PharmacoLearn

MPG102T Advanced Pharmacognosy-I, M.Pharm Semester 1

Unit 5: Pharmacovigilance of Drugs of Natural Origin

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5.1 Why natural products need safety monitoring

Pharmacovigilance is the science and the system of detecting, assessing, understanding and preventing adverse effects of medicines. Drugs of natural origin need it for reasons that are specific to them, and the first section of this unit states them plainly. Most herbal and natural products reach the public without the premarket clinical trial programme of a synthetic drug, so their safety knowledge must be built after marketing, from real world use. Their composition is variable, between species, batches and brands, so a safety signal may belong to one product or one contaminated batch and not to the herb in general. They are often self selected and self medicated, bought without a prescription and frequently not mentioned to the patient's doctor or pharmacist, so adverse events are under reported and interactions are missed at prescribing. They are used by exactly the patients most at risk from interactions: older people and people with long term conditions taking several conventional medicines. And the natural is safe assumption, held by many users, delays the recognition that a natural product can cause real harm: liver injury, kidney injury, allergy, bleeding and interactions are all documented for natural products. Pharmacovigilance of natural drugs is therefore not a suspicion of tradition; it is the ordinary safety discipline applied where the premarket evidence is thinnest.

5.2 WHO guidelines for safety monitoring of natural medicine

The World Health Organization addressed this gap directly in its guidelines on safety monitoring of herbal medicines in pharmacovigilance systems, published in 2004, which remain the WHO reference the syllabus points to. Their teaching content is as follows. Herbal medicines should be brought inside the national pharmacovigilance system rather than left in a separate traditional medicine channel, so that a herbal adverse reaction is reported, stored and assessed in the same system as any other adverse reaction. The existing spontaneous reporting forms and methods should be adapted, not replaced, with the special data a herbal report needs: the product's full name and brand, the botanical name of the plant and the part used where known, the manufacturer and batch, the source from which it was obtained, and any other medicines and products taken at the same time. The guidelines recognise the special difficulties of the field: naming chaos (one plant, many names; one name, many plants), variable products, self medication and under reporting, and contamination and adulteration as alternative explanations for an event. They direct national centres to work with the traditional medicine authorities, the manufacturers and the professional bodies, and to exchange reports internationally through the WHO global pharmacovigilance network and its database, so that a signal appearing in small numbers in many countries can be seen whole. The student's one line summary: WHO says monitor herbal medicines with the same system and the same seriousness as conventional medicines, adapted for the naming and identity problems that are unique to them.

5.3 AYUSH guidelines and safety monitoring in India

In India, the AYUSH systems (Ayurveda, Yoga and Naturopathy, Unani, Siddha and Homoeopathy) are administered by the Ministry of AYUSH, and the pharmacovigilance programme for Ayurveda, Siddha, Unani and Homoeopathy (ASU and H) drugs is the national structure the syllabus points to under AYUSH guidelines. Its design mirrors the WHO advice. It collects adverse event reports for ASU and H medicines through a network of peripheral, intermediary and a national pharmacovigilance centre, with reporting forms

adapted to traditional medicines, and it works to build a culture of reporting among AYUSH practitioners, who historically did not report. It also addresses the quality side that runs beside event reporting: surveillance for misbranded, adulterated and spurious ASU and H products, and public awareness against misleading advertisements and the assumption that a traditional label guarantees safety. The reporting flow below shows how a single report travels in a spontaneous system of this kind, in India and generally.

