four phytochemical compounds (one bioactive), is required. No inclusion of synthetic compounds
Mode of Administration	Ingestion or Topical Use Only	Oral, Injectable, Topical, and others	Ingestion or Topical Use Only
Compound(s) Characterization	Limits or range of the compounds/ compounds class/plant extract content should be listed.	Limits or range of the predominant compounds'or phytoconstituents' class content should be listed	Limits or range of a minimum *four* phytochemical compounds should be listed.
Dosage	Defined	Defined	Defined
Adverse effects	Defined	Defined	Defined
Examples	Cholecalciferol, Biotin, etc.	Veregen, Fulyzaq	Not developed yet

Table 2
Clinical evidence of Phytopharmaceutical drugs in Global/India.

S. N.	**Name of the clinical trial**	**Phytopharmaceutical Drugs/its usage**	**Plant origin**	**Scientific/ Industrial Labs involved**	**Type of clinical trial**	**Drug Dosage**	**Conclusive remark of study**	**Reference**
1.	Phase II trial of AQCH to evaluate safety and efficacy in treatment of Covid-19 patients	Purified aqueous extract of *Cocculus hirsutus* (AQCH)/Covid-19 management	*Cocculus hirsutus/*	CSIR-IIIM, collaborated with Sun Pharma –ICGEB	A phase 2, Open-label, Multicenter, Randomized Controlled Trial conducted at eight hospitals in four states (Gujarat, Karnataka, Madhya Pradesh, Maharashtra), in India; n = 210,(Clinical Trials Registry– India: CTRI/ 2020/05/025397).	Randomized (1:1) tablets of purified AQCH 400 mg orally three times a day plus standard of care alone for 10 days (treatment period).	AQCH significantly reduced time to clinical improvement, time to viral clearance, and duration of hospitalization.	(Joglekar et al., 2022)
2.	Development of novel anti-stroke phytopharmaceutical formulation from the roots of a Ashwagandha variety, NMITLI-118	NMITLI 118 variety of *Withania somnifera*/anti-stroke,neuroprotection	Roots of *Withania somnifera*	CSIR-CDRI and CSIR-CIMAP	Development of anti-stroke/neuroprotective Phytophamaceutical as per new Drug and Clinical Trial Rule, 2019 after initial approval; 5/ 258/106/2020/NMITLI	Maximum Tolerated Dose of the standardized extract acute toxicity study in rat will be done up to 2 g/kg.	Study ongoing, once permitted executing clinical trial conduct at KGMU, Lucknow and PGI, Chandigarh.	Data not published yet
3.	*Aegle marmelos* leaf juice as a complementary therapy to control type 2 diabetes – Randomised controlled trial in Gujarat, India	*Aegle marmelos*Leave juice/management of type 2 diabetes	leaf juice	–	Randomized controlled trial in Gujarat, India	Supplementation (20 g/100 ml) for 60 days		(Nigam and Nambiar, 2019)
4.	A novel herbal composition containing extracts of Boswellia serrata gum resin and Aegle marmelos fruit alleviates symptoms of asthma in a placebo controlled double-blind clinical study.	Boswellia serrata gum resin and Aegle marmelos fruit	Gum resin and fruit	–	placebo controlled double-blind clinical study	(AlvioLife®) 200 mg/day of LI13109F (n = 18) or a similar dosage of placebo (n = 18).	Effective intervention for management of mild to moderate asthma such as airway inflammation.	(Yugandhar et al., 2018)

thereof for internal or external use in humans or animals for diagnosis, treatment and palliation. (Gazette of India Notification Number G.S. R.227(E), 2019; Indian Pharmacopoeia Commission, 2022) In 2010, the Department of Ayurveda, Unani, Siddha and Homeopathy (AYUSH) introduced Rule 158(B), which requires proof of effectiveness for licensing of a patent or proprietary herbal phytopharmaceuticals or herbal medicines, laboratory-scale technology for phytopharmaceuticals, demonstrating efficacy in animal models, conducting preclinical studies as per DCG(I)/AYUSH guidelines to establish safety profile and Phase I clinical trials in collaboration with clinical trial centers. In contrast, the regulatory requirements for phytopharmaceuticals in 2015 are under the jurisdiction of the Central Drugs Standards Control Organization (CDSCO). Clinical evidence of the effectiveness and safety of herbal medicines. There are special requirements to ensure the safety and quality of herbal medicines (Fda and Rajiv, & Shaw, 2016; Bhatt, 2016; Katiyar, 2019; Nooreen et al., 2018) (see Fig. 1).

