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Herbal and traditional medicines pharmacovigilance for holistic treatment

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Compared to allopathic medicines or chemically synthesized drugs, there is a growing use of natural compounds and supplements in herbal medicine to treat various diseases as they are safe and devoid of side effects. Though, this is not completely true as many cases of the detrimental impact of herbal or traditional medicine have been reported. Herbal medicines contain unpurified plant portions or extracts which may have these side effects. How effective are the drug molecules derived from natural products, or how destructive are the undesirable compounds that must be investigated? Natural extracts are mixtures of various components, and there is uncertainty about the mechanism of action of certain herbal medicines. There may be a lot of factors involved like placebo effects, and other molecules without which medicine may not work in isolation. In this study, we have reviewed the effects of herbal medicines, possible causes for their benefits like epigenetic changes, adverse drug reactions, and the provision to control these issues. We have also explored the measures being taken at the national and international levels. There have been efforts to minimize the issues related to side effects based on reporting from the population using remedies monitored by pharmacovigilance.

Keywords: Adverse drug reaction (ADR), Epigenetic changes, Natural compounds, Safety issues, Synergistic effects

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Introduction

Herbs are part of the plants which are used for their flavour, fragrance, dietary supplements, and therapeutic purposes. People can obtain them either prescribed by a healthcare provider or over the counter. Nowadays, online purchases in the form of powders, capsules, extracts, dip sachets, and direct parts of the plant in the form of dried or fresh parts are also available. For therapeutic purposes or dietary supplements, people have used a variety of flora present in their geographical conditions for different ailments in the past and made these herbs an integral part of their lifestyle.

The emergence of the allopathic system of medicines has managed many challenging diseases and the use of these medicines has increased many folds, but these chemical-based medicines may have serious consequences like undesirable and unavoidable side effects and their long-term uses may develop some other physiological challenges for the patients.

The World health organization (WHO) has suggested moving towards traditional medicinal practices that primarily involving herbs or plants, or mineral products. These suggestions have inspired most developing countries to explore traditional practices, and recently such practices have increased tremendously. The WHO launched the 13th General Program of Work (GPW13) to ensure healthy lives and promote well-being for all age groups with the help of traditional and complementary medicine[1].

To systematically use these traditional and, complementary medicines, a common concern was felt at an international conference organized by the WHO in 2020. The scientific community's consensus

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was that there should be a collaborative effort to monitor the adverse drug reaction shown by traditional medicines. For this, individual state reporting centres and a global database centre should be set up for the pharmacovigilance of herbal medicines. This information should be used worldwide to strengthen the herbal medicines system.

Recently, the WHO published two documents for the training and practice of Ayurveda in 2022. They outlined the core knowledge involved in the practice and education of Ayurveda, as well as safety concerns about the clinical use and production of its medicines. These documents also offer basic benchmarks for the security and effectiveness of Ayurvedic treatment. The publications will guide national authorities as they build or reinforce regulatory criteria to guarantee competent training and Ayurvedic practice[2,3].

The ancient system of managing a healthy lifestyle and the treatment

The traditional system of medicine (TSM) includes Ayurveda, Siddha, Homeopathy, Unani, Yoga, and Naturopathy[4] (Fig. 1). Ayurveda has been practiced worldwide. Herbs are used commonly in Ayurveda, and it is an ancient system of a healthy lifestyle in India by following natural ways. It is suitable for developing a healthy body to follow natural practices as closely as possible to coordinate with our surroundings. These medicines are effective and offer a lifestyle change to get the maximum benefit for health. Additionally, it has been reported that modern medications are also, derived from herbs like ephedrine, paclitaxel, artemisinin, and aspirin[5]. Unfortunately, there is little preclinical proof to support the safety and effectiveness of most herbal products[6].

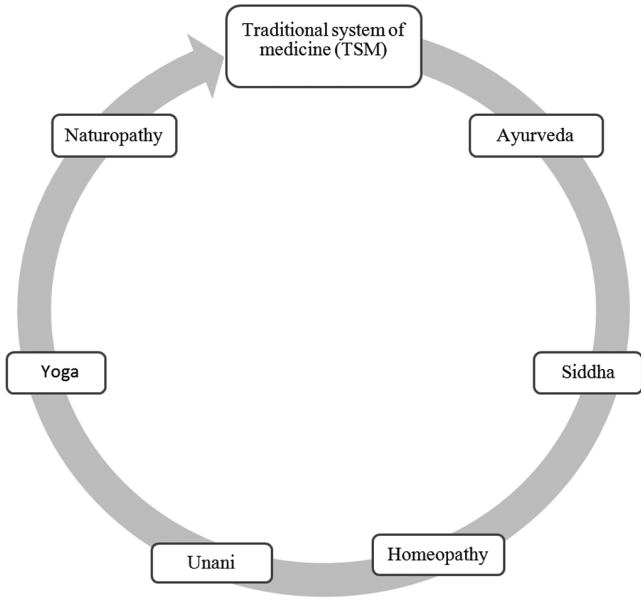

Fig. 1 — Traditional system of medicine followed all over the world.