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Patient or practitioner notices a suspected adverse event
        |
Report completed: product, botanical name, batch, other medicines
        |
Peripheral or local centre receives and checks the report
        |
Intermediary and national centre: assessment and causality review
        |
National database; signals searched across many reports
        |
Action where needed: label change, advisory, product action
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Feedback to reporters and professionals; international sharing (WHO)
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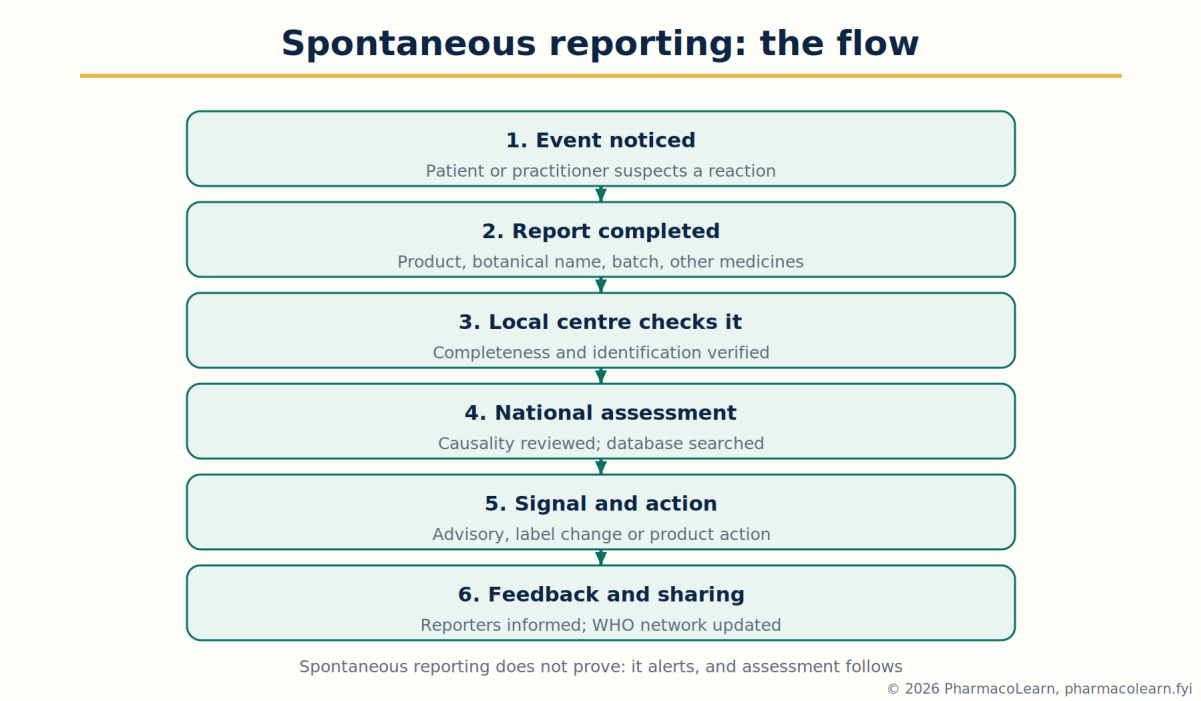

Figure: The spontaneous reporting flow for drugs of natural origin. The herbal specific fields, botanical name, plant part, brand and batch, are what make a herbal report assessable.

5.4 Spontaneous reporting schemes for biodrug adverse reactions

A spontaneous reporting scheme is a system in which health professionals, and in many systems patients themselves, report suspected adverse reactions voluntarily, as they notice them, to a central centre. The syllabus word biodrug means a drug of natural or biological origin, and a biodrug adverse reaction is a harmful, unintended response suspected to be caused by such a drug. Spontaneous reporting is the backbone of natural product pharmacovigilance because it is the one method that watches every product, in every patient, for as long as it is sold, at low cost. Its strengths are breadth and signal generation: rare and unexpected reactions, reactions in pregnancy, in children and in the elderly, and interaction reactions all surface first as spontaneous reports, and a cluster of similar reports is a signal that triggers formal assessment. Its weaknesses must be taught with it: under reporting is severe, and worse for herbal products, whose users often do not connect a symptom to a supplement or do not regard it as reportable; reports are incomplete, and for herbals often lack the botanical identity that assessment needs; and a report

count alone cannot give a rate, since neither the true number of events nor the true number of users is known. Causality assessment, judging how likely the product is to have caused the event on timing, dechallenge (the event improving when the product stops), rechallenge where it exists, alternative explanations including the patient's diseases and other medicines, and previous knowledge, is what converts a pile of reports into evidence. The standard teaching verdict: spontaneous reporting does not prove, it alerts; proof is built by assessment and follow up study.

