

The pharmacovigilance of complementary medicines: unpacking the complexities

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Abstract

Complementary medicines in South Africa are defined as substances originating from natural sources such as plants, fungi, and minerals, intended to support physical or mental well-being. Unlike allopathic medicines, which are pure chemical compounds requiring registration through rigorous safety and efficacy dossiers, complementary medicines can be registered without such evidence. While allopathic medicines are backed by clinical trials, complementary medicines, especially herbal products, often lack robust clinical data. This disparity highlights the importance of pharmacovigilance (PV) to monitor adverse reactions (ADRs) and potential interactions in complementary medicines.

Complementary herbal medicines (Category D) fall within the regulatory ambit of the South African Health Products Regulatory Authority (SAHPRA), under the Medicines and Related Substances Act 101 of 1965. These products, however, are challenging to regulate due to variability in constituency, batch-to-batch inconsistencies, and a lack of clinical trial evidence. Herbal medicines, composed of multiple active compounds, are particularly complex, with potential synergistic or antagonistic interactions with conventional medicines complicating their safety profiles. Despite their widespread use, adverse drug reactions (ADRs) from herbal products remain undetected and underreported, often due to a lack of standardisation, insufficient clinical studies, and health illiteracy among consumers.

This paper proposes a methodology for investigating ADRs from complementary medicines, including understanding the formulation, clinical presentation, and phytochemical composition. By improving pharmacovigilance practices and fostering greater collaboration among experts, a more comprehensive safety profile for herbal-based medicines can be developed, ultimately benefiting public health.

Keywords: complementary medicines, pharmacovigilance, regulatory

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Introduction

Complementary medicines, as seen within a South African regulatory modality, are seen as “substance or mixture that originates from plants, fungi, algae, seaweeds, mineral, animal or other sources, to maintain or assist in a physical or mental state”.¹ According to the South African Health Product Regulatory Authority (SAHPRA), a complementary medicine may only make health claims based on the ingredient/supplement used in the product and can be submitted to SAHPRA for registration without the need for a dossier.² In contrast, an allopathic (or recognised) medicine, however, is a pure chemical compound, with a known effect on the body, typically described in monographs such as those found in the British Pharmacopoeia (BP) or the United States Pharmacopoeia (USP).³ Allopathic medicines must be registered with SAHPRA through a dossier submission, which includes evidence of proven efficacy and safety based on their intended use.⁴ Safety data are crucial for both complementary and allopathic medicines to evaluate risk-benefit ratios as well as to understand potential side-effects, adverse interactions with other medications and toxicity.⁵ For allopathic medicines, this safety data is typically derived from large-scale clinical trials; however, such comprehensive efficacy data are often lacking for complementary medicines, especially herbal products, as many have not undergone clinical trials.⁶

In the South African regulatory framework, complementary medicines and Schedule 0 medicines are distinct yet overlapping categories. These products can fall under different schedules depending on their active ingredients. In contrast, Schedule 0 medicines are low-risk, over-the-counter (OTC) drugs that do not require a prescription and can be sold in supermarkets, pharmacies, and other general retail outlets. While some complementary medicines may be classified as Schedule 0, not all Schedule 0 medicines are complementary. The key difference lies in their purpose and classification—complementary medicines are defined by their alternative health approach, while Schedule 0 is a regulatory category for freely available, low-risk medicines.

As an integral part of post-marketing surveillance, pharmacovigilance (PV) plays a vital role in understanding how medicines act and benefit diverse populations.⁷ Medicine safety is multifaceted, relying on several factors, including pharmacological characteristics, known interactions identified during clinical trials, adherence to prescribed use and maintaining the quality of the product prior to public release.⁸ Pharmacovigilance is already a time-intensive process for just single-ingredient medicines, and this complexity increases with medicines containing multiple active ingredients. However, many of these medicines are included in pharmacopoeia's, which provide clinical trial data to inform their use and possible side-effects.^{9,10}

In contrast, herbal and complementary medicines, despite their widespread use, often lack clinical data to fully understand their mechanisms and side-effects, making post-marketing surveillance essential.¹¹

South African Legal and Regulatory Framework

Under the Medicines and Related Substances Act (Act 101 of 1965), SAHPRA is mandated to regulate, “monitor, evaluate, investigate, inspect, register and review” all medicinal and health products in South Africa.¹²

Since 2020, as part of its regulatory mandate, SAHPRA has been implementing regulations for the registration of complementary medicines.¹³ Complementary medicines are classified under category D of the Medicines and Related Substances Act, 1965 (Act 101 of 1965) as amended. These products are defined as “any substance or mixture originating from plants, fungi, algae, seaweeds, lichens, minerals, animals, or other sources as determined by the Council”. Category D medicines are intended for: “maintaining, complementing, or assisting innate healing powers or physical/mental states, or diagnosing, treating, mitigating, modifying, alleviating, or preventing disease, illness, or their symptoms in humans or animals”.

SAHPRA recognises six main disciplines within complementary medicine: Aromatherapy, Ayurveda, Homeopathy, Traditional Chinese Medicine, Unani Medicine (Unani-Tibb), and Western Herbal Medicine. This regulatory shift has increased the need for regular monitoring of adverse events and potential interactions associated with complementary medicines.