Food as medicine

A famous saying, "food thy be medicine, and medicine thy be food" means food is not only a source of nutrition, it should also be considered as medicine for better health. For a healthier life, we should take food in such a way that we do not need any other medicine. Various spices and flavouring agents from plants are incorporated into Indian cooking. Like ginger, which is added to impart flavour to food, also improves cardiovascular health by providing antioxidant, anti-inflammatory, and rheumatologic benefits. Garlic helps to regulate cholesterol, improves blood circulation, and has antimicrobial properties. Similarly, ginger is considered for treating gastrointestinal disorders, and helps to minimize cardiovascular diseases and diabetic risks[7]. In a study, natural compounds have been found useful for the treatment of chronic kidney disorder (CKD), which is the outcome of an unhealthy diet or processed food with high content of sugar, salt, and saturated fat and poor in nutrients and fibres; the food products derived from nature are useful in treating the CKD by reducing the oxidative stress, mitigate mitochondrial dysfunction, gut dysbiosis, premature ageing, and epigenetics changes[8].

Cosmetic uses of herbs

In tropical areas where the intensity of sun rays is high, there is increased use of sunscreen to protect skin from the harmful effects of UV rays. Sunscreens having synthetic chemicals are harmful to the skin, while natural compounds used in sunscreen preparations are comparatively safe and are more in demand[9]. Long polymers of chitosan like chitosan hydrochloride, chitosan acetate, chitosan lactate, carboxymethyl chitosan, and quaternized derivatives are useful for the skin care as they are impervious to skin and can be mixed in different formulation for specific uses. Chitosan-based products are used for daily care products like shampoos, hairspray, makeup, nail polish, deodorant, and dental care products[10].

Natural remedies for the treatment of infectious and non-infectious disorders

People from different lineages or age groups have been benefitted from the natural practices for different

health issues like renal lithiasis[11], obesity[12], or inducing labour pain[13]. There are different types of natural compounds obtained from plants that are helpful in treating various disorders. For example, vincristine and vinblastine alkaloid, a heterocyclic compound are used in the treatment of cancer, and flavonoids like quercetin, kaempferol, myricetin, isorhamnetin are other secondary metabolites used for the treatment of cancer and reversing multidrug resistance[14] (Fig. 2). Polyphyllin D; saponin is also useful for the treatment of tumour. A mix of these medicines is also used in combinatorial therapy by combining these drugs in different doses[15]. Terpenes alone or in combination with other natural compounds like cannabinoids help to treat mood disorders and anxiety disorders[16].

Similarly, there are inflammatory disorders caused by immune responses which include humoral secretions for cellular and vascular actions. The inflammatory load can have deleterious effects on health and can cause neurodegenerative diseases, cardiovascular disorders, etc. Terpenes are clearing off the inflammatory molecules produced during inflammation[17].

Synergistic effect of herbal medicines

In certain treatments like cancer treatments, people rely on alternate medicines which can make beneficial or harmful combinations. For example, if ginger is taken as alternative medicine in treating cancer along with crizotinib. This combination may lead to hepatic cytolysis and discontinuation of both brought it back to normal[18].

Warfarin is an anticlotting drug widely present in different food sources like spinach, kale, and broccoli. Excess of these food products can increase the content of warfarin which may have deleterious effects by inhibiting clot formation. Also, certain drugs have negatively impacted health after interaction with warfarin. For example, thymoquinone present in *Nigella sativa* inhibits the warfarin metabolism and when taken together, they can have potential food-drug interactions[19].

Occasionally, a medical practitioner prescribes more than one medicine treating particular ailment which can lead to synergistic effects. In such course of action, the multiple drug molecules can enhance or suppress the effect of other drug molecules or even create unwanted results that may cost severe consequences to the patients[20]. Nowadays, one drug-one symptom or one drug-one symptom or treatment approach is being popularized, which applies to the mono-drug approach. Trials are being done to improve the efficacy of the treatment for disorders like AIDS, cancer, cardiovascular diseases, diabetes, etc. Components, other than drug molecules present in plants, are also being tested for the synergistic effect of holistic treatment. For this, a thorough understanding of the chemical structure of each compound present in the Ayurvedic drugs or products used in traditional medicine systems is necessary to study pharmacokinetically and toxicologically to strengthen this alternative system of medicines.