6. Role of Indian Pharmacopoeia to Regulate the Phytopharmaceuticals Drug

Indian Pharmacopoeia Commission (IPC), an autonomous body of Ministry of Health & Family Welfare, Government of India, sets standards for all drugs that are manufactured, sold and consumed in India since 1955. (Ministry of Health and Family welfare, 2023) To date, a

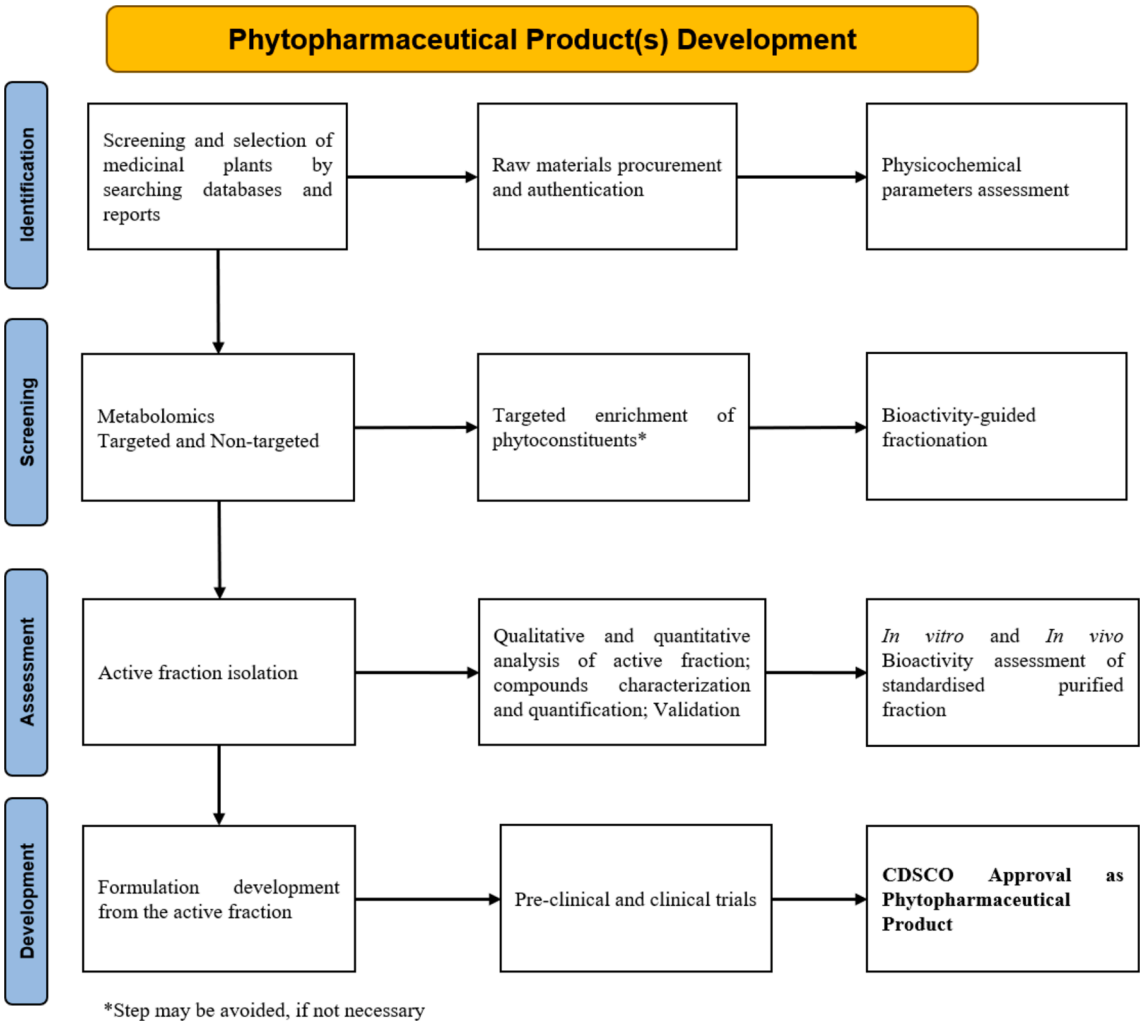

Fig. 1. A detailed process for the development of phytopharmaceutical products.

