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AN OVERVIEW OF HERBAL FORMULATIONS: FROM PROCESSING TO PHARMACOVIGILANCE

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ABSTRACT: Herbs have been a surviving unit since we were born on this planet. Currently, they are the most probed topic in the food industry or pharmacotherapy due to their multidimensional approach where one herb targets various diseases and proffers a wide range of health benefits. Moreover, some herbal supplements are merchandised globally, and people are devouring these products blithely to extract additional benefits. But taking any herbal formulation under unsupervised conditions may be subject to herbal toxicity. Hence, providing safe herbal supplements is a daunting challenge for various reasons: availability of unstandardized, contaminated, adulterated, loosely available, and unlabeled products, scanty regulations, herb-herb, and herb-drug interaction, and many others. The present article is enriched with past and most recent literature on processing crude herbs, the necessity of standardization of herbal products, the health benefits of standardized herbal medicines, and the toxicity of herbal formulations. The literature has also discussed a case study linked to herbal products, the importance of the pharmacovigilance system, and the challenges associated with the safety monitoring of herbal medicines, as reliable data on these aspects is still lacking. Thus, more investigation is needed for in-depth clarity. This review may provide an instructive insight that no therapeutic agents are free of toxic effects and may be associated with risk and beneficial effects. The article might be helpful for herbal users or other health practitioners and may serve as a stepping stone to promote further research.

INTRODUCTION: Plant-based therapy can contribute to attaining overarching Sustainable Development goal 3 (SDG 3) that, assures healthy lives and encourages the well-being of every individual. Hence, integrating the safe and efficacious herbal medicinal system with the conventional pharmaceutical system could provide additional benefits to construct and strengthen the primary healthcare services.

The survey conducted in Germany illustrated that discontentment with allopathic treatment, a multidimensional or synergistic effect of herbal medicines, traditional use, and individualistic knowledge were some of the key reasons for using herbal medicines among all age groups regardless of an expert consultation.

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Therefore, the government, physicians, pharmaceutical industry and concerned bodies should put some steps to create awareness among herbal users [1]. Emerging outbreaks such as SARS-COV-2 and fungal infection (Mucormycosis) have recently increased the burden on the conventional medication system. Due to this, interest in the domain of Phytotherapy is going under resuscitation to robust the existing healthcare system to counteract the current malicious pandemic. Thus, the inclusion of immunity-modulating herbs, herbal products, and AYUSH formulations in a daily regimen could serve as prophylactic measures. Depending on the traditional knowledge, *in-vivo* and *in-vitro* examination, positive influence, and preceding clinical evidence, the multi-pronged botanical formulations, particularly aqueous extract of Guduchi and pippali (*Tinospora cordifolia* + *Piper longum*), AYUSH 64 and Guduchi aq. extracts are endorsed as a standard code of practice in mild to moderate and asymptomatic COVID -19 patients.

Similarly, aqueous extracts of ashwagandha (*Withania somnifera*) and Guduchi are put forward as prophylactic treatment against COVID-19 [2]. The active compound 'Withaferin A' possibly served as a potential therapeutic vehicle to avert the progression of viral infection [3]. The clinical studies have also devised that ashwagandha root extract is safe to use, but long-term examination and different dosage range needs to be evaluated further [4, 5].

Above all, with the commencement of novel technologies, herbs usage is not limited to drug formulation. However, they could be served as valuable fortificant in the food industry (like in the dairy industry) for the development of functional foods (*i.e.,* dairy products) with enhanced nutraceutical value. Alongside, botanicals incorporation makes fortified foods more appealing and attractive, which paved the way for deploying underutilized herbs [6]. The recent literature has also delineated that merging various herbs in different dairy products eventually revamps their nutritional and therapeutic value. For example, fortification of Labneh (Condensed yogurt), cheese with *Moringa oleifera*, or its extract in varying ratios had improved their antioxidant power, total LAB count, antimicrobial properties, and extended the shelf-life of the products [7, 8]. Even bioactive compounds from botanicals are the pioneering material for nutraceuticals and are widely ingested by the inhabitants to impede the health challenges of the 21st century.

As with the benefits of herbal formulation, some drawbacks are associated with their use and may expose you to various mild to severe health complications, most often liver injury. Many a time, adverse events of herbal medication remain underreported. The underlying rationale behind the adverse events/health risks associated with herbs/herbal formulations is the availability of unstandardized or unlabeled herbal products, contamination with noxious substances, substandard product quality, adulteration or substitution, herb-drug contraindications, presence of inherently toxic compounds and anti-nutritional factors. Further, a lack of knowledge regarding the frequency and duration of taking herbal supplements by self-medicated people or unqualified practitioners has created additional noise on health issues. Therefore, processing, standardization, and characterization of herbal products are imperative for the purity, identification, and quality assurance of herbal ingredients or for producing a more consistent product.

In this regard, the WHO has formulated standard procedures and methods for standardizing herbal medicines. Despite conventional techniques outlined in the WHO document, novel techniques including barcoding, protein chip, metabolomics, genomic fingerprinting, analytical compound examination, spectroscopy and so, on have been arriving in the last decades for the herbs/herbal product standardization [9]. The work in this field is still in a progressive stage to develop a more effective technique to investigate the purity, authenticity and identity of raw herbs more concisely and to manufacture a more consistent phytopharmaceutical drug. Next in a row are ambiguous standards and regulations among different regions of the world, which poses a significant challenge to the herbal supplement's manufacturer to synthesize a standardized herbal product globally. Other challenges include safety monitoring of herbal formulations merchandising globally. Elsewhere, WHO and other concerned regional bodies, namely, ASEAN, European Union

(EU), United States of America (USA), and United Kingdom (UK), are taking collaborative maneuvers to establish a single regulatory framework for the safety, efficacy, and standardization of herbal medicinal product [10].

As per the updated survey on Traditional and Complementary Medicine (T & CM), 124 WHO member states had laws or regulations on herbal medicines. Amongst, few member states have exclusive regulations for herbal medicines. In contrast, others either have partially the same regulations as for conventional pharmaceuticals or the same regulations as for conventional medications. For instance, South Africa and Mexico have the same regulations as conventional pharmaceuticals. Even some countries, such as New Zealand, still have no specific regulatory framework for herbal products. However, these products are regulated via other frameworks, *i.e.*, under Dietary Supplement Regulations 1985 [11].

Further, herbal medicines were categorized under eight possible regulatory categories as of 2012 (*i.e.*, Second survey), namely, prescription medicines, herbal medicines, non-prescription medicines (OTC or self-medication), dietary supplements, functional foods, health foods, general food products, and others [11]. In India, the Department of Ayurveda, Yoga, Unani, Siddha, and Homeopathy (AYUSH) is responsible for regulating herbal medicines, which are governed under the aegis of the Ministry of Health. Later, in 2014 Ministry of AYUSH was established [11].