The complex nature of herbal medicines

Herbal extracts and powders can contain hundreds of active compounds in varying concentrations (batch-to-batch inconsistencies), with one or more “active” compounds contributing to the plant’s therapeutic effects.¹⁴ However, the concentration of these active compounds can vary significantly between batches due to factors like rainfall, temperature, fertiliser and pesticide use.^{10,15–18} While many commercially available herbal active pharmaceutical ingredients (APIs) are standardised against certain quantifiable secondary metabolites (e.g. saponins, quercetin), this does not fully account for the complexity of the secondary phytochemicals present.¹⁹ These secondary metabolites can also influence how plant extracts exert their physiological effects. Variability in raw material composition and phytochemical concentration, due to different sourcing locations, can either enhance or diminish these effects.²⁰ Various studies have shown that geographical location affects key constituents as well as efficacy of APIs in herbal medicines.^{21–24} This variability impacts the quality of the API, with other contributing factors including chemical inconsistencies, improper storage and handling methods, and the presence of constituents and adulterants.^{25–27} This calls for more stringent quality control in the handling of plant species, to ensure a more consistent batch-to-batch phytochemical mixture.

The complexity of plant materials and their extracts arises from the fact that a single plant species can contain constituents with both synergistic and antagonistic effects.^{28,29} In studies where plant material was fractionated (using liquid chromatography) and the complex matrix broken down, differences in activities between fractions were observed. For example, in *Croton betaseus*, the minimum inhibitory concentration required for pathogenic *Streptococcus mutans* was 100 mg/mL for the crude extract and only 1 mg/mL for the hexane fraction.³⁰ Similarly, in *Corbus domestica*, a wild tree grown for its fruit, a synergistic relationship between quercetin and chlorogenic acid was observed at a constant ratio of 4:1, indicating a ratio-dependent synergism between these phytochemicals.³¹ However, when flavonoids myricetin and quercetin were combined, they produced an antagonistic effect in antioxidant assays, despite both being known antioxidants when used individually.³²

The physiological effect of an herbal mixture or extract is often not due to a single constituent, but rather the interplay of various phytochemicals in the matrix.²⁸ While a multitarget approach to healthcare can be beneficial with herbal mixtures, more constituents do not necessarily lead to a greater effect.^{33–34} Known interactions exist for some commonly used medicinal plants such as St. John’s Wort, *Ginkgo biloba* and *Echinacea*; despite this, interactions of herbal medicines with allopathic medicines are still underreported.^{20–35}

Investigating adverse reactions

An adverse drug reaction (ADR) is an unintended and harmful reaction to a medication, which can include lack of efficacy or toxicity at dosages typically administered to humans. Overdosing, mishandling, or misuse of a medication can also result in an ADR. The reaction may be a new, unrecognised side-effect, or a known one. Any therapeutic agent, including excipients, whether prescribed or over the counter (OTC), has the potential to produce an ADR. Reporting such negative consequences is essential.³⁶ A presumed causal relationship between the medicine and the reaction, as established by the reporter or a reviewing healthcare professional, distinguishes a reaction from an incident.³⁷

Investigating an ADR is a complex challenge, as many factors, such as dose, time to reaction, age and concurrent medicines, can contribute to the presentation of an ADR.³⁸ There is concept of “minimum information” includes gathering the product name, batch number, patient biological sex of the patient and the details of the ADR itself, as well as additional information outlined in the steps below as per the SAHPRA guideline (<https://www.sahpra.org.za/news-and-updates/guideline-for-adverse-drug-reactions-adrs-reporting-for-healthcare-professionals/>). Report all information via the SAHPRA MedSafety App (<https://medsafety.sahpra.org.za/>) or Online Form (<https://primaryreporting.who-umc.org/za>).

The process for reporting and investigating ADRs is well-defined according to the guidelines; however, with CMs, there are several barriers to understanding the reaction and ensuring accurate dissemination of information.