total of nine editions of the Indian Pharmacopoeia, the recent one (IP-2022) consisting of more than 3000 monographs, including chemicals, vaccines, active pharmaceuticals, vitamins, amino acids, minerals, fatty acids, herbals, and newly added category – *Phytopharmaceutical ingredients*. (Prakash et al., 2017; Rastogi et al., 2022) A recognise fractionation and purification, meeting the requirements of the phytopharmaceutical drug. The purpose of the PPI monographs is to provide scientific information on the quality standards and characterization of a minimum of four of its bioactive/analytical markers to facilitate appropriate maintenance of the standards by the stakeholders. It is to be recognized that the mere inclusion of a monograph for herb or extract, or fraction in IP does not give the status of an approved drug by the drug regulator, and relevant regulations need to be complied with. IP-2022 has launched seven PPI monographs viz., *Aegle marmelos* PPI, *Andrographis paniculata* PPI, *Curcuma longa* PPI, *Gymnema sylvestre* PPI, *Lawsonia inermis* PPI, *Phyllanthus amarus* PPI, and *Silybum marianum* PPI. The commission is still rigorously working on their improvement. In the upcoming IP-2024 addendum, three new monographs viz., *Glycyrrhiza glabra* PPI, *Justicia adhatoda* PPI, and *Zingiber officinale* PPI will be included and the upgradation of *Aegle marmelos* PPI, including the qNMR assay as an optional tool will be included (Supplementary Table 2). The clinical status of *aegle marmelos* is depicted in Table 3. The process of PPI monograph development is outlined in Fig. 2.

Apart from the monograph development, IPC is encouraging several research institutes and industries for the phytopharmaceutical ingredients development. With the help of globally recognized scientists, IPC is making amendments in the PPI monographs to make this user-friendly for the small-scale pharmaceutical industries. Moreover, IPC will be providing the phytopharmaceutical reference materials (PRM) according to the monograph description, which will help in the phytopharmaceutical ingredients development.

Phytopharmaceutical drugs provides freedom to the researchers in the field of drug development from the medicinal plants, by which the phytocompounds which are in minute quantities can also be pursued for the phytopharmaceutical drug development if they show promising bioactivity, resulting to the development of more than one monographs from the same medicinal plant. Thus, IPC will design two types of PPI monographs – *General* and *Advanced* versions. General PPI monographs will define the predominant phytocompounds of the medicinal plant with known biological activities. Their presence is well defined in the medicinal plant along with their biological activities. For example – vasicine and its derivatives present in *Justicia adhatoda* leaves. Whereas, Advanced PPI monographs will be designed on the basis of the purified fraction isolation using BAGF technology, which may or may not be predominant bioactive phytocompounds. For example, cyclic polyols and sugars such as quinic acid, *myo*-inositol, and others, isolated from *Aegle marmelos* leaves. The details of existing as well as upcoming PPI monographs is provided in Supplementary Table 3. In the upcoming section we have tried to explain about one PPI monograph module – *Aegle marmelos* (L.) Correa.

Table 3
Clinical studies on *Aegle Marmelos* plant extracts and their effective drug dosage.