Herbal medicines in India are sold as prescribed and non-prescribed medicines [11] still, a vast range of herbal products sold in India are not subjected to any clinical trials before being allocated in the market, and a majority of people are taking these herbal supplements regardless of their safety. Therefore, herbal products/medicines should be substantiated as safe, effective, and of acceptable quality before allocating to the public. In recent decades, evidence has been available on herbal therapy's therapeutic effects and clinical efficacy. Still, the new thrust area is investigating the synergy of composite herbal formulation and their interaction with chemical drugs. The main objectives of the current literature underlined processing techniques requisite for manufacturing herbal formulation, the health benefits/clinical efficacy of standardized products, the necessity of standardization, and health risks associated with herb toxicity. The study has also delineated several case reports on herbal supplements/ayurvedic medicines such as slimquick, aloe vera pills, *etc*. In the last section, pharmacovigilance of herbal products is summarized and remarked on its importance in mitigating the adverse events/effects/health risk contributed by any of the attributes of herbal formulations.

Processes Involved in the Preparation of Herbal Formulation: Herbal materials or finished herbal products have already been recognized in international trade and commerce, which upsurges their economic value and significance. Therefore, herbs/herbal products are lucrative for the Indian market. However, a range of adverse effects has been stated to the regulatory authorities regarding the use of herbal formulations, which are usually associated with the abysmal quality of crude material, variability in the source herbal material, inherent toxicity of herbal medicines, and manufacturing and processing factors. Thus, correct identification of source plant species and collecting appropriate parts to prepare herbal products are some of the fundamental steps to assure their safety, quality, and effectiveness [12].

Herbal processing involves post-harvest procedures applied to crude plant materials to produce herbal materials, preparation, and finished herbal products. Post-harvest processing of raw herbs or herbal materials is imperative to assure maximum safety and efficacy and enhance the therapeutic activity and quality of finished herbal products. Therefore, Good Herbal Processing Practices (GHPP), along with Good Agricultural and Collection Practices (GACP) and Good Manufacturing Practices (GMP), have formulated a series of processing methods for the production and manufacturing of herbal medicines [12]. The "processing" of herbal materials encompasses primary and secondary processing, as shown in **Fig. 1**. However, herbal processing may vary from herb to herb.

Hence, specific primary processing includes various simple prerequisite procedures such as washing, cleaning, sorting, size reduction, garbling,

parboiling (blanching), leaching, and drying. In addition to primary processing, a myriad of herbal materials requires "specific processing" prior to direct use as decocting material for the instant therapeutic activity or as starting material for producing finished herbal products. These processes include cutting, sectioning, comminution (fragmentation), sweating/aging, roasting, boiling or steaming, stir-frying, and fumigation. Secondary processing will ensure the purity of raw herbs and ameliorate their therapeutic profile, such as reducing toxicity or improving clinical efficacy [13]. For example, Aconite root is processed either by boiling in water or steaming before consumption as it contains toxic compounds (aconitine and related alkaloids) if taken in its crude form. Research has indicated that decocting *Aconitum* tuber in boiling water reduced the highly toxic metabolic compound diester-diterpenoid alkaloids (*i.e.*, aconitine) into less toxic alkaloid compounds, *i.e.*, benzoylaconine and aconine [14]. "Herbal materials" consist of herbs and other crude botanical ingredients, viz. gums, resins, exudates, and balsams. In contrast "Herbal preparation" are produced when botanical ingredients are subjected to various physical or biological processes such as extraction (in water, alcohol, supercritical CO_2, or other solvents), fractionation, purification, concentration, fermentation, and many other techniques. They can also be formulated by steeping or heating herbal material in alcoholic beverages, honey, or other media. The resulting herbal preparation may contain fragmented or powdered herbal material, extracts, tinctures, essential oils, decoction, expressed plant juices, and cold and hot infusions. From the above concept, herbal material could serve as a starting material, and herbal preparation might be considered an intermediate material for manufacturing finished herbal products or herbal dosage forms for therapeutic use. Finished herbal products contain either one or more herbal preparation formulated from one or more herbs. The products composed of various plant materials are known as "mixture herbal products [15].

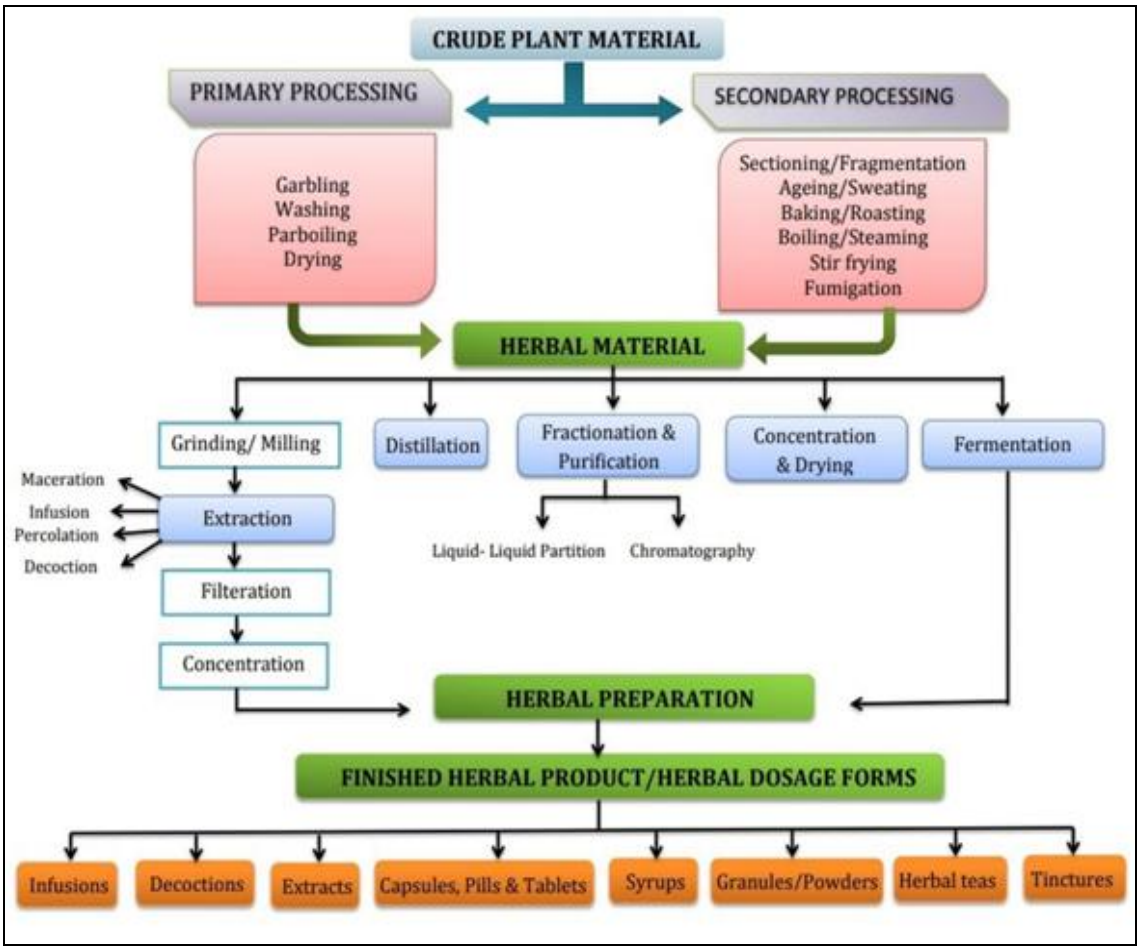

FIG. 1: REPRESENT STEPS INVOLVED IN THE PROCESSING OF HERBS/HERBAL MATERIAL

Standardization of Herbal Formulations: Herbal preparations are extensively available "over the counter," and large chunks of the population are gulping down these herbal preparations without knowing their safety, quality, purity, and clinical efficacy. Standardization and quality control of herbal supplements/products are mandatory before being allocated in the marketplace to circumvent serious health complications. However, unlike synthetic/chemical medicines, specifications and methods to control the quality of final herbal products, especially those containing a mixture of herbs, are much more complex because the quality of finished products depends on the quality of herbal raw material procured [15].