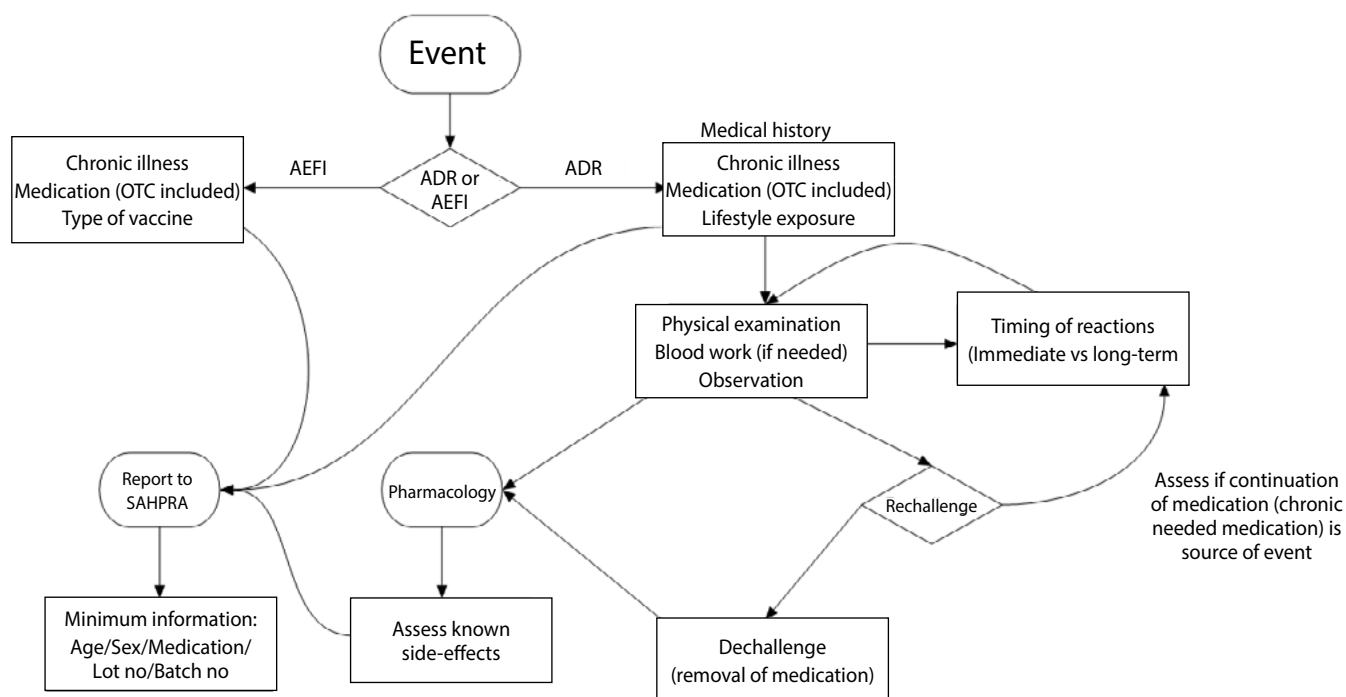


Figure 1: Overall processes involved in adverse drug reactions (ADRs) and adverse events following immunisation (AEFI) investigations. OTC: over-the-counter medicines, SAHPRA: South African Health Products Regulatory Authority.³⁸

Barriers to complementary medicine pharmacovigilance

Lack of standardisation

Standardisation of herbal APIs involves establishing consistent standards or inherent characteristics, including fixed parameters and definitive qualitative and quantitative values. This process ensures the quality, efficacy, safety, and reproducibility of the marketed herbal medicines. It involves developing and agreeing on technical standards through experimentation and observation, which define the specific characteristics of each herbal medicine. Thus, standardisation is a crucial tool for quality control (QC).³⁹

In allopathic medicines, QC is standardised in the Common Technical Document (CTD) submitted for registration, where the API is strictly controlled with built-in standardised QC checks to ensure a pure API is used in the final product.⁴⁰ However, herbal medicine APIs face several quality issues that are not applicable to synthetic medicines. Herbal APIs are typically mixtures of multiple constituents, and the active compounds are often unknown. Additionally, selective analytical methods or chemical reference standards may not always be commercially available. The chemical and natural variability of plant materials, along with the existence of chemo-varieties and chemo-cultivars, and the variability in raw material sources, further complicate the standardisation and quality control of herbal medicine.⁴¹

Even when properly authenticated, different batches of the same herbal ingredient can vary in quality due to several factors. Inter- or intra-species variation, which is largely genetically controlled and often related to the country of origin, can influence constituent levels. Environmental factors such as climate, altitude, and cultivation conditions also affect quality. The timing of harvest

is crucial for some herbs, as constituent concentrations can fluctuate during the growing cycle or even throughout the day. Additionally, the part of the plant used is important since active constituents usually differ between parts. Adulteration with other parts of the plant or with previously extracted, 'exhausted' material may occur to increase batch weight.⁴² Post-harvesting factors like storage conditions and processing treatments significantly impact quality; for instance, improper storage can lead to microbial contamination, and drying processes can cause the loss of heat-sensitive constituents.⁴³

The quality of herbal medicines is influenced by methods of harvesting, drying, storage, transportation, and processing, such as the mode of extraction and the polarity of the extracting solvent. Currently, there are no official standards for many herbal preparations. While some guidance exists within specific disciplines, many combinations and formulations have not been officially investigated. Manufacturers often use their own preliminary parameters when testing their formulations. Identifying all the ingredients in a formulation is challenging, making it crucial to develop parameters that can confirm the presence of all ingredients. Various chromatographic and spectrophotometric methods, along with evaluations of physicochemical properties, can be used to identify different ingredients. These methods can also enable the quantitative estimation of bioactive compounds like alkaloids, flavonoids, and polyphenolic components.⁴⁴

This standardisation extends to both dosing and medicinal claims. APIs sourced from different producers or harvested in different regions can reduce the efficacy of the proposed medicinal claim. The claims are often built using terms like "contributes", "assists", "helps", "aids", or "maintains" form the basis for efficacy claims,

supported by a beneficial physiological effect grounded in generally accepted scientific evidence, according to SAHPRA.¹³

Different perspectives on herbal products and health can create a divide regarding the reported safety of herbal medicines. Proponents often highlight that herbal medicine comes from nature, is a part of green therapy, is safe for long-term use, and is free from toxins or negative side effects.⁴⁵ However, misuse of herbal medicine can lead to serious adverse events, while some adverse event reports may cause anxiety and fear. It is essential to recognise that while herbal medicines are often regarded as less dangerous than synthetic medicines, there remains a risk of toxicity or adverse effects.⁴⁶ While curative statements are not advised for CMs, due to the lack of clinical studies, such claims still influence the use of these products in clinical settings.

