MAGISTER NATURAE

HERBS & MEDICATIONS

A Guide to Safe Combinations

33 of the most commonly used medicinal plants and supplements — checked against EMA, WHO, Cochrane, and PubMed sources, with clear warnings about drug interactions.

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A Note Before You Read

This book is an educational guide, not a substitute for the advice of a pharmacist or physician. Every plant and supplement described here can interact with medications in ways that depend on dose, form (tea versus concentrated extract), health status, and the other medications a person is taking — generalizations are useful for orientation, not for making treatment decisions on your own.

Before combining any plant or dietary supplement with a prescribed medication, always consult a pharmacist or physician — especially if you take narrow-therapeutic-index drugs (warfarin, digoxin, immunosuppressants, antiepileptics), if you are pregnant or breastfeeding, or if you have a chronic liver, kidney, or heart condition.

“Natural” does not mean “harmless.” Most plants in this book are safe in ordinary, culinary, or traditional amounts — risk almost always rises with concentration (extracts, capsules, essential oils) and duration of use, not with a plant's mere presence on the market.

Every claim in this book has been checked against official sources (EMA/HMPC herbal monographs, WHO monographs, Cochrane systematic reviews, peer-

reviewed clinical literature) or is explicitly flagged as anecdotal / insufficiently proven.

The information in this book is accurate according to the sources available at the time of writing — pharmacological research and regulations change, so checking the current state of affairs with a pharmacist or physician is recommended.

The authors are a pharmacist and a botanist, but reading this book does not constitute a professional consultation and does not establish a pharmacist–patient relationship. For questions about your own treatment, consult a pharmacist or physician familiar with your medical history.

The authors and publisher accept no responsibility for the consequences of applying information from this book on your own, without prior consultation with a healthcare professional.

About This Book

This is a compact companion volume in the Magister Naturae series: a guide to the 33 most commonly used medicinal plants and dietary supplements, chosen specifically because they are the ones most likely to already be in your kitchen cabinet, your medicine cabinet, or your daily supplement routine — and therefore the ones most likely to be combined, often unknowingly, with a prescription medication.

Each entry follows the same structure used throughout the series: traditional use, the active compound and its effect, what the science actually shows (proven separated from anecdotal), preparation and dosage, contraindications, drug interactions with the mechanism behind each one, and a pharmacist's note highlighting something most people would not expect.

Contents

How to Use This Book

Plants are listed in the same order as the original edition — use the Contents to quickly find the plant you're looking for. In the Preparation and Dosage and Drug Interactions sections, short bold labels (a dosage form, or a drug name marked with ⚠ or **ℹ**) are followed by their description or mechanism — read them as a pair.

At the back of the book you'll find the Interaction Index — if you take a particular class of medication (e.g. warfarin, statins, antidepressants), you can quickly see there which plants and supplements in the book require special attention in combination with that class.

Ashwagandha *(Withania somnifera)*

● **MODERATE RISK** mostly safe short-term; interactions with thyroid medications and immunosuppressants require caution

> *A plant whose Sanskrit name means "smell of horse and strength of horse" is today one of the most extensively studied adaptogens — but also one of the rare herbal remedies to land on conventional endocrinologists' radar, since it can throw off thyroid function tests enough to baffle a doctor who doesn't know about it.*

▶ Traditional Use

Ayurvedic medicine has used the plant's root for more than 3,000 years: as a rasayana (a vitality-restoring remedy), a tonic for exhaustion, nervous weakness, and sexual dysfunction, and as a sedative and analgesic. The leaves and seed are occasionally mentioned for topical and antiparasitic use, but modern research tracks almost exclusively root extracts.

▶ Active Compound → Effect

The key compounds are withanolides — steroidal lactones (chiefly withanolide A and withaferin A).

Withanolides modulate the HPA axis (hypothalamus–pituitary–adrenal), lower cortisol, and act as adaptogens. Withaferin A shows immunomodulatory and antiproliferative activity in vitro and in animal models, but its clinical relevance at supplement doses has not been established.

Secondary metabolites (the alkaloids somniferine and withanine) likely contribute to the sedative effect, but their contribution has not been precisely measured.