5.5 Biodrug-drug interactions

A biodrug-drug interaction occurs when a drug of natural origin changes the effect of a conventional medicine, or the medicine changes the natural product's effect, by a pharmacokinetic route (absorption, metabolism or excretion changed, most famously through liver and gut enzymes such as CYP3A4 and transporters such as P-glycoprotein) or a pharmacodynamic route (the effects add or oppose at the site of action). The watch points figure below collects the interaction types, and the standard examples follow it.

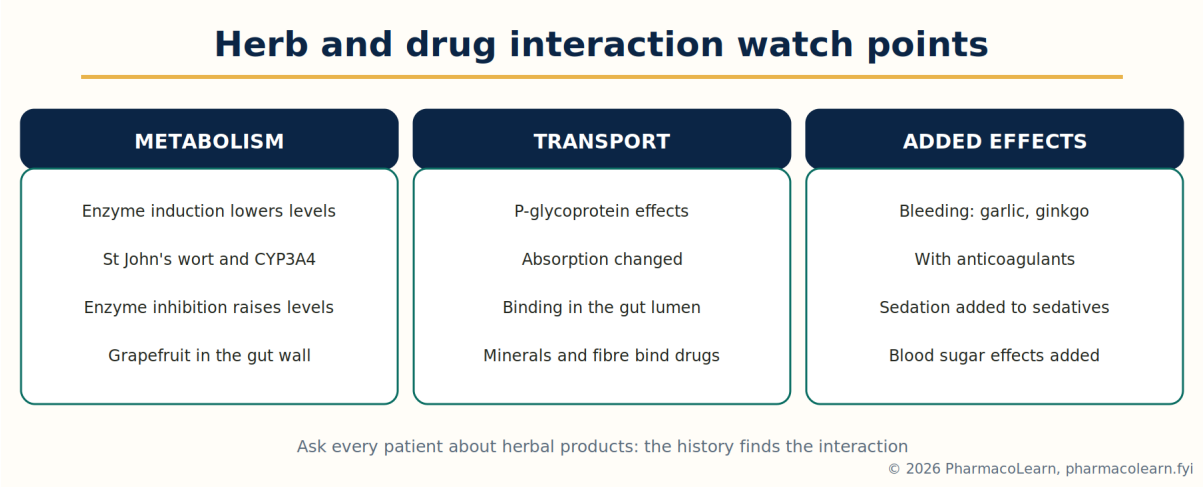

Figure: The interaction watch points for drugs of natural origin: metabolic induction, metabolic inhibition, transporter effects, and additive pharmacodynamic effects.

The classic examples, each standard in teaching, are these. St John's wort, the herbal antidepressant, induces CYP3A4 and P-glycoprotein and thereby lowers the blood levels and the effect of many medicines, including ciclosporin (with transplant rejection reported), oral contraceptives (with contraceptive failure reported), and several antivirals and anticancer drugs; it is the single most important herbal interaction example. Garlic and ginkgo, each with antiplatelet activity, can add to the bleeding risk of warfarin and other anticoagulant and antiplatelet medicines, and ginseng has also been reported to interact with warfarin. Liquorice, through its glycyrrhizin, causes potassium loss and sodium retention with continued heavy use, opposing antihypertensive treatment and increasing the risk from digoxin. Herbal products with sedative action add to prescribed sedatives. And any herbal product taken by a patient on antidiabetic medicines must be watched for additive blood sugar lowering where the herb itself has such an action. The clinical rule that closes the topic: the interaction is usually discovered by the history, so the history must ask about herbal and supplement use directly, because patients rarely volunteer it.