So, for that purpose, WHO has devised four documents that give technical guidance in the critical areas where quality control is necessary for the production of herbal medicines, are as follows: WHO guidelines on good agricultural and collection practices (GACP) for medicinal plants [13], WHO guidelines on assessing the quality of herbal medicines concerning contaminants and residues [16], Good processing practices for herbal materials (in preparation) and Analytical methods for chemical identification of ingredients/ constituents for quality control of herbal medicines [15].

As per European Pharmacopoeia, "standardization means adjusting the herbal substance/herbal preparation to a defined content of a constituent or a group of a constituent with known therapeutic activity respectively either by adding excipients or by blending batches of the herbal substances or herbal preparation like standardized extracts [17].

Even the content of constituents "with known therapeutic activity" in standardized herbal preparation should be specified with the lowest possible tolerance (both upper and lower limits). If powdered herbal substances are standardized, then the quantity of herbal substance or original preparation must be represented as a range according to a prescribed amount of constituents with known therapeutic activity [17]. Standardized herbal substances/ herbal preparations have been prioritized over unstandardized extracts as they ensure the identification "that the herb is what it is claimed to be."

Additionally, herbal medicinal products with a defined content could be considered a prerequisite for clinical trials. Nevertheless, advancements in chemical and biological techniques provide the scientific basis for manufacturers to produce standardized herbal products.

Standardization and quality control of mono- or polyherbal formulation/blend is a very exhausting and arduous job as crude herbs are susceptible to a diverse range of variations because of different factors, primarily, the identity of the botanicals, seasonal variation, geographical location, harvesting time and procedure, method of collection, manufacturing processes (*i.e.*, selection, drying, purification and extraction), genetic variability, diurnal variation, ecological conditions (like insect manifestation, microbial infection), and different parts of the plant. In addition, the factors mentioned above affect the plant materials' chemical composition and therapeutic value, which causes batch-to-batch variation of herbal products [18].

Apart from that, other elements such as adulteration or contamination with microbes, heavy metals, pesticides, and any other foreign agent could alter herbal product quality, safety, and efficacy. Therefore, standardization of herbal products involves a trans-disciplinary approach that is augmented from the birth of the plant to its clinical application or final usage. **Table 1** indicates some standardized herbal products available in the market with their health benefits/clinical efficacy.

TABLE 1: CLINICAL EFFICACY OF STANDARDIZED HERBAL PRODUCTS

Product Name	Herbal Components	Composition	Chemical Components	Clinical efficacy
Neocare Herbal Tea (NHT)	*Alcornea cordifolia* (Christmas bust) *Azadirachta indica* (Neem leaves) *Pteridium acquilinum* (Fern)	25 25 50	NHT possesses high anticholinesterase activity (99.7%) and moderate antioxidant activity (77.43%) along with phenolic properties	The research manifested that the three standardized products viz. NHT, HCT & PHT used in Eastern Nigeria as ethnomedicine exhibited anticholinesterase and antioxidant activities along

Herbalin Complex Tea (HCT)	*Hippocratea volubilis* (Hepocreatea pollens) *Viscum album* *Thymus pulegiodes* (Mother thyme)	50 25 25	HCT extract showed anticholinesterase and antioxidant activities i.e., 73.77% and 82.13% respectively.	with phenolic components. Thus, herbal extracts could be used as neuroprotective and future medicaments for Alzheimer diseases[19]
Phytoblis Herbal Tea (PHT)	*Urtica dioica* (Stinging nettles) *Hippocratea volubilis* (Hepocreatea pollens) *Thymus vulgaris* (Thyme) Aloe vera	25 50 25 25	PHT extract have least anticholinesterase and antioxidant properties but exhibited more total phenolic and total flavonoid content compared to NHT & HCT	
Flucam	*Matricaria Recutita* (Blue Chamomile) *Salvia officinalis* (flowers, leaves of garden sage), *Tuglans regia* (Circassian walnut), *Urtica dioica* (urtica dioica), *Hypericum perforatum* L (St. Johns' wort), *Meslissa officinalis* (Lemon balm), *Glycyrrhiza glabra* (Spanish licorice root), *Lappa officinalis*(burdock), *Taraxacum offlcinale* (milk-govan) and *Quercus robur* (oak bark)	-	It contains tannins and glycyrrhizic acid as the main active components.	The study suggested that Flucam could be recommended as an immunomodulatory drug[20]
Canephron N (containing BNO 2103)	Powdered rosemary leaves (*Rosmarinus officinalis L*), lovage root (*Levisticum officinale Koch*), and centaury herb (*Centaurium erythraea Rafn*)	1:1:1	-	*In-vitro* and *in-vivo* studies showed anti-inflammatory properties that may be due to the suppression of prostaglandin E2 and leukotriene B4 formation[21]
NW Roselle	Roselle calyx (*Hibiscus sabdariffa*), Olive leaves (*Olea europaea*)	300mg 200 mg	-	Clinically effective and safe in reducing hypertension in subjects diagnosed with grade 1 hypertension[22]
Immunostimulant Deep Immune (DI)	*Astragalus membranaceus* (root), *Codonopsis pilosula* (root), *Ganoderma lucidum* (root) *Eleutherococcus senticosus* (fruiting body), *Ligustrum lucidum* (fruit), *Schisandra chinensis* (fruit), *Atractylodes macrocephala* (rhizome) *Glycyrrhiza spp*. (root & Stolon)	50mg/ml 37.5mg/ml 37.5mg/ml 50mg/ml 25 mg/ml 25 mg/ml 25mg/ml 10mg/ml	Triterpenoids (29.85%) and polysaccharides/sugar (15.95%)	*In-vitro* and *in-vivo* studies in TRAMP mice demonstrated that daily intake of DI was found to be effective in preventing the progression of low-risk prostate cancer by significantly suppressing the tumor size with decreased histopathologic scores [23]