▶ What the Science Actually Says (Proven vs. Anecdotal)

Proven (moderate quality evidence — RCTs, small samples):

Several randomized controlled trials show a statistically significant reduction in serum cortisol, decreased perceived stress (PSS scales), and improved sleep quality in adults with chronic stress. Standardized extracts (KSM-66, Sensoril) were tested at 200–600 mg/day for 8–12 weeks.

There is moderate evidence for improved anaerobic power and recovery in athletes, as well as a mildly favorable effect on male fertility (sperm count and motility).

Anecdotal / insufficiently proven:

Nootropic effects (memory, concentration), aphrodisiac action, antidiabetic effects, a direct anxiolytic role outside a stress context — [evidence is mostly of poor

quality, small samples, short duration; replication needed]

▶ Preparation and Dosage (Specifics)

Standardized extract (KSM-66 / Sensoril)
300–600 mg daily, in 1–2 doses with a meal. Duration: 8–12 weeks, then a break. The most extensively studied form.

Root powder (non-concentrated)
3–6 g daily; traditionally taken in milk or ghee. Withanolide concentration is far lower — effects are harder to predict.

Tincture (1:5)
[No standardized dosing recommendations exist for the tincture — extrapolating from the studies is unreliable]

Essential oil
Not used systemically. Do not use internally — withaferin A is toxic at higher concentrations.

⚠ A "pinch of powder" ≠ 300 mg of standardized extract. The difference in withanolide concentration can be 10–20-fold.

▶ Contraindications (Who Should NOT Use It)

Pregnancy — stimulates the uterus; a documented abortifacient effect in animal studies. Absolute contraindication.

Autoimmune diseases (MS, lupus, RA, Hashimoto's) — its immunostimulatory action may worsen the disease.

Thyroid disorders — especially hyperthyroidism and Graves' disease (see interactions).

Breastfeeding — insufficient data; avoid.

Upcoming surgery — discontinue at least 2 weeks beforehand (sedative, potentially hypotensive effects).

▶ Drug Interactions (+ Why)

> ⚠ **Levothyroxine (Euthyrox, Letrox)**
> Mechanism: Ashwagandha stimulates the synthesis and conversion of thyroid hormones (raises T3 and T4). Combined with levothyroxine, this can produce an additive effect → symptoms of hyperthyroidism (tachycardia, insomnia, weight loss). TSH/fT4 should be monitored before and during use.

> ⚠ **Immunosuppressants (cyclosporine, methotrexate, corticosteroids)**
> Mechanism: The immunostimulatory effects of withanolides may antagonize immunosuppressive therapy → risk of transplant rejection or worsening of autoimmune disease.

⚠ Sedatives, anxiolytics, antiepileptics (benzodiazepines, barbiturates, gabapentinoids)

Mechanism: Additive CNS-depressant effect — ashwagandha enhances GABAergic transmission. Risk of excessive sedation. Especially relevant with alcohol.

⚠ Antihypertensives and diuretics

Mechanism: Ashwagandha's mild hypotensive effects (likely through lowered cortisol and direct vasodilation) may be additive with antihypertensives. [Clinical significance not precisely quantified — caution at low blood pressure values]

i Antidiabetics (insulin, metformin)

Mechanism: Ashwagandha's mild hypoglycemic action (potential insulin-sensitizing effect). A theoretical risk of hypoglycemia with antidiabetics, but clinically documented cases are rare. [No robust clinical data]

▶ Pharmacist's Note (Unexpected)

Ashwagandha belongs to the Solanaceae — the same family as tomato, pepper, and deadly nightshade. Withaferin A, which shows antiproliferative effects in vitro, is cytotoxic at higher doses. Extract standardization generally targets 2.5–5% withanolides — but standardization methods vary between manufacturers and are not regulated in the EU the same way medicines are. Isolated cases of hepatotoxicity have been reported [likely dose-dependent or linked to contaminated raw material —

causality has not been firmly established; the EMA's HMPC flags these cases as a caution].

Garlic *(Allium sativum)*

● **MODERATE RISK** Safe as a spice, but concentrated extracts and essential oils carry a real risk of interactions with anticoagulants and may increase bleeding.