Lack of clinical studies

Most herbal medicinal treatments lack sufficient pharmacokinetic, pharmacological, and clinical data, which significantly contributes to the uncertainty surrounding the safety and efficacy of these products. The difficulty of regulating herbal pharmaceuticals is further compounded by the large disparity in meeting the legal requirements for research on herbal medicines.⁴⁷ However, clinical research on herbal products should be supported to expand their acceptance. It is recommended that single, consistent batches of formulations be used in clinical studies to demonstrate efficacy.⁴⁸

Several concerns arise in the planning of herbal clinical trials, including Study design, finances, ethics, product standardisation (QC), and regulatory procedures prior to registering an experimental new medicine for the purpose of carrying out significant phase III trials.⁴⁹

Misinformation and health illiteracy

The rise of social media has contributed to increased health illiteracy – the inability to understand and apply medical information to make informed decisions about one's health. Teenagers who lack

digital health literacy could be more likely to come across false information and be swayed by organisations that have their own agendas.⁵⁰ This can spread false or biased ideas and actions, causing anxiety and inaccurate self-diagnosis and treatment, which may lead to bad or even deadly health consequences.⁵⁰ This negatively impacts how the general public perceives healthcare. With the growth of e-commerce, many health claims are not "fact checked" by healthcare professionals, leaving consumers unprotected due to their limited understanding.⁵¹ South Africa faces the unique challenge of having eleven different national languages, making it difficult to provide important medical material in all languages.⁵²

Underreporting and education

Underreporting of ADRs is a known issue in healthcare systems, with only 6–10% of ADRs being reported.^{53,54} This significant underreporting has two major effects: first, it delays the activation of warning signals, impacting public health; second, it hinders the measurement of ADRs, making it difficult to evaluate their incidence and associated risks.⁵⁵ A recent study found that healthcare professionals were the primary reporters in 68.86% of cases, with doctors reporting the most (39.66%) and pharmacists the least (4.45%) occurrences.⁵⁶ Community pharmacists, as the most accessible healthcare provider, play a critical role in ensuring medication safety by identifying and reporting ADRs.⁵⁷ However, a survey of SA pharmacists revealed that half felt they lacked the clinical expertise to identify ADRs, and 57% said reporting ADRs was too time-consuming.⁵⁸ Since many complementary medicines are freely available in pharmacies, this highlights a potential area for generating signals and assessing the educational needs of pharmacists. Also, many, if not all, complementary medicines are sold without the supervision of a pharmacist or healthcare practitioner, leaving many side effects unreported due to the lack of knowledge of sales floor staff.

A study out of the United States of America shows that 34% of 127 community pharmacists felt confident in their ability to advise patients on herbal medicines. About half of pharmacists

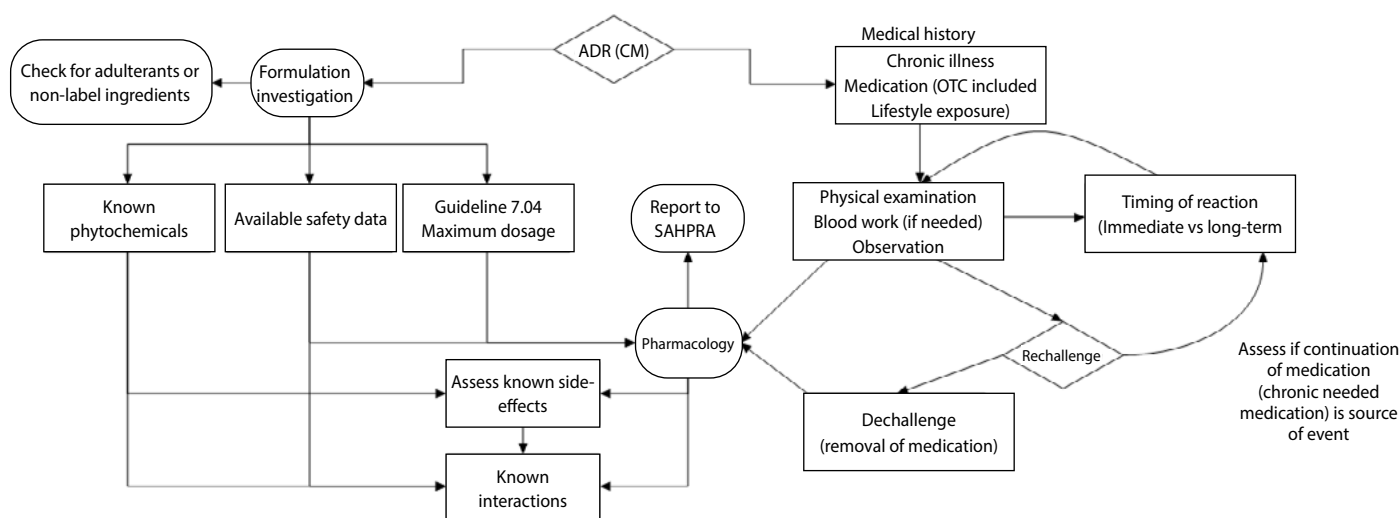


Figure 2: Possible flow of processes involved in adverse drug reactions (ADRs) in complementary medicines (CM) investigations. OTC: over-the-counter medicines, SAHPRA: South African Health Products Regulatory Authority.

surveyed said they never or rarely asked patients about their use of herbal medicines, and 80% said they never or rarely recorded such usage. Additionally, just 25% of pharmacists said they always discuss adverse effects with patients using herbal medicines, and only 19% always discuss potential interactions between herbs and medications.⁵⁹ In a South African study on pharmacists' attitudes and knowledge about herbal medicines, 85% admitted they did not feel sufficiently qualified to counsel patients on the safe, effective, and responsible use of herbal medicines.⁶⁰

A possible methodology for investigating complementary medicine ADRs

With approximately 50,000 plant species reported to have medicinal properties, it is unrealistic to expect any healthcare professional to have comprehensive knowledge of all these species.⁶¹ Therefore, a new methodology is required to utilise pharmacovigilance reports in understanding the mechanisms by which these side effects occur (Figure 2).