The Necessity of Standardization: The modern medicinal system is constructed on specific standards, well-established experimental data, toxicity data, and human clinical trials. While in the case of herbal medicinal products, there is a paucity of unanimous standards, ambiguous regulatory network (*i.e.*, varies from country to country), insufficient evidence on toxicity and a lack of human clinical studies. The dearth of standardization has myriad repercussions, such as variability in the quantity or absolute omission of the known active compound, which is known for its therapeutic activity. Investigation in this field has ventured that many herbal products commonly accessible in the market vary in their chemical constituents when scrutinized quantitatively. For example, *Withania somnifera* (ashwagandha) and ginseng, the herbs merchandised globally, are predisposed to variation in their active or marker compounds. A review study has inspected 507

ginseng products available in the market for authenticity. Amongst various species, *Panax ginseng*, *P. notoginseng* and *P. quinquefolius* are traded globally. All of the ginseng products were procured from 12 countries distributed over six continents. The scrutiny of the chemical and botanical identity of all the ginseng-containing herbal supplements proclaimed that 76% were authentic and 24% were adulterated. Correspondingly, across six continents highest adulteration was seen in South America (100%) and the lowest in Asia (21%), followed by no adulteration in Africa (0%). At the national level, Taiwan ranked highest (49%) in ginseng adulteration, whereas products purchased from the South Korean market were found authentic. Most often, *Panax spp*. labeled on the product were substituted with other *Panax spp*. In many scenarios, the therapeutic part of the ginseng plant (root) was substituted with other plant parts, i.e., flowers, leaves, and stems. One of the main reasons for the intentional adulteration is the price of the ginseng supplement, which varies according to the product's species, quality and purity [24].

The latest study highlighted the variation in the concentration of four different ginsenosides (Rg 18, Rg3, Rs11, and Re7) in ginseng roots procured from different spp. The study showed that the total concentration of ginsenosides was maximum in ginseng harvested from *P. quinquefolius*, *i.e.,* 186 µg/g, *Geumsan*, *i.e.,* 185 µg/g, and White ginseng, *i.e.*,150 µg/g [25].

Thus, many past and current studies have depicted that acquiring superior-quality and authentic ginseng products with proven safety and clinical efficacy is a daunting challenge for both herbal users and health care practitioners. Nevertheless, G115 is a well-characterized and standardized ginseng extract that exists in the market, having well-established clinical data on its safety and efficacy profile [26].

The research has also enlisted a similar variation in commercial ashwagandha products. The authenticity of the root and powder samples of the ashwagandha product purchased from the market was done by DNA barcoding. The results stipulated that 77% of products were authentic while 22% were non-authentic products in powder format, followed by root samples (1%). As observed above, powder samples were more vulnerable to adulteration than root samples [27].

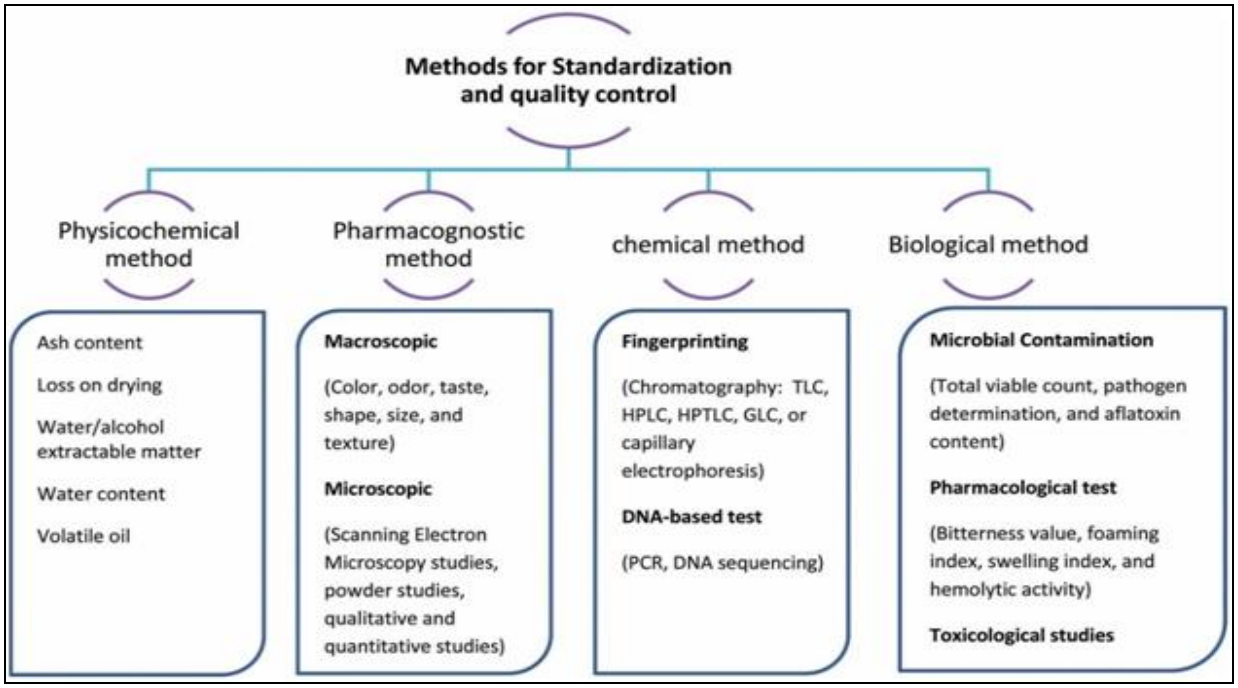

FIG. 2: METHODS OF STANDARDIZATION AND QUALITY CONTROL

Besides, inadequate quality standards have led to numerous adverse events ranging from organ toxicity to death. So, considering the above investigations, standardization and characterization of herbal products must be lined in the process for identity, purity, and quality assurance of herbal

ingredients and the production of a more consistent product. Three pharmacopoeial features desirable for standardization and quality assurance of herbal medicinal products are identity, purity, and assay. First, the identification section assures that the herbal medicine under scrutiny is the one mentioned on the label. It also claims that herbal raw material is authentic. Identification tests are required to confirm herbal medicine's identity, including macroscopic and microscopic evaluation, chemical analysis, DNA-based tests, and fingerprinting [28]. These tests will not fully authenticate the herbal product's chemical composition. However, they expected to offer some degree of assurance or confirmation that it is the one declared on the label. The second attribute, purity, assures that plant raw material is free from adulterants or malicious substances. Finally, the assay section comprises chemical and biological profiling of herbal medicine, where herbs' chemical constituents with known therapeutic activity should be assessed quantitatively. If the chemical component accounted for known therapeutic action is unknown, pharmacopeia may include tests to determine the chemical constituent that serves as the analytical or active marker [28]. The methods used to standardize plant-based products are depicted in **Fig. 2**.

Toxicological Profile of Herbs and Herbal Formulations: Even though 'Nature is curable,' 'nature may be toxic too' because taking any supplement/drug without supervision may turn into mayhem. So, this is the case with the herb *Tinospora cordifolia* (TC, also termed as Giloy or Guduchi), the principal herb for many ayurvedic herbal formulations that have become a part of COVID management protocol due to its immunity-boosting attribute [29].