> *Surgeons around the world routinely tell patients to stop taking garlic two weeks before an operation — not because of the smell, but because it literally changes their blood clotting time.*

▶ Traditional Use

For more than 5,000 years in Ayurvedic, Chinese, and Mediterranean medicine — primarily as a "natural antibiotic" for respiratory infections, and as a remedy for the heart and blood vessels. In Serbian folk medicine: a clove on an empty stomach, garlic syrup with honey, garlic brandy for "cleansing the blood."

▶ Active Compound → Effect

Allicin (formed only once a clove is crushed or cut — the enzyme alliinase breaks down alliin into allicin) → antimicrobial, antifungal, mildly lowers blood pressure and LDL cholesterol.

Ajoenes and disulfides → antiplatelet action (prevent platelets from sticking together).

S-allyl cysteine (present in "aged garlic extract") → antioxidant, better tolerated by the stomach.

⚠ Allicin is unstable — heat treatment (cooking) breaks it down quickly. Raw, crushed garlic = maximum activity. Cooked garlic = almost no allicin.

▶ What the Science Actually Says (Proven vs. Anecdotal)

actually says:

Clinically confirmed (moderate level of evidence):

A mild reduction in blood pressure (systolic ~5–8 mmHg in meta-analyses of hypertensive patients).

A mild reduction in total cholesterol and LDL (the effects are statistically significant but clinically modest).

Antiplatelet action — measurable in laboratory and clinical studies.

⚠ **Weak or inconsistent evidence:**

Prevention and treatment of the common cold — a Cochrane systematic review (Lissiman et al., CD006206, last updated 2014) identified only one quality study (146 participants, 12 weeks): fewer colds in the garlic group (24 vs. 65), but no difference in the number of days to recovery. The Cochrane review's conclusion: the evidence is insufficient for a firm recommendation, and more quality studies are needed.

"Cleaning out the arteries" — a marketing claim that overstates the actual findings.

□ Anecdotal / unproven:

Treating serious infections (it does not replace antibiotics).

Anticancer effects in humans — in vitro findings do not equal clinical efficacy; there is not sufficient human clinical evidence of an anticancer effect.

▶ Preparation and Dosage (Specifics)

> **| Form | Amount | Frequency | Note |**
> |---|---|---|---|

> **| Fresh, crushed clove | 1–2 cloves (4–8 g) | 1× daily | Crush and wait 10 minutes before use — activates allicin |**
> | Powder (standardized) | 200–400 mg | 2–3× daily | Check the allicin percentage on the label |

> **| "Aged garlic extract" (AGE) | 600–1200 mg | 1–2× daily | Contains no allicin, but rich in S-allyl cysteine; gentler on sensitive stomachs |**
> | Essential oil | □ NOT oral without professional supervision | — | Highly concentrated, hepatotoxic at higher doses |

> **Duration: Studies typically run 8–12 weeks. Long-term use of fresh garlic as food — no time limit. Extracts used for longer than 3 months → consult a doctor.**

> "A pinch in a dish" ≠ a therapeutic dose — and conversely: a therapeutic dose of extract ≠ a harmless seasoning amount.

▶ Contraindications (Who Should NOT Use It)

Before surgery (at least 2 weeks prior — stop taking extracts/supplements).

Active peptic ulcer — may aggravate irritation of the gastric mucosa.

Allergy to plants of the genus Allium (onion, chives, leek).

Pregnancy at high (supplemental) doses — [the safety of high doses has not been sufficiently studied in human trials; culinary use is considered safe].

▶ Drug Interactions (+ Why)

> **Warfarin and other anticoagulants (Sintrom, Xarelto, Eliquis)**
> → Garlic inhibits platelet aggregation (ajoenes block thromboxane A2) and may potentiate warfarin's effect through a mechanism that is not fully understood (a partial contribution from CYP2C9 inhibition is suspected, alongside the antiplatelet effect) — the interaction is well documented through case reports and clinical observation, though the precise relative contribution of each mechanism has not been quantified. Result: prolonged bleeding time, greater risk of hematoma.

Antiplatelet drugs (aspirin, Plavix/clopidogrel)
→ Additive effect on platelet aggregation — the double inhibition can be clinically significant, especially in cardiac patients on therapy.