5.6 Biodrug-food interactions

A biodrug-food interaction runs in either direction across the same table: a food changes the effect of a drug of natural origin, or a natural product, itself often eaten as a food, changes the effect of a conventional medicine. The outstanding example of the second direction is grapefruit: grapefruit and its juice contain furanocoumarins that irreversibly inhibit intestinal CYP3A4, so medicines normally broken down in the gut wall reach the blood in higher amounts, with raised effect and raised toxicity; the affected list is long and

includes several statins, calcium channel blockers and immunosuppressants, and the effect lasts beyond a day because the enzyme must be remade. Note the teaching loop this closes: the grapefruit flavonoid naringin was met in Unit 4, and grapefruit is where Unit 4's chemistry becomes Unit 5's safety lesson. Other standard food interaction teaching includes vitamin K rich green vegetables opposing warfarin's action when intake changes sharply; high fibre products and mineral supplements binding medicines in the gut and reducing their absorption when taken together (Sections 3.3 and 3.6); alcohol adding to sedative herbs and medicines; and tyramine rich foods interacting with monoamine oxidase inhibitor medicines, a drug-food interaction of the conventional side that completes the pattern. Timing advice, separating the medicine from the interacting food or supplement by an interval where the interaction is one of binding or absorption, and consistency advice, keeping vitamin K intake steady on warfarin, are the practical outputs of this section.

5.7 Assessment, signals and the professional's duties

The unit closes with the professional's working duties: ask what herbal products, supplements and traditional medicines the patient uses, and record the answer; recognise the high risk combinations, enzyme inducers and inhibitors, anticoagulant partners, and products in pregnancy, in children, in the elderly and in liver and kidney disease; report suspected adverse reactions with the full herbal identification the WHO guidelines require, and encourage patients to report; check identity and quality as safety work, since adulteration with undeclared synthetic drugs and contamination are recurring real world causes of supposed herbal adverse reactions; and teach the sentence that carries the whole unit: natural products are pharmacologically active, which is why they can help, and exactly why they can harm and interact.

5.8 Unit 5 in one view

Pharmacovigilance of drugs of natural origin applies the standard safety system, detection, assessment, understanding and prevention of adverse effects, to products whose premarket evidence is thin and whose use is often invisible to prescribers. WHO guidelines bring herbal medicines into the national spontaneous reporting system with herbal specific identification fields; the AYUSH pharmacovigilance programme does the same for ASU and H drugs in India. Spontaneous reporting generates signals, causality assessment tests them, and the interaction teaching, St John's wort induction, garlic and ginkgo with anticoagulants, liquorice with digoxin and blood pressure medicines, and grapefruit with CYP3A4 substrates, gives the pharmacist the watch list that prevents the commonest harms.

Frequently Asked Questions

Q: What are Current Good Cultivation Practices and Current Good Collection Practices, and how do they differ?

Both are quality systems for getting a plant drug from nature to the factory with its identity and chemistry intact. Cultivation practices govern a grown crop: species and variety selection, site and crop management, and harvest of the correct part at the correct stage, all recorded. Collection practices govern wild gathered material: certain identification at collection, correct part and sustainable method, clean handling and collection records. One controls a farm, the other controls a gathering; the discipline of identity, timing, cleanliness and traceability is the same.

Q: Compare in-situ and ex-situ conservation of medicinal plants.

In-situ conservation protects the species in its natural habitat, in protected areas and by law, keeping the whole population, its genetic range and its ecosystem, but failing if the habitat is destroyed. Ex-situ conservation protects it away from the habitat, in botanical gardens, field and seed gene banks and tissue

culture or cryopreserved collections, giving security and material for research and reintroduction, but holding only a sample of the genetic range under artificial conditions. Sound conservation uses both.

Q: Outline the general method for isolating a marine natural product.

Collect and identify the organism with expert taxonomy and preserve a voucher specimen. Preserve the material promptly, extract with suitable organic solvents, and partition the crude extract between immiscible solvents by polarity. Fractionate by chromatography under bioassay guidance, following the active fractions, and purify the active compound by HPLC. Determine the structure by mass spectrometry, NMR and supporting UV and IR spectra, and characterise the pure compound fully.