The current hospital-based observation study outlined the adverse effects of Giloy consumption faced by six patients, particularly drug-induced autoimmune-like hepatitis. Four of six patients ingested boiled extract of Giloy plant twigs, whereas the remaining two consumed it in commercially available tablet and syrup format. All subjects' median interquartile range of taking herbal formulation was 90 days. As per the updated RUCAM score, around four patients had shown possible DILI, and two had a probable drug-induced liver injury. Out of 6 patients, four female patients who experienced chronic liver damage due to Giloy ingestion were also associated with other co-morbidities such as two had type-2 diabetes, and the other two had hypothyroidism [30]. This study highlighted liver injury that may be either due to autoimmune-like hepatitis as a result of Guduchi consumption or due to exposure to the quiescent chronic auto-immune liver disorder. Although TC has many health benefits, it benefitted the mass of people via stimulating immune response even though it activates the auto-immune response. Hence, it is crucial to be cautious about the potential adverse effect of the Guduchi administration [30].

But before formulating any generalization regarding the adversities of Giloy, one should also consider its ingestion by a large community amid a pandemic under supervised or unsupervised conditions [31]. Even sufficient evidence of carcinogenicity in experimental animals averred that few herbs particularly, Aloe vera (Whole leaf extract), goldenseal root powder, *Ginkgo biloba*, kava extract, and pulegone, have been recognized as a possible carcinogen (Group 2B) in humans by the International Agency for Research on Cancer (IARC) [32]. Another example of herb toxicity is aristolochic acids (AA), found in *Aristolochia* plants and were formerly used as an herbal remedy for various ailments, namely, pneumonia, stroke, hepatitis, arthritis, and gout. Hence, AA was extensively used in several herbal products and traditional medicines. But research has delineated inevitable adverse consequences of AA ingestion, particularly kidney failures and urinary tract cancer.

Consequently, IARC considered AA a cancer-causing compound (Group 1) based on substantial evidence. Despite this, it is widely used in regions like China, South Korea, Japan, Southeast Asia, North America, and Europe [33]. Herbs/herbal formulations are more often consumed with pharmaceutical drugs and raise the concern of herb-drug interaction mainly occurring due to alteration in metabolic enzymes or pharmacokinetics of prescribed medication [34]. The research has postulated that induction or inhibition of hepatic cytochrome P450 enzyme and transport or efflux proteins are the two critical pathways involved with

HDIs [35]. Moreover, Huges [36] had reported a case of a 27-year-old man who was found intoxicated after ingesting a lethal amalgam of herb and chemical drug, namely, quetiapine and mitragynine (active component of Kratom plant, *Mitragyna speciosa*). The case has underlined the possible herb-drug interaction posed by the interference of mitragynine with the metabolism or clearance of quetiapine, perhaps due to the inhibitory action of mitragynine on hepatic enzymes *i.e.*, upon different cytochrome P450 enzymes or suppression of P-glycoprotein, a cellular transport protein [37]. Thus, these two pathways (cytochrome P450 enzymes and P-glycoprotein) are associated with the elimination or metabolism of the drug (quetiapine) that may be hindered by concurrent use of mitragynine. Likewise, more cases of polypharmacy came ahead, which directed people's life at risk or may lead to organ injury. For example, *in-vivo* investigation in mice has demonstrated that administration of herb (aqueous extract of aloe vera) and synthetic drug (glimepiride) in combination was found to exert hypoglycemic effects in high intensity in contrast to taking either of two alone. Hence, it was essential to readjust the drug dose and monitor glucose levels to avert hypoglycemia [38]. Thereby, botanicals or their derivatives having specific pharmacological activity shall not be combined with synthetic medicines with the same pharmacological function [39].

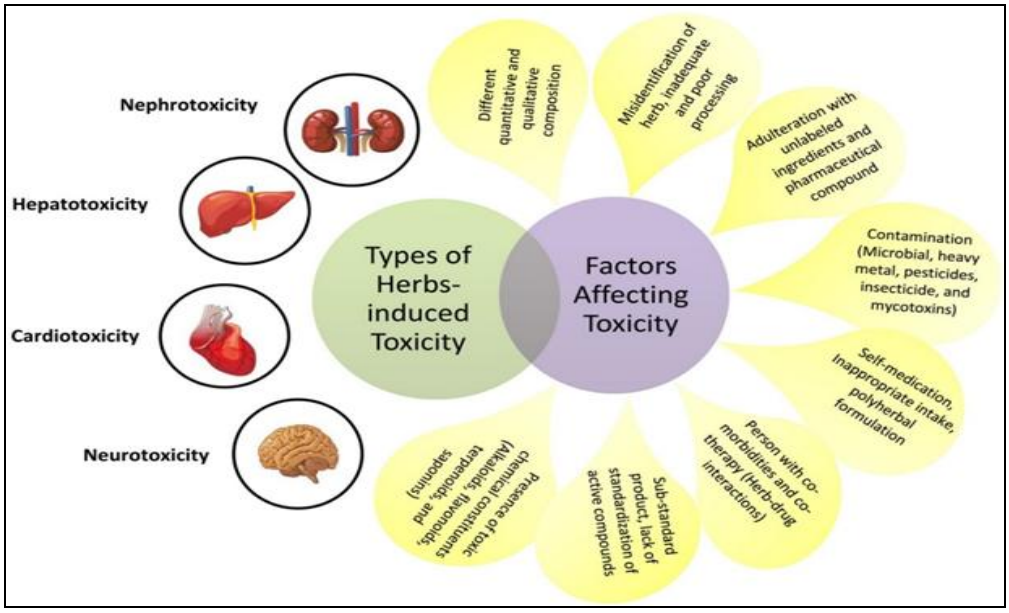

FIG. 3: TYPES OF HERB-INDUCED TOXICITY AND FACTORS AFFECTING IT

Succeeding on a ladder of toxicity is metal toxicity due to ingestion of Ayurvedic and other herbal products now become a public health problem. The study conducted by Mikulski [40] evaluated 252 samples of Ayurvedic medicine for heavy metals and metalloids (Ag, Ba, Cd, Cr, Hg, Ni, Pb, As, and Sb), among them, lead (Pb), mercury (Hg) and arsenic (As) were found in a range 65%, 38% and 32% of the total sample respectively. Lead was the leading element detected in most samples with a maximum concentration of 43200mg/kg, followed by mercury and arsenic with the highest concentration of 279000mg/kg and 44800 mg/kg of samples, respectively. Additionally, metals like Pb, Hg, As and Cd were present in samples at a concentration exceeding the recommended daily intake. Surprisingly, the metal content was varied with the product, even though the same product proffered by the same provider contained varying levels of the same element. This problem may occur due to small producers' production of these Ayurvedic formulations by hand. Hence, issues like product consistency, purity and possible toxicity are often neglected. Moreover, this study has also highlighted the dearth of regulations in the production and purity of Ayurvedic supplements that could cause notable public health concerns. Apart from this, other factors that induce herb toxicity are depicted in **Fig. 3**. Two factors ascribable for the toxicity of herbal medicines are intrinsic and extrinsic; the former includes toxicity that could be caused by active chemical compounds

present in the botanicals. Later toxicity may be caused by erroneous substances such as contaminants and adulterants in the herbal medicines/products. Botanical preparations are responsible for inducing different types of toxicity such as cardiotoxicity, hepatotoxicity, nephrotoxicity, neurotoxicity, skin toxicity and many others. Further, the critical analysis of the enlisted herb-induced toxicities database suggested that the incidence of hepatotoxicity and nephrotoxicity are more frequently dominated. Perhaps these organs (*i.e.,* liver and kidney) are involved in the first-pass metabolism of toxic compounds. In addition, they are major organs included in detoxifying and filtrating drug metabolites or toxic components from the body. **Table 2** underlying below outlined a few studies that indicated adverse events associated with herbal material.