Step 1: Understand the formulation

Regulations governing the presentation of herbal medicine content aid investigators in identifying the mixture and the potential range of phytochemicals present in these herbal medicines. However, uncertainty persists regarding the effectiveness, safety, and quality of certain herbal products, raising safety concerns.⁶² While many herbal constituents lack safety information, data on some phytochemicals and their potential activities may be available.

Step 2: Clinical presentation

The patient's medical history and clinical symptoms should be considered to help investigators identify which physiological system is responsible for the presentation of the symptoms. Where the presentation of the ADR is directly linked to the system that is being affected. If the patient has a history of certain symptoms, it could mean the medication is exacerbating an underlying issue.

Step 3: Investigating phytochemicals

Plants evolved secondary metabolites over thousands of years, many of which have specific roles, such as promoting plant growth or defending against competitors, pathogens, or predators.⁶³ Identification of these phytochemicals is time consuming, resource-intensive, and requires specialised skills.⁶⁴ However, ADR can guide the identification of causative phytochemicals in well-known herbal ingredients. For example, liquorice, the root of *Glycyrrhiza glabra*, has known hypertensive effects, as shown in case studies with glycyrrhizic acid and glycyrrhetic acid identified as the causative agents.⁶⁵⁻⁶⁶

Although the collection of this high level of information is essential, many herbal pharmacopoeia's are either behind paywalls or expensive to access, and some are outdated.⁶⁷ A comprehensive literature collection is needed to ensure up-to-date information is available to understand the interactions between known phytochemicals and allopathic medicines.

Understanding the phytochemical fingerprint of an herbal medicine is a highly specialised task, requiring collaboration from a team of experts.⁶⁸ Multiple techniques, solvents, and advanced equipment are used to determine the composition of the mixture and verify the presence of active constituents.

Step 4: Investigating the APIs

During the investigation, it may be necessary to assess the APIs used in the formulation. This step can help answer key questions. Evaluation of the APIs may reveal issues such as adulteration, tampering or misidentification of the APIs used.⁶⁹ Laboratories specialising in the identification of chemotaxonomic markers and phytochemicals will need to employ a variety of specialised methods, including high-performance liquid chromatography (HPLC), liquid chromatography mass spectrometry (LC-MS) or gas chromatography mass spectrometry (GC-MS).^{70,71}

Step 5: Collating information

The investigation into the ADR should conclude with a report identifying the causative herbal ingredient. The report should state whether the ADR was an isolated incident (i.e. no issues seen in APIs) or whether a recall is warranted (i.e. discrepancies found with the APIs). This step directly impacts the safety and quality of the medicine but may also damage consumer confidence in the product.⁷² Product recalls have been associated with a reduced confidence in the product and stakeholder communications can be seen as a way to mitigate this drop in confidence.⁷³ Transparency is needed, such as after the Tylenol crisis in the 1980s.⁷⁴

Conclusion

The implementation of additional steps in ADR investigations could provide investigators with a comprehensive understanding of potential interactions and safety profiles of herbal-based complementary medicines. However, it may be beneficial to investigate the existing knowledge of healthcare workers to identify currently unknown barriers, as well as to investigate current communication lines from SAHPRA to the professional and then to the consumer. Moreover, there is a need for more specialised services and experts who can accurately identify phytochemicals and their interactions with conventional medicines and compile this information into a more accessible safety database for South African healthcare professionals.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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References