Effect of natural products on Genes, their regulation, and epigenetic changes

Herbal medicines have an impact on the expression of the gene. It is reported that herbal medicines like Icaritin, a traditional Chinese herbal medicine impact on the treatment of prostate cancer. Icariin regulates the gene expression of the Ubiquitin Conjugating Enzyme (UBE2C) an oncogene in prostate cancer[21]. Also, a correlation has been found in bioinformatic analytical studies that the role of different herbal medicines in the treatment of various diseases like liver disorder, cardiovascular disorders, hypertension, infection and inflammation, malaria, myasthenia gravis, tetanus, alopecia, insomnia, diabetes mellitus, Alzheimer's disease, asthma, cancer, epilepsy[22], and COVID-19[23]. Other than changing gene expression,

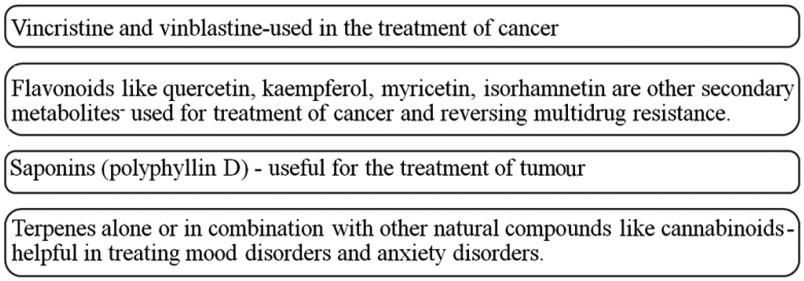

Fig. 2 — Natural compound examples utilized for treatment of different disorders.

post-replication epigenetic modifications like DNA methylation, histone modifications, non-coding RNA, and many others are suggest epigenetic changes as the mechanism of action of traditional medicines. Some phytochemicals like tea, polyphenols, resveratrol, indole-3-carbinol, curcumin, etc., have been researched for their role in causing epigenetic changes[24].

Regulation and quality control issues with herbal medicines

Herbal products' safety is still a mystery. Although it is believed that these items are safe since they have been around for so long. Experts have discovered several safety issues with herbal products. The herbal goods are made from a various plants and each includes hundreds of natural compounds, some of which are also unknown. Few of these compounds have a pharmacological function, while others lack pharmacological efficacy and may possess harmful activities[25,26]. Public health concerns about the safety of herbal medicinal products are becoming more publicly acknowledged as their use around the globe is growing quickly[27]. Even though numerous herbal medications are utilized, some show promising efficacy. Surprisingly, very little is known about their possible side effects, because many of them have not been evaluated, and are not being taken under supervision. Due to this, it is challenging to determine the most reliable and safe therapies to encourage the responsible use of herbal medicine[27]. Furthermore, low quality, improper processing techniques, and supply of inferior/misbranded/adulterated herbal drugs result in unanticipated toxicity of herbal products[28]. In addition, little regulation and information is available on their use, efficacy, and safety. In many nations, the regulatory status of herbal products varies. Typically, the national regulatory system includes qualified suppliers and distributors of the relevant medicines[29]. The national regulatory agencies and the national safety monitoring and/or pharmacovigilance centres frequently do not exchange information on national regulations on herbal medicines[29]. Quality assurance and control procedures, such as national quality requirements and standards for herbal ingredients, good manufacturing practices (GMP) for herbal medicines, labelling, and licensing schemes for manufacture, importation, and marketing, should be in place in any nation that governs herbal medications[27,29]. These steps are essential to ensure the quality and effectiveness of herbal medications. For the safety assessment of herbal medicines, pharmacovigilance must be employed. This is only practicable if herbal goods are subject to regulation to track adverse effects. By establishing GMP standards for production, better regulation can partially alleviate these quality difficulties. Poor quality goods are expected to continue to be a concern since medicinal plants and products come from different nations with varying production standards and implementation of laws[29].

Preparation and formulation of herbal medicine

It is well known that Ayurvedic preparations are nature-based and prepared from herbal or medicinal plants. These Ayurvedic preparations are a mixture of many components in addition to the core drug molecules. These unwanted components may have hidden effects. In addition the different geographical locations, parts of the plant, harvesting time, processing method, storage, etc., can change the scenario of Ayurvedic drugs from the plant sources[28]. The poor-quality control and variations in the preparations from batch to batch may affect the efficacy of the medicines[30]. Natural compounds beneficial for therapeutic purposes can also possess heavy metal ions. These ions pose nephrotoxic risks. For example, different plants like *Artemisia herba-alba*, *Glycyrrhiza glabra*, *Euphorbia paralias*, and *Aloe vera* used for treatments are involved in nephrotoxicity. Heavy metals can seep into natural products depending on the area they are grown and the concentration of heavy metals in the soil for example, dichromate, cadmium, and phenylbutazone present in herbal products cause kidney damage[11].