S. No.	Plant parts	Extract/Doses	Usage/Relevance	Clinical trial status/ Type of study	Approval/On-trial of clinical trials	Reference
	Fruit	ethanolic fruit pulp extract	anti-proliferative activity; anti-breast cancer activity; hepato-renal protective effect	Dose-response study	Anugrah Narayan College (A. N. College), Patna, Bihar	(Akhouri et al., 2020)
	Leaves	leaf juice (supplementation (20 g/100 ml) for 60 days	type 2 diabetes	Randomized controlled trial	Veraval, Gir-Somnath, Gujarat, India	(Nigam and Nambiar, 2019)
	Fruit	(AlvioLife®) 200 mg/day of LI13109F (n = 18) or a similar dosage of placebo (n = 18).	Effective intervention for management of mild to moderate asthma, such as airway inflammation.	Placebo-controlled double-blind clinical study	Clinical Pharmacology unit of ASR Academy of Medical Sciences, Eluru, Andhra Pradesh, India	(Yugandhar et al., 2018)
	Fruit	The dose of 7 g fruit pulp powder for 21 days	type 2 diabetes	Phase 3 clinical trial	Bangladesh Institute of Research and Rehabilitation in Diabetes, Endocrine and Metabolic Disorders (BIRDEM), Dhaka, Bangladesh	(Aziz et al., 2021)
	Leaves	dichloromethane (DCM) leaves extract	anti-obesity effect	Observational study	National Institute of Pharmaceutical Education and Research (NIPER), Mohali campus, India.	(Karmase et al., 2013)
	Leaves	Leaves powder	antidiabetic activity	Randomized study	Department of Pharmacy, Higher College of Technology, Sultanate of Oman	(Mohammad et al., 2009)
	Leaves, pulp and seed powder	Leaves, pulp and seed powder	Diabetes	Survey based study	Punjab Agricultural University Hospital and Civil hospital of Ludhiana	(Singh and Kochhar, 2013)
	Leaves	Leaves extract of Aegle Marmelos (300mg/kg).	Diabetes Mellitus	Pre-clinical study	Institute of Molecular Biology andBiotechnology (IMBB), The University of Lahore,Pakistan.	(Kiran Ch et al., 2016)
	Leaves, stem bark and root	dose of trial drug root, stem bark and leaves were taken 50 ml bd after food for 2 weeks and follow up were taken for 2 weeks.	Oedema	Randomized, Parallel Group Trial	OPD AND IPD Dravyaguna dept IPGTRA, GUJARAT	https://ctri.nic.in/Clinicaltrials/pubview.php CTRI/2015/09/006166
	Fruit	Churna	Madhumeha (Diabetes Melitus)	Randomized, Parallel Group, Active Controlled Trial	Govt Ayurvedic College and Hospital Balangir,ORISSA	https://ctri.nic.in/Clinicaltrials/pubview.php CTRI/2022/12/048589
	Fruit	*Aegle Marmelos* oil (26 drops for 21 days), Route- Otic	Tinnitus	randomized double blind clinical trial	Government Ayurved Hospital Vadodara,GUJARAT	https://ctri.nic.in/Clinicaltrials/pubview.php CTRI/2023/07/055314
	Fruit	Aegle Marmelos mother tincture form	clinical practice	Interventional	Jawaharlal Nehru Homoeopathic Medical College and Hospital,GUJARAT	https://ctri.nic.in/Clinicaltrials/pubview.php CTRI/2023/09/058088
	Leaves	Combination of unripe Aegle marmelos and Mangifera indica leaves mouthwash	Anti-microbial	Interventional	Morarji Desai Residential School, KARNATAKA	https://ctri.nic.in/Clinicaltrials/pubview.php CTRI/2024/02/063033
	Leaves	Effect of Bilwa or bael and Spinach based toothpaste	Tooth sensitivity.	Interventional	KAHER's KLE Vishwanath Katti Institute of Dental Sciences, KARNATAKA	https://ctri.nic.in/Clinicaltrials/pubview.php CTRI/2024/05/067196

7. *Aegle marmelos* PPI – An exemplary PPI monograph

Aegle marmelos (L.) Correa (Family: Rutaceae) is known for its various therapeutic activities. *A. marmelos*, commonly known as Bael, Bilva, Bengal quince or Golden-apple Stone-apple, "*Shivadruma*" (Sanskrit – the tree of Lord Shiva), is indigenous to the Indian subcontinent, has spiritual and religious significance in Hinduism. (Neeraj et al., 2017) Its importance is described in our ancient texts – Rig Veda and Charak Samhita. The fruit is known to balance *kapha* and *vaat* dosh. (Bhardwaj and Nandal, 2015; Neeraj et al., 2017) While the leaves (Bilva patra) are known to balance all three doshas and relieve pain, dyspepsia, gastritis, and abdominal colic pain. (Sarkar et al., 2020) Its roots are known to improve digestion, while the stem is efficacious for rheumatoid arthritis and heart disease. (Kaushik et al., 2021; Sarkar et al., 2020) *A. marmelos* fruit powder is known to be one of the necessary items in Ayurvedic formulations. Protective effects against the wound, radiation, microbes, free radical generation, and depression have also been exhibited by *A. marmelos*. (Kumawat et al., 2021; Rahman and Parvin, 2014; Sarkar et al., 2020).