1. Africa RoS. Medicines and Related Substances Act, 1965 (Act 101 of 1965). Government Gazette. 2017. 41064.
2. Dureja H, Dhiman S. SAHPRA-Relevance of the New South African Health Products Regulatory Authority and Opportunities Ahead. *Journal of Regulatory Science*. 2021;9(2):1-14. <https://doi.org/10.21423/JRS-V09I2DUREJA>.
3. Chan K, Cheung L. Interactions between Chinese herbal medicinal products and orthodox drugs. 2000: CRC Press. <https://doi.org/10.4324/9781482298222>.
4. Jordan D. An overview of the Common Technical Document (CTD) regulatory dossier. *Medical Writing*. 2014;23(2):101-5. <https://doi.org/10.1179/2047480614Z.000000000207>.
5. Shaw D, Ladds G, Duez P, et al. Pharmacovigilance of herbal medicine. *J Ethnopharmacol*. 2012;140(3):513-8. <https://doi.org/10.1016/j.jep.2012.01.051>.
6. Zhang J, Onakpoya IJ, Posadzki P, Eddouks M. The safety of herbal medicine: from prejudice to evidence. *Evid Based Complement Alternat Med*. 2015. <https://doi.org/10.1155/2015/316706>.
7. World Health Organization. The importance of pharmacovigilance. 2002.
8. Weaver J, La Granade L, Kwon H, Avigan M. Finding, evaluating, and managing drug-related risks: approaches taken by the US Food and Drug Administration (FDA). *Dermatol Ther*. 2009;22(3):204-15. <https://doi.org/10.1111/j.1529-8019.2009.01233.x>.
9. Li Y, Wu Y, Jiang T, et al. Opportunities and challenges of pharmacovigilance in special populations: a narrative review of the literature. *Ther Adv Drug Saf*. 2023;14. <https://doi.org/10.1177/20420986231200746>.
10. Belz DS. The pharmacopoeia. An important pillar of drug safety: Ein wichtiger Pfeiler der Arzneimittelsicherheit. *Bundesgesundheitsblatt-Gesundheitsforschung-Gesundheitsschutz*. 2006;49:1205-11. <https://doi.org/10.1007/s00103-006-0090-9>.
11. Shaw D. Toxicological risks of Chinese herbs. *Planta Med*. 2010;76(17):2012-8. <https://doi.org/10.1055/s-0030-1250533>.
12. Medicines And Related Substances Act No. 101 of 1965. 196.5.
13. (SAHPRA), SAHPRA, Roadmap And Transitional Process For The Regulation Of Complementary Medicines. 2021;14.
14. Krueger RJ. *Drugs of Natural Origin. A Textbook of Pharmacognosy*. By Gunnar Samuelson. Swedish Pharmaceutical Press, Stockholm. 2005, ACS Publications. <https://doi.org/10.1021/np058229l>.
15. Nogue S, Allen DJ, Morison JLL, Baker NR. Ultraviolet-B radiation effects on water relations, leaf development, and photosynthesis in droughted pea plants. *Plant Physiol*. 1998;117(1):173-81. <https://doi.org/10.1104/pp.117.1.173>.
16. Janas KM, Cvikrova M, Palagiewicz A, Szafranska K, Posmyk MM. Constitutive elevated accumulation of phenylpropanoids in soybean roots at low temperature. *Plant Science*. 2002;163(2):369-373. [https://doi.org/10.1016/S0168-9452\(02\)00136-X](https://doi.org/10.1016/S0168-9452(02)00136-X).
17. Stewart AJ, Chapman W, Jenkins GI, et al. The effect of nitrogen and phosphorus deficiency on flavonol accumulation in plant tissues. *Plant Cell and Environment*. 2001;24(11):1189-97. <https://doi.org/10.1046/j.1365-3040.2001.00768.x>.
18. Hancianu M, Aprotosoaie AC. The effects of pesticides on plant secondary metabolites. *Biotechnological Production of Plant Secondary Metabolites*. 2012;176. <https://doi.org/10.2174/978160805114411201010176>.
19. Yadav N, Dixit V. Recent approaches in herbal drug standardization. *Int J Integr Biol*. 2008;2(3):195-203.
20. Izzo AA, Ernst E. Interactions between herbal medicines and prescribed drugs: a systematic review. *Drugs*. 2001;61(15):2163-75. <https://doi.org/10.2165/00003495-200161150-00002>.
21. Rubegeta E, Makolo F, Kamatou G, et al. Exploring the chemogeographical variation of a commercially import medicinal tree (*Prunus africana* (Hook. f.) Kalkman) using a metabolomics approach. *Journal of Applied Research on Medicinal and Aromatic Plants*. 2024;100568. <https://doi.org/10.1016/j.jarmap.2024.100568>.
22. Kasote D, Bankova V, Viljoen AM. Propolis: chemical diversity and challenges in quality control. *Phytochem Rev*. 2022;21(6):1887-911. <https://doi.org/10.1007/s11011-022-09816-1>.
23. Orchard A, Moosa T, Motala N, et al. Commercially available *viola odorata* oil, chemical variability and antimicrobial activity. *Molecules*. 2023;28(4):1676. <https://doi.org/10.3390/molecules28041676>.
24. Schripsema J, Augustyn W, Viljoen A. Characterisation of *Sclerocarya birrea* (marula) seed oil and investigation of the geographical origin by applying similarity calculations, differential NMR and hierarchical cluster analysis. *Phytochem Anal*. 2023;34(8):959-69. <https://doi.org/10.1002/pca.3264>.
25. Jesus ASD, Blank AF, Alves MF, et al., Influence of storage time and temperature on the chemical composition of the essential oil of *Hyptis pectinata* L. *Poit. Revista Brasileira de Plantas Medicinai*s. 2016;18(1 suppl 1):336-340. <https://doi.org/10.1590/1983-084X/15.177>.
26. Peterson B, Jacobsz C, Hamman J, Viljoen A, Steyn D. Pharmacokinetic interactions: The effects of selected herbal extracts on permeation of P-glycoprotein substrate drugs across excised pig intestinal tissue. *Journal of Herbmed Pharmacology*. 2021;11(1):121-30. <https://doi.org/10.34172/jhp.2022.14>.
27. Sindhura SDK, Jain V. Challenges in formulating herbal cosmetics. *Int J App Pharm*. 2018;10(6):47-53. <https://doi.org/10.22159/ijap.2018v10i6.27377>.
28. Caesar LK, Cech NB. Synergy and antagonism in natural product extracts: when 1+1 does not equal 2. *Natural Product Reports*. 2019;36(6):869-88. <https://doi.org/10.1039/C9NP00011A>.
29. Chen X, Li H, Zhang B, Deng Z. The synergistic and antagonistic antioxidant interactions of dietary phytochemical combinations. *Crit Rev Food Sci Nutr*. 2022;62(20):5658-77. <https://doi.org/10.1080/10408398.2021.1888693>.
30. Da S Rocha AR, Sousa HG, do Vale Júnior EP, et al. Extracts and fractions of *Croton* L.(Euphorbiaceae) species with antimicrobial activity and antioxidant potential. *Lwt*. 2021;139:110521. <https://doi.org/10.1016/j.lwt.2020.110521>.