Health challenges due to inappropriate doses

Due to a common notion that natural products are safe, available online information, globalization, and increasing online shopping trends, there is an increased usage without consultation with a medical practitioner. This may result in inappropriate doses and ineffectiveness of the disease treatments. One must be aware that overdoses can have side effects and underdose will not be effective, creating the impression that the treatment is not working.

Other issues related to adverse reaction

Due to various factors, having the same quality of herbal medicine for all species is not always possible.

Sometimes there are look-alike plants that can be misidentified and cause ineffective treatment or can be toxic as they produce some toxic compounds, and are not available in the expected plant[12].

Caffeine is known to increase endurance and is taken in various means like tea and coffee etc.[31]; caffeine overdose may lead to serious complications like presyncope, agitation, QRS tachycardia, metabolic acidemia, and severe hypokalemia[32]. Spice overdose like myristicin in nutmeg, functions serotonergic, results in psychomimetic symptoms. Ulceration and dermatitis may be caused by exposure to cinnamon oil while inhalation of powder form can result in chronic pulmonary inflammation and fibrosis[33]. A study found that too much garlic can cause problems like heartburn, diarrhoea etc.[34].

Global pharmacovigilance of herbal medicines

Pharmacovigilance monitors and acts in case of adverse reactions related to drugs or medicines in the market (Fig. 3). Different agencies in different countries work in pharmacovigilance. Today, when we have so many communication facilities, we must report the benefits and harmful effects of the treatments given by health practitioners. There are certain portals worldwide where reporting can be done to bring the side effects or adverse reactions. To encourage appropriate monitoring of drugs, the World Health Organization (WHO), US Food and Drug Administration (FDA), and European Medicines Agency (EMA) developed pharmacovigilance laws[29,35,36]. FDA launched a national electronic system named "Sentinel Initiative" in May 2008 to monitor the safety of FDA-regulated products including pharmaceuticals, vaccines, biopharmaceuticals, and healthcare products. Pharmacovigilance of herbal medicine is also a section in the overall pharmacovigilance of medicines. The reports of probable toxic effects and risk factors have grown along with the usage of herbal medications. Such unintended reactions may be caused by i) side effects, typically detectable by pharmacodynamics and frequently predictable; ii) effects resulting from an overdose, tolerance, dependence, and intoxication; iii) allergic reactions; iv) long-term toxic effects, such as renal, cardiac, liver, and neurotoxicity. In addition, it has been reported that there are several possible interactions between herbal remedies and prescription drugs regarding pharmacodynamics and pharmacokinetics. These interactions may have serious adverse effects, including fatal ones[37-39] (Table 1). These interactions rely on several variables, including the patient's characteristics, co-administered medications, place of origin, active constituents, and dose regimens used. Further, controlled research to investigate the interaction of herbal constituents with

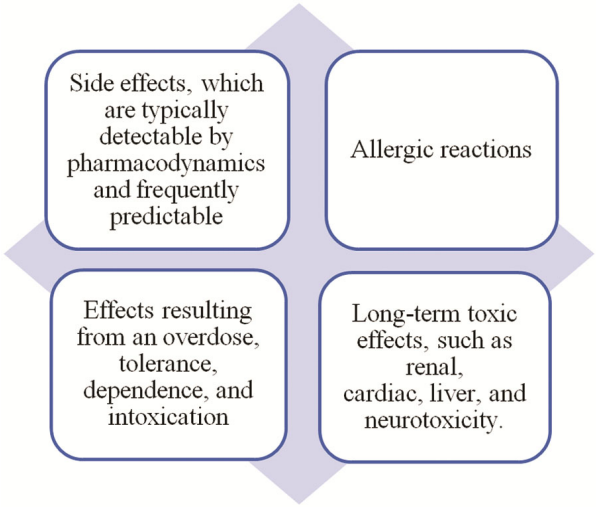

Fig. 3 — Possible adverse drug reactions observed during pharmacovigilance of herbal medicine.