On the basis of the documented therapeutic effects and folklores, this plant is pursued for pharmacological research since decades. The pharmacological and therapeutic properties of *A. marmelos* plant was extensively searched through PRISMA approach (Supplementary Fig. 1). More than 150 literatures, including reports, reviews, and research papers were searched and analysed. Approximately 40 research papers and review articles have reported *in vitro* and *in-vivo* studies conducted on

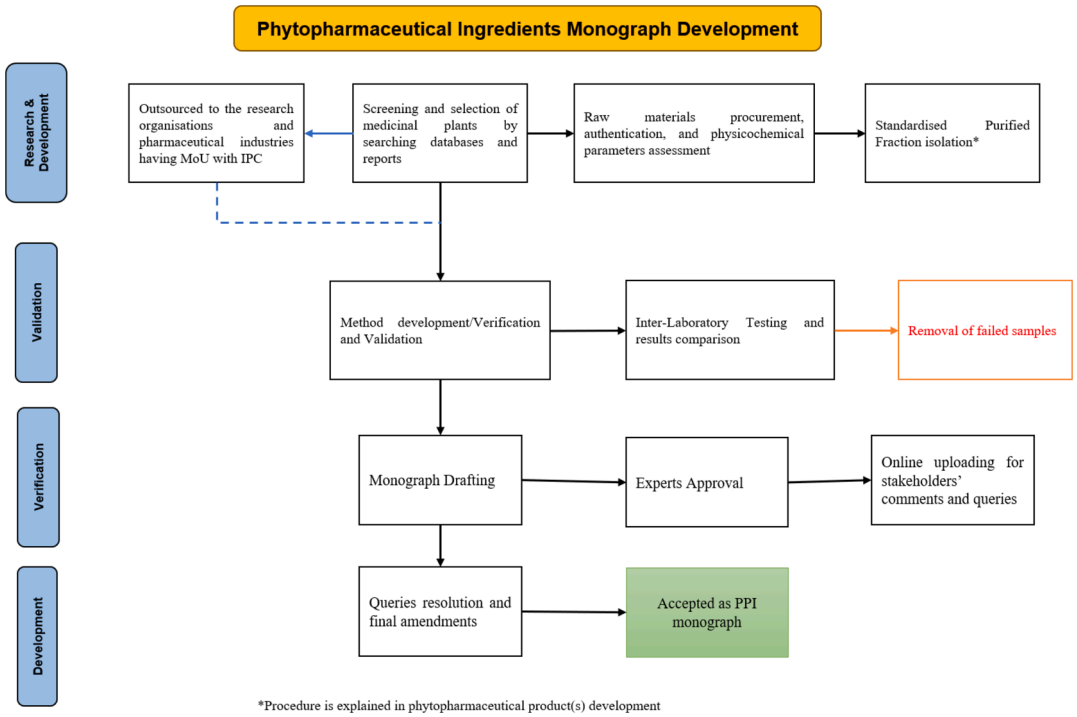

Fig. 2. Phytopharmaceutical Ingredients monographs development procedure.

the different parts of the plant can be found, proving the plant's therapeutic effect. Recent research and clinical studies on the crude extracts of the various plant parts showed the anti-diarrhoeal, antimicrobial, antiviral, chemopreventive, analgesic, anti-ulcerative, anti-diabetic, and anti-inflammatory properties (Supplementary Table 3). Due to its promising therapeutic effect, the plant is extensively used in several herbal formulations. (Jagtap et al., 2004; Rajaram and Vanaja, 2018) Additionally, the U.S. Pharmacopoeia 2023 has included the plant fruit as a dietary supplement (USFDA, 2023).

The genus "*Aegle*" consists only two species – *Aegle marmelos* (L.) Correa, and *Aegle decandra* Fern. Vill. Previously, the latter species was named *Bilacus decandra* Kuntze. However, after extensive verification, it was accepted in the *Aegle* genus on 23rd March 2012. (World Flora Online, 2023) As previously stated, *A. marmelos* is native and cultivated in the Indian Sub-continent, while the other species is confined in Philippines. This dramatically reduces the geographical variation in the plant, thus ideal for PPI development. Moreover, several studies have reported the presence of a variety of phytoconstituents, coumarins as the predominant phytoconstituents such as marmelosin, marmelide, psoralen, alloimperatorin, rutaretin, scopoletin, aegeline, umbelliferone, marmelin, fagarine, marmesin, luvangentin and auroptene (Chaubey and Dubey, 2020; Rahman and Parvin, 2014; Tiwari, Mishra, Danaboina, et al., 2023).