31. Rutkowska M, Olszewska MA, Kolodziejczyk-Czepas J, Nowak P, Owczarek A. *Sorbus domestica* leaf extracts and their activity markers: Antioxidant potential and synergy effects in scavenging assays of multiple oxidants. *Molecules*. 2019;24(12):2289. <https://doi.org/10.3390/molecules24122289>.
32. Hidalgo M, Sánchez-Moreno C, de Pascual-Teresa S. Flavonoid-flavonoid interaction and its effect on their antioxidant activity. *Food Chemistry*. 2010;121(3):691-6. <https://doi.org/10.1016/j.foodchem.2009.12.097>.
33. Wagner H, Ulrich-Merzenich G. Synergy research: approaching a new generation of phytopharmaceuticals. *Phytomedicine*. 2009;16(2-3):97-110. <https://doi.org/10.1016/j.phymed.2008.12.018>.
34. Cseke LJ, Kirakosyan A, Kaufman PB, et al. *Natural Products from Plants*. 2016. <https://doi.org/10.1201/9781420004472>.
35. Williamson EM. Synergy and other interactions in phytomedicines. *Phytomedicine*. 2001;8(5):401-9. <https://doi.org/10.1078/0944-7113-00060>.
36. Strauss J, Greeff OBW. Excipient-related adverse drug reactions: a clinical approach. *Current Allergy & Clinical Immunology*. 2015;28(1):24-27.
37. Aronson JK, Ferner RE. Clarification of terminology in drug safety. *Drug Saf*. 2005;28(10):851-70. <https://doi.org/10.2165/00002018-200528100-00003>.
38. European Medicines Agency. Guidelines on Good Pharmacovigilance Practices (GVP)-Introductory Cover Note, Last Updated with Chapter P. III on Pharmacovigilance for the Use of Medicines by Pregnant and Breastfeeding Women. 2019, European Medicines Agency Amsterdam, The Netherlands.
39. Kunle OF, Egharevba HO, Ahmadi PO. Standardization of herbal medicines-A review. *International Journal Of Biodiversity And Conservation*. 2012;4(3):101-12. <https://doi.org/10.5897/IJBC11.163>.
40. Haider SI, Asif SE. Quality control training manual: comprehensive training guide for API, finished pharmaceutical and biotechnologies laboratories. 2016.
41. Wani M, Parakh SR, Dehghan MHG, Polshettiwar SA. Herbal medicine and its standardization. *Pharmaceutical Reviews*. 2007;5(6):411038-49.
42. Mishra M, Kotwal P, Prasad C. Harvesting of medicinal plants in the forest of Central India and its impact on quality of raw materials: A case of Nagpur District, India. *Ecoprint: An International Journal of Ecology*. 2009;16:35-42. <https://doi.org/10.3126/ecov.16i0.3471>.
43. Pandey A, Savita R. Harvesting and post-harvest processing of medicinal plants: Problems and prospects. *The Pharma Innovation Journal*. 2017;6(12):229-35.
44. World Health Organization. General guidelines for methodologies on research and evaluation of traditional medicine. 2000. Available at: <https://www.who.int/publications/i/item/9789241506090>.
45. Health Nio. 1025 Natural Doesn't Necessarily Mean Safer, or Better, in Advances in Surgical and Medical Specialties. Jenny Stanford Publishing. p. 1025-1027.
46. Chan TY. Monitoring the safety of herbal medicines. *Drug Saf*. 1997;17(4):209-15. <https://doi.org/10.2165/00002018-199717040-00001>.
47. Bansal D, Hota D, Chakrabarti A. Research methodological issues in evaluating herbal interventions. *Open Access Journal of Clinical Trials*. 2010;15-21. <https://doi.org/10.2147/OAJCT.S9029>.
48. Wu KM, Farrelly J, Birnkrant D, et al. Regulatory toxicology perspectives on the development of botanical drug products in the United States. *Am J Ther*. 2004;11(3):213-7. <https://doi.org/10.1097/00045391-200405000-00010>.
49. Ahluwalia HPS, Kaur I. Clinical trials of traditional herbal medicines in India: current status and challenges. *Int J Pharmacogn*. 2014;1(7):415-21.
50. Freeman JL, Caldwell PHY, Bennett PA, Scott KM. How adolescents search for and appraise online health information: A systematic review. *J Pediatr*. 2018;195:244-55. <https://doi.org/10.1016/j.jpeds.2017.11.031>.
51. Raynor DK, Dickinson R, Knapp P, Long AF, Nicolson DJ. Buyer beware? Does the information provided with herbal products available over the counter enable safe use? *BMC Medicine*. 2011;9:1-9. <https://doi.org/10.1186/1741-7015-9-94>.
52. Kangira J. Challenges of the implementation of language policies in southern Africa: what is the way forward? *Inkanyiso*. 2016;8(2):156-61. <https://doi.org/10.4102/ink.v8i2.221>.
53. Hazell L, Shakir SA. Under-reporting of adverse drug reactions: a systematic review. *Drug Saf*. 2006;29(5):385-96. <https://doi.org/10.2165/00002018-200629050-00003>.
54. Herdeiro MT, Figuerias A, Polonia J, Gestal-Otero JJ. Physicians' attitudes and adverse drug reaction reporting : a case-control study in Portugal. *Drug Saf*. 2005;28(9):825-33. <https://doi.org/10.2165/00002018-200528090-00007>.
55. Goldman SA. Limitations and strengths of spontaneous reports data. *Clin Ther*. 1998;20(Suppl C):C40-4. [https://doi.org/10.1016/S0149-2918\(98\)80007-6](https://doi.org/10.1016/S0149-2918(98)80007-6).
56. Matlala MF, Lubbe MS, Steyn H. Profile of adverse drug reaction reports in South Africa: An analysis of VigiBase(R) for the year 2017. *S Afr Med J*. 2023;113(6):26-33. <https://doi.org/10.7196/SAMJ.2023.v113i5.16522>.
57. Hadi MA, Neoh CF, Zin RN, Elrggal ME, Cheema E. Pharmacovigilance: pharmacists' perspective on spontaneous adverse drug reaction reporting. *Integr Pharm Res Pract*. 2017;6:91-98. <https://doi.org/10.2147/IPRPS105881>.
58. Jordaan PH. Pharmacists' perception towards pharmacovigilance and the reporting of adverse drug reactions in South Africa. 2020, North-West University (South-Africa).
59. Carr A, Santanello C. Pharmacists' knowledge, perceptions, and practices regarding herbal medicine. *Innovations in Pharmacy*. 2019;10(3). <https://doi.org/10.24926/iip.v10i3.2059>.
60. Brijlal N, Khoza N, Mbonane NA, Meyiwa S. The attitudes and knowledge of pharmacists towards the use of herbal medicine. *SA Pharmaceutical Journal*. 2011;78(7):35-37.