Table 1 — Adverse reaction of the excess consumption of herbal drugs

Name of the compound	Plant source	Dose required	Adverse reaction	Reference
Ephedrine	*Ephedra vulgaris*	5-10 mg IV bolus (Akovaz, Corphedra, Emerphed, generics) 4.7-9.4 mg IV bolus (Rezipres)	Nervousness, anxiety, dizziness, headache, loss of appetite, tachycardia, sweating, vomiting, chest pain and arrhythmia in severe case	12
Ginkgo	*Ginkgo biloba*	60 mg to 240 mg	Interaction with other drugs like Efavirenz (HIV treatment), Ibuprofen	13
Taxol	*Taxus brevifolia*	60 mg of per square meter of body surface area, 4 mg per kg body weight	Gastrointestinal, haematological, musculoskeletal, dermatological, neurological effects	14-16, 17
Aspirin	*Salix* sp.	325 to 650 mg four times a day	Interacts with NSAIDs and blood thinners	8,14
Aloe vera	*Aloe vera*	50-200 mg daily (capsule of gel)	Carcinogenic, genotoxic, hepatotoxic, haemorrhagic, Purgative effects, male infertility and nephrotoxic effects	9

pharmaceuticals and to define the underlying mechanism is required to optimize the use of herbal medicines[37].

Pharmacovigilance is crucial for identifying adverse responses since many herbal medications in the market have not been tested extensively for their pharmacological and toxicological effects[40,41]. WHO started an International Drug Monitoring Program in which almost 70 member states participated to assess adverse events associated with herbal. However the reported effects of these herbal medications by different nations were rare. Furthermore, there is an absence of efficient communication on this issue at all levels, from the global to the local. According to a recent WHO study, around 90 nations regulate herbal products. Even fewer of these countries have policies regulating or validating natural medicine suppliers. Additionally, there are significant differences in legislation among nations, which has a negative impact on the accessibility and distribution of these items internationally[42].

Recently, WHO issued a publication which included interaction issues between herbal medicines and other medicines and the safe and effective use of herbal medicines[3]. Over the past 20 years, it has been well documented through *in vivo*, *in vitro*, and case report studies that herbal medicines can interact with other medications, including conventional medications or other herbs[38]. Several nations have reporting systems for herb-drug interactions, including Morocco, Malaysia, Canada, China, Japan, The United Kingdom, Philippines, South Africa, and New Zealand. In the United States, the FDA's MedWatch program accepts reports of alleged adverse drug reactions to herbal medications (marketed and used as dietary supplements). The "yellow-card scheme" in the United Kingdom reports approximately 20,000 complaints annually of which 100 are related to herbal products. Similarly, Australia has a "blue card scheme"[28].

In China, special treatment is used to cure of various diseases, including cancer, called Traditional Chinese Medicine (TCM). The different natural products or their components used in these medicines work on the principle of imbalances of two opposing energy forces, Ying and Yang. In recent research, it was reported that these medicines have an epigenetic effect. For example, curcumin, a turmeric component used as a spice, is an inhibitor of DNA methylation. It blocks thiolate in DNA methyl transferase and inhibits the expression of certain transcription factors in vitro and in vivo in acute myeloid leukaemia cell line[43]. Tripterygium, is used in TCM for the treatment of rheumatic disease. (5R)-5-hydroxytriptolide, a compound extracted from Tripterygium was tested for its epigenetic effects on transcriptomes like mRNAs and long non-coding RNA, and a clear relationship between the compound and fibroblast-like synoviocytes in rheumatoid arthritis cells was found[43,44]. Different epigenetic changes like DNA methylation, post-translational histone modification, and non-coding RNA functions have been reported to affect the gene expression related to the disorder. In 1989, a pharmacovigilance cell for adverse drug reaction monitoring system was established for monitoring both TCM and western drugs, which monitors the adverse drug reactions based on reporting. Around 10-15% of TCM have been reported to have adverse reactions. This model is still being explored, which requires understanding every aspect of drugs formulated starting from their origin, processing, packaging, storage, and intake during treatment[45]. A network was created in China to assess the effect of herbal medicines in the treatment of different diseases called HERB (High-Throughput Experiment, and Reference-Guided Database with TCM)[46].

In Japan, Traditional Japanese herbal (Kampo) medicines are used to treat many disorders[47]. For instance, for stomatitis and mucositis, a combination of medicines is used like Hangeshashinto, Orengedokuto, Inchinkoto, Orento, Byakkokaninjinto, Juzentaihoto, Hochuekkito, and Shosaikoto is used. The combinations are made to treat the disorder by inhibiting the infection, inflammation, oxidative stress caused by inflammation, and other causes of the disorder [47]. In another study, Orengedoku-to, kakkon-to, were found helpful in post-operative uveitis, and Goshajinki-gan, Hachimijio-gan, keishi-bukuryo-gan Sho, and many other herbs are helpful in Diabetes mellitus related retinopathy[47]. In an incidence in 1990, a Kampo formula Shosaikoto which is the root product of *Bupleurum falcatum* L. was found to be associated with intestinal pneumonia and deaths[48]. Incidences like this created increased awareness due to reporting system. To address these issues, there is a Japanese Adverse Drug Event Report database (JADER database) is maintained by Pharmaceutical and medical devices agencies (PMDA) that collect information related to ADR in medicines including Kampo medicines[49].