Leaves are known to contain essential oils, alkaloids, terpenes, and other phytoconstituents such as γ-sitosterol, aegelin, lupeol, rutin, marmesinin, β-sitosterol, flavone, glycoside, etc. (Manandhar et al., 1978) Besides these, the leaves are also known to be rich in phenolic compounds, sugars, polyols, and lignans (Mohammed et al., 2016; Govindachari and Premila, 1983; Shoeb et al., 1973).

Therefore, the commission has developed a PPI monograph on *Aegle marmelos* fruit. The present monograph provides a quantitative description of five phytocompounds viz., marmelosin, marmesin, psoralen, scopoletin, and umbelliferone, present in the fruit. The upcoming version includes the three-step processing – crude herb, crude extract, and standardized purified fraction. Apart from the five phytochemical markers, the monograph gives a general direction for the enrichment and purification of the above-mentioned phytocompounds. Moreover, the limit of a negative marker (toxic compound) aegeline has also been included. The five phytocompounds are divided into two groups viz., – major marker compounds and minor marker compounds. The assay of these phytomarkers consists of two methodologies – HPLC and qNMR (an optional tool). The qNMR assay methodology is being introduced first time in the Indian Pharmacopoeial monographs. The upcoming PPI monographs will provide a scaffold to several small-scale industries for the development of phytopharmaceuticals.

The aim of categorizing phytopharmaceutical drugs from the herbal drugs and products is to promote research and innovation in the herbal industries by delineating the stereotypical method of medicine preparation. Therefore, the commission is designing an advanced *Aegle marmelos* PPI monograph using leaves of *A. marmelos*. The data pertinent to developing phytopharmaceuticals ingredient monograph is accessible in Table 4 containng the advancement of computer tools.This monograph will be dedicated to the cyclic polyols and sugars present in the leaves of *A. marmelos*, targeting quinic acid, *myo*-inositol, ferulic acid, and shikimic acid as the principal markers.

8. Recommendation and limitations

Indian Pharmacopoeia Commission is rigorously putting efforts into the promotion of phytopharmaceuticals. (Pandey et al., 2013; Rastogi et al., 2022) The commission is developing the PPI monographs on important medicinal plants, describing the content of principal phytoconstituents with bioactivity, which the pharmaceutical industries can pursue (Danaboina et al., 2023b; Tiwari, Mishra, Kumar, et al.. 2023) With the help of eminent scientists, these monographs are being updated to provide details regarding the significant and minor phytoconstituents in the plant part. The upcoming edition of Indian Pharmacopoeia will also offer the various conventional and modern techniques that can be utilized for plant extraction and general guidance concerning the enrichment of phytoconstituents class from the plant extracts. These tools will come in handy in developing the standardized purified fraction as a phytopharmaceutical ingredient (Tiwari, Mishra, Danaboina, et al., 2023). Complying with the PPI monographs provided in the IP, the commission will soon launch a kit containing the standard botanical

Table 4
Phytopharmaceutical drug: *Aegle marmelos*- multi-componenet drug discovery, combinatory drug discovery and validation via spectroscopic and chromatographic studies.

Aspect	Technique	Description	References
Multi-Component Drug Discovery	Chromatographic Techniques (HPLC, TLC)	Separation and identification of multiple active components from *Aegle marmelos* using techniques like HPLC or TLC.	(Pynam and Dharmesh, 2018)
Combinatorial Drug Discovery	Network Pharmacology and CADD	Exploring the synergistic effects of different phytochemicals in *Aegle marmelos* using network pharmacology and computer-aided drug discovery.	(Shah & Solanki, 2023)
Combinatorial Drug Discovery	Network Pharmacology and CADD	In Silico Analysis of Phytocompounds from Aegle marmelos Against Potential Targets using network pharmacology and computer-aided drug discovery.	(Gopakumar et al., 2023)
Validation through Spectroscopy	UV–Vis, NMR	Validating the chemical structure and composition of the identified components through spectroscopy techniques such as UV–Vis and NMR.	(Tiwari et al., 2020)
Validation through Chromatography	HPTLC, GC–MS	High-Performance Thin-Layer Chromatography and Gas Chromatography-Mass Spectrometry for validating and quantifying the multi-component extracts.	(Fawzi Mahomoodally et al., 2018)
Validation through Computer-Aided Drug Discovery	Molecular Docking	Using molecular docking techniques to predict interactions between *Aegle marmelos* phytochemicals and target proteins.	(Sharma et al., 2022)
Validation through Computer-Aided Drug Discovery	Molecular Docking	Using molecular docking techniques to predict therapeutic activity	(Dr Geetha Jayaprakash et al., 2023)
Validation through Network Pharmacology	Pathway Analysis	Employing network pharmacology to identify the pathways affected by the phytochemicals in *Aegle marmelos* and their potential combinatory therapeutic effects.	(Ibrahim et al., 2022)