Antihypertensives
→ Mild additive blood-pressure lowering — generally not a problem in well-controlled patients, but hypotension is possible if combined with multiple blood pressure medications.

Antidiabetics (insulin, metformin)
→ Garlic can mildly lower blood glucose. Additive effect — monitor blood sugar in diabetics on therapy.

HIV medications (saquinavir and similar protease inhibitors)
→ There are indications that garlic at high doses reduces the bioavailability of some antiretroviral drugs (mechanism: presumed induction of intestinal transporters) — the level of evidence is limited (mostly small studies and reports), but potentially clinically relevant given the narrow therapeutic range of these drugs.

▶ Pharmacist's Note (Unexpected)

Standardization is chaotic — two products both labeled "garlic extract" can have a 10-fold difference in allicin concentration. Look for "allicin yield" or "allicin potential" on the label, not just "garlic extract." Garlic

essential oil is never taken internally without dilution and professional supervision — even 1–2 drops of the pure oil can cause esophageal burns.

Black Pepper *(Piper nigrum)*

● **MODERATE RISK** As a spice: safe. As a concentrated extract/piperine supplement: proven, clinically relevant interactions with multiple drugs (inhibition of CYP3A4, CYP2C9, and P-gp transporters).

> *It's in every curry powder, in every salami — but neither your grandmother nor her doctor probably knows that a pinch of pepper can raise carbamazepine blood levels by nearly 50%.*

▶ Traditional Use

In Ayurvedic medicine, black pepper is so central that it appears in roughly two-thirds of all traditional formulations — chiefly as a bioenhancer, boosting the absorption of other herbal remedies. It has traditionally also been used for digestion, bloating, sore throat, and as a general digestive stimulant.

▶ Active Compound → Effect

The key compound is piperine — the alkaloid that gives pepper its characteristic pungency. Piperine acts in two ways:

1. It inhibits the enzymes that break down drugs and nutrients in the intestine and liver (CYP3A4, CYP2C9, CYP1A2) — as a result, substances remain in the blood longer at higher concentrations.

2. It blocks P-glycoprotein (P-gp) — the pump that actively expels drugs from the intestine back into the lumen, reducing absorption. When piperine shuts down that pump, the drug stays in the body.

Research shows piperine can increase the absorption of curcumin (from turmeric) by 30–60%, and in one study even more dramatically — 20 mg of piperine with 2 g of curcumin increased curcumin's bioavailability 20-fold. [Addendum S23 — IMPORTANT CRITICAL NUANCE: the original "2000%" figure (Shoba et al. 1998) is a real published study, but it has not proven generalizable — a critical 2025 pharmacokinetic reanalysis shows that piperine does NOT increase unconjugated (biologically active) curcumin in plasma, only the total level (predominantly inactive conjugated metabolites); the mechanism is inhibition of glucuronidation, which carries its own risks (glucuronidation protects against toxins and participates in the metabolism of many drugs). Claims of "enhanced bioavailability" based only on total curcumin overstate the actual benefit.]

▶ What the Science Actually Says (Proven vs. Anecdotal)

Clinically proven:

Piperine at a dose of 20 mg/day for 10 days increased the AUC (area under the curve — a measure of total drug exposure) of carbamazepine by 48% in healthy volunteers, consistent with CYP3A4 inhibition.

In another clinical study, the same dose of piperine increased the AUC of fexofenadine (an antihistamine) by 68%, likely through P-gp inhibition.

Pretreatment with 15 mg of piperine daily for three days increased midazolam bioavailability by 20% in a clinical study on healthy subjects.

Anecdotal / preclinical (insufficient clinical evidence):

Anti-inflammatory, antioxidant, and potential antitumor properties of piperine — extensively studied in animals and in the lab, but clinical evidence in human medicine is still modest. [Need to check whether solid Cochrane reviews exist for these indications.]

▶ Preparation and Dosage (Specifics)

> **| Form | Dose | Note |**
> |---|---|---|

> **| Ground pepper as a spice | ~1–5 mg piperine per meal | Safe for daily use |**
> | Standardized extract (BioPerine® or generic) | 5–20 mg piperine/day | Clinically active range — interactions possible |

> **| Black pepper essential oil | [Not recommended for oral use without professional supervision] | Piperine concentration varies, no standardized dosing |**
> Important distinction: A pinch of pepper on food provides only a few milligrams of piperine. Extract

> capsules can contain 5–20 mg of piperine in a single dose — precisely the range in which clinically relevant interactions have been documented. Do not equate a "natural spice" with a "supplement."