In Australia, herbal treatments were not much encouraged after the invasion of Europe. In low-income countries like Africa, there are other challenges faced during pharmacovigilance. There are plenty of local languages, therefore, translating the reports of adverse reactions to the general public is challenging. Administration of drugs at a mass scale is also difficult in these places due to negligence and poor information system[33].

Pharmacovigilance is an essential pillar of the world health organization, and it has member countries all over the world collaborating for common pharmacovigilance including herbal medicines. The problem of identifying the herbs used for medicine preparation has been proposed to resolve through botanical nomenclature instead of vernacular names. Also, sections of the plants and methods for the preparation must be updated. In this direction, the Upsala Monitoring Centre has a traditional medicine monitoring program that encourages reporting for herbal and traditional medicines[50]. The international society of pharmacovigilance is a special interest group that collects data and responds accordingly to adverse reactions to herbal and traditional medicines.

In India, the ancient system of medicine, Ayurveda, multiple herbal products and used for the treatment of a number of disorders since time immemorial. With the increased information technology, adverse reactions have been reported as these medicines are used in India and other Asian and Western countries[51]. To evaluate the side effects of herbal medicinal products and herb-drug interaction, a "herb-vigilance" system must be established within the country. Also, to get relevant data, information from healthcare practitioners and patients must be collected to identify pharmacovigilance indications.

In India, the Indian Pharmacopeia Commission has a special cell for monitoring adverse drug reactions related to herbal medicines and natural products; now, it has been shifted to the All-India Institute of Ayurveda in Delhi. This institute harbours a section where adverse drug reactions caused by herbal medicines can be reported (Fig. 4).

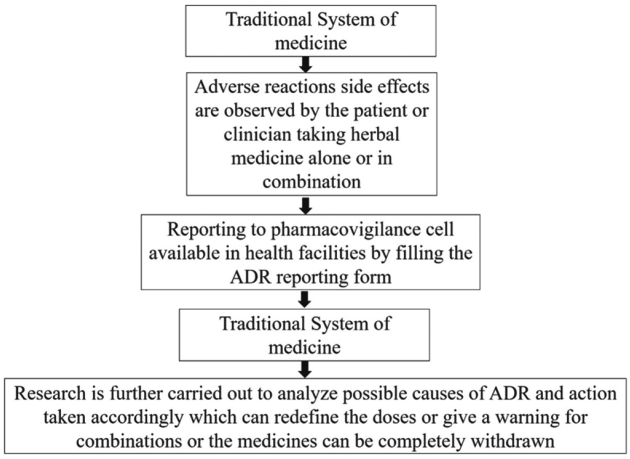

Fig. 4 — Process of pharmacovigilance of herbal medicines (herb -vigilance).

Current challenges and prospects

Today when people are more concerned about their health and are shifting towards natural, herbal, or organic products, there is a growing need for a database to facilitate the collection of information about natural and herbal medicines. It is possible through collaborative efforts only. The information about herbal medicines should be shared as they are locally available and should be utilized for the holistic treatment of the same disorder in other geographical areas. Information sharing through pharmacovigilance must be carried out through the nodal offices in different member countries. It will develop a common consensus about the safer use of medicines.

As we discussed earlier, various factors are involved in adverse drug reactions, unequal distribution of information in different ethnicities, and many obstacles to reporting adverse herbal drug reactions. To overcome these challenges; pharmacovigilance programs should be conducted to train more people from different lineages to spread awareness to the masses, as it will help to handle these health problems.

Conflict of interest

The authors declare no conflict of interest.

References

1 WHO global report on traditional and complementary medicine 2019, https://www.who.int/publications/i/item/978924151536.

2 WHO: WHO benchmarks for the practice of ayurveda https://www.who.int/publications/i/item/9789240042674.

3 WHO: WHO benchmarks for the training of ayurveda https://www.who.int/publications/i/item/9789240042711.

4 Jaiswal Y S and Williams L L, A glimpse of Ayurveda–The forgotten history and principles of Indian traditional medicine, *J Tradit Complement Med*, 2017, **7**(1), 50-53.

5 Yuan H, Ma Q, Ye L and Piao G, The traditional medicine and modern medicine from natural products, *Molecules (Basel, Switzerland)*, 2016, **21**(5). doi: 10.3390/molecules21050559.

6 Bent S, Herbal medicine in the United States: Review of efficacy, safety, and regulation: Grand rounds at University of California, San Francisco medical center, *J Gen Intern Med*, 2008, **23**(6), 854-859.