TABLE 2: ADVERSE EVENTS ASSOCIATED WITH HERBAL MATERIAL

Herbs	Toxic Agents	Health risks/ Clinical Symptoms
Tripterygium wilfordii Hook F. (TWHF)	Triptolide	The plant causes acute triptolide-induced hepatotoxicity by accelerating the synthesis of reactive oxygen species, lower depolarization of mitochondria, a decline in ATP generation, mitochondrial fragmentation, and imbalance of mitochondrial dynamics in Lo2 cells [41]
	Celastrol	The active compound responsible for causing cardiotoxicity by suppressing hERG route activity [42]
Averrhoa carambola (Star fruit)	Caramboxin and oxalate	Nephrotoxicity that mainly caused due to blockage of tubules by calcium oxalate crystals. A case report of four patients showed the development of nephropathy in acute and chronic kidney injury after consuming starfruit in varying amounts (i.e., 3-6 fruits). Acute intoxication elicits the most common symptoms: vomiting, abdominal discomfort, backache, nausea, and a decrease in urine volume followed by elevation of serum creatinine level within hours to days[43] A case study where a 43-year-old man presented with acute nephrotoxicity and neurotoxicity within 12 hours or less after consumption of concentrated star fruit juice (consisting of around 20 fruits). However, the man had no history of kidney and neurological disturbance[44]
Gynura japonica	Pyrrolizidine alkaloid (PA)	Causes Herb-induced liver injury (HILI) augmented by hepatic sinusoidal obstruction syndrome, a liver disorder[45]
Ginkgo biloba	Biflavonoids (Sciadopitysin, bilobetin, genkgetin, amentoflavone, and isoginkgetin)	In-vivo study where rats were treated with all bioflavonoid compounds intragastrically (Dosage: 20 mg/kg/day, seven days) indicated acute bioflavonoids-induced nephrotoxicity. Moreover, all five bioflavonoids are perhaps more toxic to the kidney compared to the liver[46]
Evodia rutaecarpa	Evodiamine	Cardiotoxicity due to evodiamine[47]
Datura stramonium (root, seeds or entire plant)	Atropine, hyoscyamine, and scopolamine	A case report stipulated the intoxication of 22 years old male after ingesting datura and experienced symptoms such as tachycardia, urinary retention, and fever[48]
Datura stramonium (seed extract)	-	It causes multiple organ toxicity (i.e., liver, kidney, heart, and brain) as a result of lipid peroxidation that induces oxidative stress in the target organ[49]
Aconitum (Aconite roots and tubers)	Aconitine, and related alkaloids such as monoester diterpene, lipoalkaloid, and dieter dieterpene	Responsible for ventricular tachycardia and cardiac arrest and neurotoxic too because they act on voltage-sensitive sodium channels of the cell membranes of excitable tissues like nerves and muscles[50] A retrospective study reviewed from 2004-2015 in China indicated mortality related to aconite poisoning. The case reports recorded 40 cases of poisoning that caused 53 deaths[51]

In some instances, herbs or herbal products such as aloe vera, *Tinospora cordifolia* are allied with drug-induced liver injury (DILI). However, the underlying mechanisms related to herb-induced liver injury (HILI) are challenging to assess because of the small fractions of reported cases. However, most DILI cases from herbal materials seem idiosyncratic instead of intrinsic type due to the dearth of well-established evidence [52]. Moreover, assessing the etiology of idiosyncratic HILI in humans is arduous because it is sporadic, affects only susceptible people, has rare congruent relation with dosage and is more miscellaneous in its presentation [53, 52]. Nevertheless, systematic

review and meta-analysis evidence had displayed that nearly 79 types of herbs or herbal materials were linked to herb-induced liver injury (HILI). Green tea extract, kava kava, ma huang, senna, aloe vera, *Garcinia cambogia*, *etc*., were frequently used supplements associated with HILI. Additionally, around 82.8% of patients completely recovered from liver injury. On the other hand, nearly 6.6% of cases required transplantation, while 1.5 % and 10.4% of the cases were correlated with chronic liver disease and fatality, respectively [54]. A similar case report also came ahead that was related to herbs usually found in weight-loss dietary supplements, *i.e., Garcinia cambogia*.

TABLE 3: CASE REPORTS OF HERBAL SUPPLEMENTS

Herbal Supplements	Case details	Health risks
Garcinia Cambogia active ingredient in weight loss supplement	Acute liver failure was noticed in a 21-year-old obese female patient after ingestion of weight-loss herbal supplements. The patient was taking a supplement for four weeks and experienced abdominal discomfort for one week coupled with vomiting, fatigue, anorexia, nausea, and myalgias. The laboratory report confirmed that the adverse reactions were due to the ingestion of herbal supplements	Acute Liver failure[57]
Aloe vera pills, juices, tablets, capsules, and gel	A retrospective literature review scrutinized case reports from 2007-2017 on aloe vera toxicity and suggested that possible toxicities were frequently related to the intake of aloe vera medication (in excess amount), juice, gel, tablet, powder and extract. Patients' most common symptoms were nausea, vomiting, abdominal pain, dermatitis, weakness, and fatigue. However, symptoms disappeared upon cessation of the product	Hepatitis, liver failure, acute serositis, hypothyroidism and jaundice[58]
	A female patient aged 68 years old presented with acute liver injury. This may be due to the ingestion of Aloe vera pills for the last several months. Although her past case history unveiled type 2 diabetes managed with metformin, dyslipidemia medicated with rosuvastatin, and hypertension controlled with valsartan but had no case history of liver diseases. So, consumption of Aloe vera pills could be the possible reason, and liver functioning was improved within 51 days upon cessation of *Aloe vera* pills	Acute liver injury[53]
Hydroxycut (fat burner)	A 64-year-old female having a history of cholecystectomy and obesity encountered nausea, abdominal pain and jaundice for one month after taking herbal supplements. The liver biopsy of the patient indicated acute cholestatic and drug-induced liver injury	Acute liver injury[59]
SLIMQUICK (weight loss product)	The prospective study evaluated 1091 cases where six cases were associated with the herbal product (SLIMQUICK) induced liver injury. Three cases were admitted to an emergency department, and one patient went through a liver transplant. But no case of fatality was reported. Here, Green tea extract or its derivative compound catechins was most probably presented in five of six herbal products	Serious acute hepatocellular liver injury[60].
Niao Suan Wan, Chinese proprietary medicinal product	A case study of a 36-year-old man hospitalized due to manifestation of psychiatric disorder after consuming an herbal product. Further interviewing revealed that the man had taken Chinese medicine for gouty arthritis, and within one day, his pain was resolved. Therefore, the patient continued to take that medicine for additional benefits. However, he suddenly experienced florid manic symptoms a week after. The scrutiny of herbal medicine at the National Pharmaceutical Regulatory Authorities (NPRA) of Malaysia pinpointed that the product was earlier examined for adverse effects. The NPRA document has also shown the development of Cushing syndrome in a patient after intake of the same product within two years, and an investigation of the product stipulated the presence of dexamethasone in it	Psychiatric disorder[61]