61. Barboza GE, Cantero JJ, Nunez C, et al. Medicinal plants: A general review and a phytochemical and ethnopharmacological screening of the native Argentine Flora. *Kurtziana*. 2009;34(1-2):7-365.
62. Ekor M. The growing use of herbal medicines: issues relating to adverse reactions and challenges in monitoring safety. *Front Pharmacol*. 2014;4:177. <https://doi.org/10.3389/fphar.2013.00177>.
63. Molyneux RJ, Lee ST, Gardner DR, Panter KE, James LM. Phytochemicals: the good, the bad and the ugly? *Phytochemistry*. 2007;68(22-24):2973-85. <https://doi.org/10.1016/j.phytochem.2007.09.004>.
64. Altemimi A, Lakhssassi N, Baharlouei A, Watson DG, Lightfoot DA. Phytochemicals: extraction, isolation, and identification of bioactive compounds from plant extracts. *Plants (Basel)*. 2017;6(4):42. <https://doi.org/10.3390/plants6040042>.
65. Falet JP, Elkrief A, Green L. Hypertensive emergency induced by licorice tea. *CMAJ*. 2019;191(21):E581-E583. <https://doi.org/10.1503/cmaj.180550>.
66. Obolentseva G, Litvinenko VI, Ammosov SA, Popova TP, Sampiev AM. Pharmacological and therapeutic properties of licorice preparations (a review). *Pharmaceutical Chemistry Journal*. 1999;33(8):427-34. <https://doi.org/10.1007/BF02510095>.
67. Chinou I, Knoess W, Calapai G. Regulation of herbal medicinal products in the EU: an up-to-date scientific review. *Phytochemistry Reviews*. 2014;13(2): 539-45. <https://doi.org/10.1007/s11101-014-9354-4>.
68. Donno D, Boggia R, Cerutti AK, et al. Phytochemical fingerprint and chemometrics for natural food preparation pattern recognition: an innovative technique in food supplement quality control. *J Food Sci Technol*. 2016;53(2):1071-83. <https://doi.org/10.1007/s13197-015-2115-6>.
69. Jairoun AA, Al-Hemyari SS, Shahwan M, Zyoud SH. Adulteration of weight loss supplements by the illegal addition of synthetic pharmaceuticals. *Molecules*. 2021;26(22):6903. <https://doi.org/10.3390/molecules26226903>.
70. Feng Y, Lei D, Hu C. Rapid identification of illegal synthetic adulterants in herbal anti-diabetic medicines using near infrared spectroscopy. *Spectrochim Acta A Mol Biomol Spectrosc*. 2014;125:363-74. <https://doi.org/10.1016/j.saa.2014.01.117>.
71. Feng W, Li M, Hao Z, Zhang J. Analytical methods of isolation and identification, in *Phytochemicals in human health*. 2019, IntechOpen. <https://doi.org/10.5772/intechopen.88122>.
72. Freedman S, Kearney M, Lederman M. Product recalls, imperfect information, and spillover effects: Lessons from the consumer response to the 2007 toy recalls. *Review of Economics and Statistics*. 2012;94(2):499-516. https://doi.org/10.1162/REST_a_00162.
73. Mafael A, Raithel S, Hock SJ. Managing customer satisfaction after a product recall: the joint role of remedy, brand equity, and severity. *Journal of the Academy of Marketing Science*. 2022;50(1):174-194. <https://doi.org/10.1007/s11747-021-00802-1>.
74. Andrews R. Crisis communications and the Tylenol poisonings. *Encyclopedia of Public Relations*. 2005;1:224-226.