7 Imo C and Za'aku J S, Medicinal properties of ginger and garlic: A review, *Curr Trends Biomed Eng Biosci*, 2019, **18**, 47-52.

8 Mafra D, Borges N A, Lindholm B, Shiels P G, Evenepoel P, *et al.*, Food as medicine: Targeting the uraemic phenotype in chronic kidney disease, *Nat Rev Nephrol*, 2021, **17**(3), 153-171.

9 Morocho-Jácome A L, Freire T B, de Oliveira A C, de Almeida T S, Rosado C, *et al.*, *In vivo* SPF from multifunctional sunscreen systems developed with natural compounds- A review, *J Cosmet Dermatol,* 2021, **20**(3), 729-737.

10 Morin-Crini N, Lichtfouse E, Torri G and Crini G, Applications of chitosan in food, pharmaceuticals, medicine, cosmetics, agriculture, textiles, pulp and paper, biotechnology, and environmental chemistry, *Environ Chem Lett*, 2019, **17**(4), 1667-1692.

11 González A F, Pieters L and Hernández R D, Effectiveness of herbal medicine in renal lithiasis: A review, *Siriraj Med J*, 2020, **72**(2), 188-194.

12 Maunder A, Bessell E, Lauche R, Adams J, Sainsbury A, *et al.*, Effectiveness of herbal medicines for weight loss: A systematic review and meta-analysis of randomized controlled trials, *Diabetes*, *Obes Metab*, 2020, **22**(6), 891-903.

13 Zamawe C, King C, Jennings H M, Mandiwa C and Fottrell E, Effectiveness and safety of herbal medicines for induction of labour: A systematic review and meta-analysis, *BMJ Open*, 2018, **8**(10), e022499.

14 Kopustinskiene D M, Jakstas V, Savickas A and Bernatoniene J, Flavonoids as anticancer agents, *Nutrients*, 2020, **12**(2), 457.

15 Choudhari A S, Mandave P C, Deshpande M, Ranjekar P and Prakash O, Phytochemicals in cancer treatment: From preclinical studies to clinical practice, *Front Pharmacol*, 2020, **10**, 1614.

16 Ferber S G, Namdar D, Hen-Shoval D, Eger G, Koltai H, *et al.*, The "entourage effect": terpenes coupled with cannabinoids for the treatment of mood disorders and anxiety disorders, *Curr Neuropharmacol*, 2020, **18**(2), 87-96.

17 Prado-Audelo D, Luisa M, Cortés H, Caballero-Florán I H, González-Torres M, *et al.*, Therapeutic applications of terpenes on inflammatory diseases, *Front Pharmacol*, 2021, **12**, 2114.

18 Revol B, Gautier-Veyret E, Arrivé C, Fouilhé Sam-Laï N, McLeer-Florin A, *et al.*, Pharmacokinetic herb-drug interaction between ginger and crizotinib, *Brit J Clin Pharmacol*, 2020, **86**(9), 1892-1893.

19 Wang Z, Wang Z, Wang X, Lv X, Yin H, *et al.*, Potential food-drug interaction risk of thymoquinone with warfarin, *Chem-Biol Interact*, 2022, **365**, 110070.

20 Zhou X, Seto S W, Chang D, Kiat H, Razmovski-Naumovski V, *et al.*, Synergistic effects of Chinese herbal medicine: A comprehensive review of methodology and current research, *Front Pharmacol*, 2016, **7**, 201.

21 Hu J, Wu X, Yang C, Rashid K, Ma C, *et al.*, Anticancer effect of icaritin on prostate cancer via regulating miR-381-3p and its target gene UBE2C, *Cancer Med*, 2019, **8**(18), 7833-7845.

22 Med J A H, In-silico studies in herbal drugs: A review, *J Ayu Herb Med*, 2018, **4**(1), 43-47.

23 Yuan H, Ma Q, Ye L and Piao G, The traditional medicine and modern medicine from natural products, *Molecules (Basel, Switzerland)*, 2016, **21**(5), 559.

24 Khan T, Ali M, Khan A, Nisar P, Jan S A, *et al.*, Anticancer plants: A review of the active phytochemicals, applications in animal models, and regulatory aspects, *Biomolecules*, 2019, **10**(1), 47.

25 Boullata J I and Nace A M, Safety issues with herbal medicine, *Pharmacother: J Human Pharmacol Drug Ther*, 2000, **20**(3), 257-269.

26 George P, Concerns regarding the safety and toxicity of medicinal plants-An overview, *J Appl Pharm Sci*, 2011, **1**(6), 40-44.

27 Ekor M, The growing use of herbal medicines: Issues relating to adverse reactions and challenges in monitoring safety, *Front Pharmacol*, 2014, **4**, 177.