Certain studies have reported a few complications such as acute hepatitis, hepatic failure, and acute liver injury related to intake of this herb [55]. The case report where a 35-year-old female had consumed *G. cambogia* extract in an amount higher than what was stated and resulted in ocular complications. She had also experienced nausea, headache, and dizziness. Albeit, the symptoms resolved after the cessation of the extract [56]. Therefore, nutritionists or physicians must consult their patients about the possible adverse effects of taking higher doses of the herbal extract. So, herbs or herbal supplements can be your friend if taken sensibly or cautiously. Otherwise, it may turn into a

foe in case of overdosing. Hence, individuals should be vigilant before self-medication with herbal treatment. Numerous other case reports related to the use of herbal supplements are put forth in **Table 3**. Thus, toxicity tests for herbal medicines are conducted for data profiling and safety. Therefore, herbs should be tested exclusively before being included in the research to assess their toxicity. The principal goal of conducting toxicity studies is to retrieve information on the drugs' biological function and mode of action. The facts generated from experiments are used to identify the hazard and manage the risk associated with the drugs. Preclinical studies such as literature review collect information from historical use, pharmacodynamics study, and pharmacological and toxicological test are carried out to examine the safety of the medicinal products. Afterward, clinical examinations are performed to validate the safety and efficacy of traditional herbal medicines. Other cases where clinical studies may be conducted include examining the biological activity of active compounds extracted from herbal medicine to produce a new herbal drug, alter the dosage formulation, or change the delivery passage [62]. The underlying research procedure to assess the safety and efficacy of herbal medicines is elucidated in **Fig. 4**.

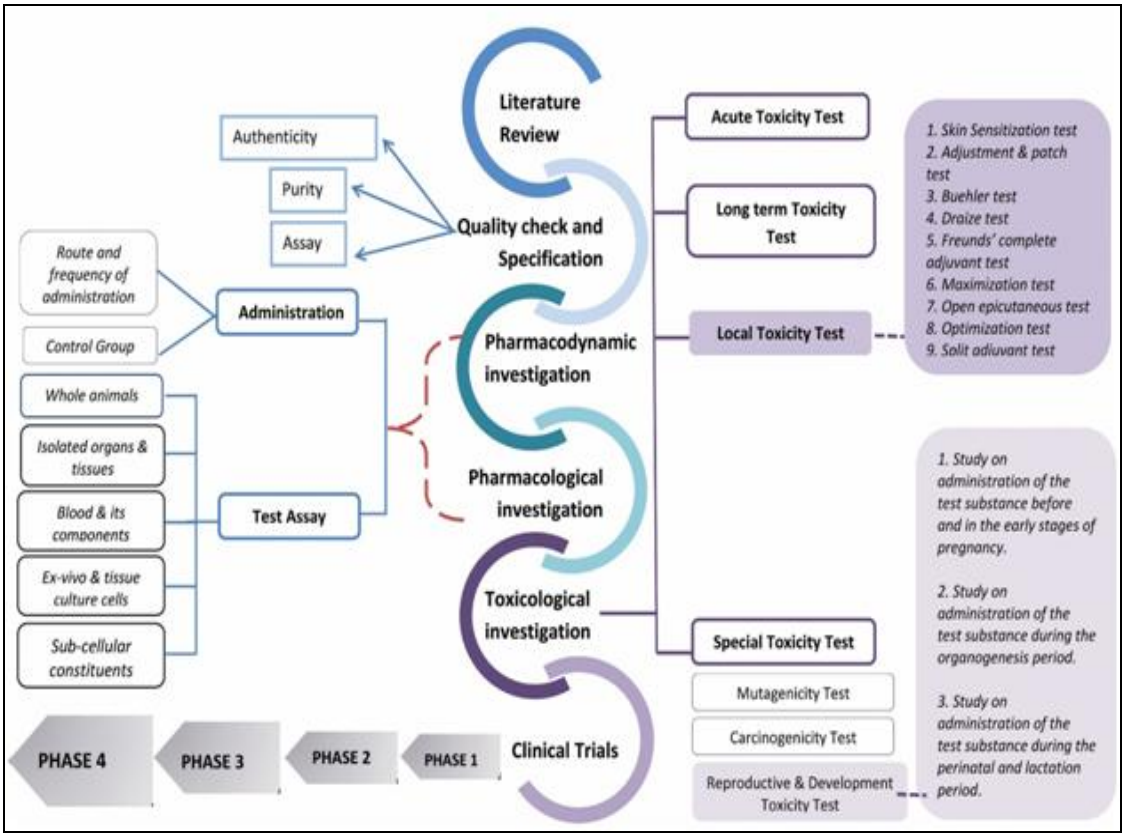

FIG. 4: RESEARCH PROCEDURE TO ASSESS THE SAFETY AND EFFICACY OF HERBAL MEDICINES

Pharmacovigilance of Herbal Formulations: The notion that "Nature is a true healer and safer" is illusionary because certain plants or herbs known for their therapeutic property are inherently toxic in their crude form. Hence, they required specific processing to neutralize their toxic compounds before consumption. Alike all other medicines, drugs, and supplements of botanical origin could also be associated with particular side effects that may be linked to various issues, mainly substandard product quality or inappropriate use. Other associated factors include scanty regulatory measures, ungoverned distribution channels (*i.e.*, *via* E-commerce route), and inadequate quality control systems. Further, the adverse events connected to the below-par quality of products involve adulterating or substituting herbal products with unlabeled ingredients and potent pharmaceutical compounds, for instance, corticosteroids and NSAIDs [63].

Some other incidents may also occur due to erroneous use of incorrect plant species, improper dosing, herb-drug interaction, and use of products defiled with hazardous substances (*e.g.,* heavy metals, pathogenic microorganisms, pesticides, and related agrochemical residues). On that account, the safety of herbal products has become a vital concern for both national health authorities and the community.