Q: Name the major marine toxins and state how the best known of them act.

Saxitoxin and tetrodotoxin block voltage gated sodium channels; saxitoxin causes paralytic shellfish poisoning and tetrodotoxin is the puffer fish toxin. Ciguatoxins and brevetoxins also act on sodium channels. Palytoxin, from Palythoa zoanthids, acts on the sodium potassium pump and is among the most potent non protein toxins known. Okadaic acid inhibits protein phosphatases and causes diarrhetic shellfish poisoning. Their potency and selectivity make them both seafood hazards and valued research tools.

Q: What problems are faced in marine drug research, and what are their solutions?

The syllabus problems are taxonomical identification, answered by expert taxonomy, voucher specimens and DNA barcoding, and chemical screening of extreme, salty, dilute mixtures, answered by dereplication against known compound databases and bioassay guided fractionation. Around them stand supply, answered by aquaculture, fermentation of the true microbial producer, total synthesis and analogues; structural complexity, answered by modern NMR and mass spectrometry; and variability, answered by full collection records and controlled culture.

Q: What is a nutraceutical, and how are nutraceuticals regulated in India?

A nutraceutical is a food derived product taken for a health benefit beyond basic nutrition, sold as a food or supplement and not as a licensed medicine. In India it is regulated under the Food Safety and Standards Act, 2006 by FSSAI: licensing of the business in tiers, product standards, and dedicated regulations for health supplements and nutraceuticals controlling permitted ingredients, ranges and claims. Control is by composition, licence and labelling, not by drug style marketing authorisation, and disease cure claims take a product out of the food system.

Q: Give the marker compounds and their chemical nature for Spirulina, ginseng, garlic and turmeric.

Spirulina is standardised on phycocyanin, a blue phycobiliprotein pigment protein of the alga Arthrospira platensis. Ginseng is standardised on the ginsenosides, triterpenoid saponin glycosides of Panax roots. Garlic is standardised on allicin, the organosulfur thiosulfinate formed from alliin when the bulb of Allium sativum is crushed. Turmeric is standardised on the curcuminoids, chiefly curcumin, diarylheptanoid phenolic compounds of the Curcuma longa rhizome.

Q: Distinguish tocopherols from tocotrienols, and state where each is found.

Both are vitamin E compounds built on a chromanol head with a long side chain, in alpha, beta, gamma and delta forms. Tocopherols carry a saturated side chain and occur widely in seed and vegetable oils; alpha tocopherol is the reference form for vitamin E activity. Tocotrienols carry an unsaturated side chain with three double bonds, are concentrated in palm oil, rice bran oil and annatto, and are marketed and researched for their own distinct profile.

Q: What are withanolides, vascine and taxol, and why does each matter?

Withanolides are the steroidal lactone markers of ashwagandha root, Withania somnifera, on which its extracts are standardised. Vascine is the quinazoline alkaloid of vasaka leaves, Adhatoda vasica, a traditional expectorant constituent and the structural lead from which bromhexine and ambroxol were designed. Taxol (paclitaxel) is the taxane diterpene anticancer drug from yew, which stabilises microtubules; its supply was solved by semisynthesis from needle derived taxanes and plant cell culture after the original bark source proved unsustainable.

Q: State the WHO position on safety monitoring of herbal medicines, and give two major herb-drug interactions.

The WHO guidelines on safety monitoring of herbal medicines in pharmacovigilance systems direct that herbal medicines be monitored inside the national pharmacovigilance system, using the standard spontaneous reporting system adapted with herbal specific fields: botanical name, plant part, brand, manufacturer, batch and all other products taken. Two major interactions: St John's wort induces CYP3A4 and P-glycoprotein and lowers the levels of ciclosporin, oral contraceptives and many other medicines; and garlic or ginkgo adds antiplatelet effect to warfarin and related medicines, raising bleeding risk. Grapefruit inhibition of intestinal CYP3A4 is the standard biodrug-food example.

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