reference material (BRM), standardized extract, and standardized purified fraction. These reference materials will fall under Indian Pharmacopoeia Botanical Reference Substances (IPBRS). These standardized kits will help the industries authenticate their phytopharmaceutical preparations in three steps: crude herb identification, extraction, and isolation of the purified fraction.

The major challenge in PPI development is the unavailability of most phytocompounds for standardization. (Garg et al., 2012; Indrayanto, 2022; Zerazion et al., 2016) Most of these natural chemical entities are highly expensive, hence unaffordable for many small-scale pharmaceutical industries. (Indrayanto, 2022; Zerazion et al., 2016) Simultaneous characterization and quantification of four phytocompounds in a plant extract presents significant challenges. As well as the evaluation of all four compounds exhibiting synergy for a particular pharmacological/biological response. IPC has included the qNMR assay for the plant extracts as an additional quantification method, alongside the conventional HPLC assay in the forthcoming IP edition, to address these concerns more effectively. The commission will also propose other robust quantification methods, such as LC-MS/MS and GC–MS technologies, further smoothening the process. In the upcoming time, the commission will make the digital data available as the NMR and MS online library, effectively cutting the cost and time for phytopharmaceutical development. However, pharmaceutical industries will take time to adopt these new technologies over the conventional HPLC assay for compound quantification. Therefore, IPC will establish the "Phytopharmaceutical Reference Standards Repository of Bharat", partnering with other government-aided research institutes isolated from the plants. It strives to standardise pharmacopoeial regulations by forming partnerships and collaborations with reputable organisations, thus facilitating the global expansion of pharmaceutical companies. The establishment of a "Herbovigilence, Phytopharmacovigilance, Pharmacovigilance, and Materiovigilance World Collaborative Centre" is an important initiative aimed at proactively monitoring and controlling adverse effects, marking a significant milestone in advancing the pharmaceutical industry. In line with its objective to elevate the standards of pharmaceutical products globally. IPC renewed its Memorandum of Understanding (MoU) with USP on November 18, 2019. Another MoU was signed with the British Pharmacopoeia on February 18, 2021, to exchange regulatory information on pharmaceutical products. It is a breakthrough for the Indian Pharmaceutical industry that the Pharmacopoeia Discussion Group (PDG) has welcomed the IPC as a participant in the global expansion pilot, which commenced at the virtual PDG Annual Meeting in October 2022. Subsequently, the MoU with USP was renewed on March 14, 2024, to sustain collaborative efforts.

Through persistent endeavours, the Indian Pharmacopoeia has garnered recognition and acceptance in countries such as Afghanistan, Ghana, Nepal, Mauritius, Suriname, Nicaragua, Bhutan, Mozambique, Solomon Islands and Shri Lanka under the Indian Mission, paving the way for the recognition of Indian Pharmacopoeia in countries.

9. Conclusion

The advancement of modern medicines has brought immense benefits to society by playing a pivotal role in combating various infectious diseases. These medications not only relieve symptoms but also work towards eradicating the targeted illnesses. However, in the last fifty years, there has been a noticeable rise in cases of drug-resistant infections and the emergence of significant adverse effects. Consequently, there has been a growing emphasis on harnessing traditional knowledge to prevent and treat diseases. Progress in this field would mark a significant milestone for the global phytopharmaceutical industry.

CRediT authorship contribution statement

Ritu Tiwari: Writing – original draft, Software, Resources, Investigation, Formal analysis, Conceptualization. **Smita Mishra:** Writing – review & editing. **Aishwarya Chauhan:** Writing – review & editing, Methodology. **Poornima Gulati:** Writing – review & editing. **Mahaveer Dhobi:** Investigation, Formal analysis, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jsps.2024.102185.

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