28 Shaw D, Graeme L, Pierre D, Elizabeth W and Kelvin C, Pharmacovigilance of herbal medicine, *J Ethnopharmacol*, 2012, **140**(3), 513-518.

29 World Health Organization. WHO guidelines on safety monitoring of herbal medicines in pharmacovigilance systems, 2004.

30 Muyumba N, Mutombo S, Sheridan H, Nachtergael A and Duez P, Quality control of herbal drugs and preparations: The methods of analysis, their relevance and applications, *Talanta Open*, 2021, **4**, 100070.

31 Lara B, Ruiz-Moreno C, Salinero J J and Del Coso J, Time course of tolerance to the performance benefits of caffeine, *PLoS One*, 2019, **14**(1), e0210275.

32 Andrade A, Sousa C, Pedro M and Fernandes M, Dangerous mistake: An accidental caffeine overdose, *Case Rep*, 2018, **2018**, bcr-2018-224185.

33 Johnson-Arbor K and Smolinske S, Stoned on spices: A mini-review of three commonly abused household spices, *Clin Toxicol*, 2021, **59**(2), 101-105.

34 Banerjee S K, Mukherjee P K, Maulik S K, Garlic as an antioxidant: The good, the bad and the ugly, *Phytother Res*, 2003, **17**(2), 97-106.

35 FDA's Sentinel Initiative. https://www.fda.gov/safety/fdas-sentinel-initiative.

36 Directive 2010/84/eu of the european parliament and of the council. https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2010:348:0074:0099:EN:PDF.

37 Shi S and Klotz U, Drug interactions with herbal medicines, *Clin Pharmacokinet*, 2012, **51**(2), 77-104.

38 Izzo A A and Ernst E, Interactions between herbal medicines and prescribed drugs, *Drugs*, 2001, **61**(15), 2163-2175.

39 Izzo A A and Ernst E, Interactions between herbal medicines and prescribed drugs: An updated systematic review, *Drugs*, 2009, **69**(13), 1777-1798.

40 Shaw D, Toxicological risks of Chinese herbs, *Planta Medica,* 2010, **76**(17), 2012-2018.

41 Rodrigues E and Barnes J, Pharmacovigilance of herbal medicines, *Drug Saf*, 2013, **36**(1), 1-12.

42 General guidelines for methodologies on research and evaluation of traditional medicine, Geneva: World Health Organization, 2000.

43 Yu J, Peng Y, Wu L-C, Xie Z, Deng Y, *et al.*, Curcumin down-regulates DNA methyltransferase 1 and plays an anti-leukemic role in acute myeloid leukemia, *PloS One*, 2013, **8**(2), e55934.

44 Guo S, Liu J, Jiang T, Lee D, Wang R, *et al.*, (5R)-5-Hydroxytriptolide (LLDT-8) induces substantial epigenetic mediated immune response network changes in fibroblast-like synoviocytes from rheumatoid arthritis patients, *Sci Rep*, 2019, **9**(1), 1-11.

45 Zhang L, Yan J, Liu X, Ye Z, Yang X, *et al.*, Pharmacovigilance practice and risk control of traditional chinese medicine drugs in China: Current status and future perspective, *J Ethnopharmacol*, 2012, **140**(3), 519-525.

46 Fang S, Dong L, Liu L, Guo J, Zhao L, *et al.*, HERB: A high-throughput experiment-and reference-guided database of traditional Chinese medicine, *Nucleic Acids Res*, 2021, **49**(D1), D1197-D1206.

47 Hayasaka S, Kodama T and Ohira A, Traditional Japanese herbal (kampo) medicines and treatment of ocular diseases: A review, *Am J Chinese Med*, 2012, **40**(05), 887-904.

48 Teng L, Pharmacovigilance for herbal and traditional medicines in Japan, In *Pharmacovigilance for Herbal and Traditional Medicines*, (Springer), 2022, 371-383.

49 Arai I, Harada Y, Koda H, Tsutani K, Motoo Y J T, *et al.*, Estimated incidence per population of adverse drug reactions to Kampo medicines from the Japanese adverse drug event report database (JADER), *Tradit Kampo Med*, 2020, **7**(1), 3-16.

50 Barnes J, The International society of pharmacovigilance (ISoP) special interest group on herbal and traditional medicines: Towards progress in pharmacovigilance for herbal and traditional medicines and other “Natural Health” Products, *Drug Saf*, 2020, **43**(7), 619-622.

51 Wal A, Wal P, Gupta S, Sharma G and Rai A, Pharmacovigilance of herbal products in India, *J Young Pharm*, 2011, **3**(3), 256-258.