Nevertheless, other various problems countered with the use of herbal products are underlying below:

- **Adulteration of Herbal Products:** A study conducted in China where Traditional Chinese medicines (TCM) were assessed for adulteration from 2003-2017 revealed the presence of 166 adulterants in adulterated TCM and herbal products. Amongst investigated products, 158 contaminants were detected in TCM preparations, followed by 43 in herbal supplements, and 35 adulterants were commonly found in both. They can be categorized into three main classes: substitution with non-drug compounds, illegal incorporation of non-drug element/foreign compounds, and addition of pharmaceutical drugs. TCMs primarily susceptible to adulteration belong to the following domain: sexual dysfunction, pain relief, sleep, and rheumatism [64]. Similarly, a study indicated that jamu, an antidiabetic traditional herbal medicine majorly consumed in Indonesia, has been adulterated with the pharmaceutical drug glibenclamide, a member of sulfonylurea. Out of five samples of jamu, a synthetic drug (glibenclamide) was detected in one jamu sample at a level of 1.88 µg/g when analyzed with HPLC [65]. Another study has also illustrated the adulteration of some herbal medicines that aid erectile dysfunction with PDE5 inhibitors (sildenafil) and alpha-blockers. The investigation of 12 herbal products using ambient mass spectrometry showed that three products manifested sildenafil at 0.5% to 18% levels [66].

- **Misidentification and Deceitful Claims of Herbal Products:** In the herbal industry, they are the major drawbacks that require vigilance to prevent or minimize adverse consequences. For example, there are many cases of intoxication reported due to misleading identification of foxgloves (*Digitalis purpurea* L.) with borage (*Borago officinalis L.*) as both the plant resembles and create confusion. Though, borage is consumed as a food ingredient and also a part of Italian dishes in many countries since historical eon. However, mistaken ingestion of foxgloves leads to poisoning and may also be fatal due to cardiac glycoside (probably, digitoxin).

  A case study of female patients aged 55 years old experienced various symptoms like weakness, nausea, vomiting, and fatigue after ingestion of homemade savory pie prepared by leaves procured from botanical taken in a nursery as borage. Later, testing confirmed gitoxin presence could be the possible reason for clinical toxicity instead of digoxin[67].

- **Microbial contamination of Herbal Products:** In many cases, herbal products are perhaps loaded with microbial contaminants. One such instance is outlined in the current update where the FDA has issued an alert statement to buyers and healthcare practitioners regarding the voluntary recall of all the batches of goldenseal root powder due to complaints of bacterial contamination of the product with various pathogens in high amounts [68]. Recently, a microbial contamination case was reported in Nairobi, Kenya, in 86 herbal preparations used to manage chronic diseases. Amongst, 26 herbal products were contaminated with pathogenic bacteria *E. coli, Salmonella spp., and Enterobacteriaceae* family, and overall, 41 products were failed to comply with the British Pharmacopoeia (2019) specifications for microbiological quality [69]. Similarly, many cases of contamination exist in the community, but sometimes they remain underreported. Thus, there is an urgent need for strict regulatory policies on quality assurance of herbal products to protect people from contaminated and defiled herbal medicines [69].

After considering all the adverse drug reactions (ADR) pertaining to the application of herbal medicines or herbal products, there is an underscoring need for a cohesive Pharma-

covigilance system to detect disagreeable reactions and generate authentic information on the safety of herbal products. In this regard, WHO has drafted certain guidelines for the safety monitoring of herb-based supplements/drugs within the existing pharmacovigilance framework.

Pharmacovigilance is the science and actions necessary for detecting, assessing, understanding, and averting adverse events or other plausible drug-related matters. It has broadened its concerns which cover herbals, biological, traditional, and complementary medicines, vaccines, etc. The WHO International Drug Monitoring Program, unified with the WHO Collaborating Centre, the Uppsala Monitoring Centre (UMC), has installed a cogent action plan for pharmacovigilance. This plan of action includes setting up a program to exchange dialogues on safety, maintaining the global WHO database consisting of reports on adverse drug reactions (ADR), and the provision of various guidelines on monitoring the safety of drugs [70]. These guidelines acknowledge the specific challenges in monitoring the safety of herbal drugs or products and suggest strategies to overcome them. The guidelines focused on the reporting system of adverse effects linked to herbal medicines and analysis of the precipitation of the adverse reactions outlined. The action plan also includes training workshops to reinforce the national capacity for safety monitoring of herbal medicines and traditional methods [70].

National pharmacovigilance centers operating under WHO International Drug Monitoring Program are accountable for collecting, processing, and evaluating the case reports of surmised adverse events provided by the clinician or health care practitioners [70]. In contrast, the functioning of national pharmacovigilance is coordinated and facilitated by WHO and UMC.

Additionally, in India, The Ministry of AYUSH is the governing body that tackles the quality issues and safety concerns of Ayurveda, Siddha, Unani, and Homoeopathy (ASU & H) medicines. It has launched a new Central Sector Scheme to strengthen the pharmacovigilance system for ASU & H medication, intending to inculcate the culture of reporting adverse events; manage the monitoring of the safety of AYUS&H drugs, and inspect deceptive claims conveyed by printed and electronic media.

Besides, need for unanimous regulatory standards for the pharmacovigilance of plant-based medicines. The people of this globe should also take collaborative action for the safety monitoring of botanical products. Above all, The Knife-edge of any pharmacovigilance system is dependent on how suspected adverse events are conveyed.

CONCLUSION: Since, our forefathers' era, botanical have been deployed as the first line of treatment to avert several existing or new-emerging diseases and improve humans' overall health. In recent years, advancement in scientific and technological aspects has paved the way to utilize bioactive compounds and their structural analogs as potential pioneering agents for drug discovery [71].

Indeed, herbs have exuberant beneficial effects, but ingesting any therapeutic agent beyond their limit could lead to herbal toxicity. The herb-based complications perhaps arise due to mistaken procurement of the wrong species of medicinal herbs, incorrect dosing, adulteration or substitution, contamination with impecunious substances, unstandardized herbal products, unregulated distribution channels, ineffective quality control systems, and scattered regulatory measures. Beyond that, the most prevalent herb toxicity has been caused due to herb-herb/herb-drug interactions. Therefore, it is always advised not to combine pharmaceutical drugs with herbal medicine as both may exhibit the same pharmacological activity and may eventually cause serious health complications. Nevertheless, as per the current situation, health risks due to herb toxicity require special consideration to protect public health. So, the health risks highlighted in this review taught us a noteworthy lesson that not all the therapeutic compounds taken by people can be pondered fully ‘safe’. Hence, both risk and benefits must be taken into account.

The present literature has also envisaged sufficient data on herb toxicity. However, the data on herb-drug or herb-herb toxicity and the underlying mechanism needs to be investigated, as most liver injury precipitated by herb toxicity is idiosyncratic. Hence, research must be directed to assess the

principal mechanism for herb-induced liver injury or other organ injuries. Scarce human clinical trials, ambiguous regulatory measures, marketing of unstandardized herbal products, and weak pharmacovigilance systems of herbs/supplements/ formulations are perhaps new thrust areas where research is needed further.

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