▶ Contraindications (Who Should NOT Use It)

Pregnancy and breastfeeding — [Insufficient data; animal studies suggest possible reproductive toxicity at high doses; avoid supplements.]

Before surgery (≥2 weeks prior to the procedure) — possible effect on the metabolism of anesthesia and anticoagulant drugs.

Active diseases of the stomach and esophagus (ulcer, GERD) — the pungency can worsen symptoms.

Children under 2 years old — risk of mucosal irritation.

▶ Drug Interactions (+ Why)

> **This is the most important part — and it applies chiefly to piperine-extract supplements, not to pepper used in cooking in normal amounts.**
>
> Mechanism: Piperine inhibits the CYP3A4 and CYP2C9 enzymes in the intestinal mucosa and liver — these are the "breakdown factories" for a huge number of drugs. When those factories slow down, drugs are broken down more slowly → their blood levels rise → the effect (and toxicity) is amplified. At the same time, it inhibits

P-gp, which otherwise reduces drug absorption from the intestine.

Clinical studies show that piperine (usually at doses of 20 mg/day) can inhibit CYP3A4, CYP2C9, and P-gp, resulting in a moderate rise in plasma concentrations of substrates of these enzymes — including carbamazepine, midazolam, diclofenac, phenytoin, and possibly warfarin and digoxin.

Specifically:

Carbamazepine (antiepileptic): ↑ level → risk of toxicity (dizziness, double vision, confusion)

Phenytoin (antiepileptic): ↑ level → narrow therapeutic window, caution warranted

Warfarin (anticoagulant): Piperine inhibits formation of warfarin's main metabolite (7-hydroxywarfarin) in vitro, and there is also evidence it can displace warfarin from plasma proteins — the net effect would be an increase in free warfarin and a bleeding risk; a clinical study in rats showed no statistically significant change, but the authors explicitly recommend clinical testing before use in patients on anticoagulant therapy.

Digoxin (cardiac glycoside): [No clinical data yet, but in vitro P-gp inhibition suggests a potential risk — patients on digoxin should not take piperine supplements without consulting a doctor.]

HIV medications (protease inhibitors), immunosuppressants (cyclosporine, tacrolimus), statins — all are CYP3A4 substrates with a

narrow therapeutic window; an interaction is plausible.

Propranolol and theophylline: [An older 1991 clinical study documented increased bioavailability of both drugs with piperine — the original reference needs to be checked.]

▶ Pharmacist's Note (Unexpected)

Piperine can enhance the absorption of drugs and nutrients by increasing gastrointestinal blood flow, reducing hydrochloric acid secretion, increasing the intestine's emulsifying capacity, and stimulating transport enzymes in the intestinal mucosa. That's why piperine is deliberately added to many commercial curcumin supplements — but that same property makes it a potential enhancer of drugs that should not be enhanced.

Another surprising fact: piperine stimulates melanocyte replication and the formation of melanocyte dendrites, which is being studied as a potential treatment for vitiligo.

Lingonberry *(Vaccinium vitis-idaea)*

● **MODERATE RISK** safe as food and as fruit tea; the leaf contains arbutin, which the body breaks down into hydroquinone, a substance with potential toxicity at high doses or with long-term use

> *In Russian and Belarusian pharmacopoeias, lingonberry leaf holds official status as a medicine for the urinary tract — but in Western European pharmacies, that very same plant sits exclusively on the jam shelf. Who's hiding what from whom?*

▶ Traditional Use

Leaf tea has been used for centuries in northern and eastern Europe for urinary tract infections, as a mild diuretic, and for "cleansing the blood." The leaves and fruit have traditionally been used in Asia and Europe as a natural remedy for the urinary tract. The fruit is eaten fresh or as jam, and in the Scandinavian countries it is an everyday food. In the Russian pharmacopoeial tradition, the leaf is also an ingredient in "Brusniver," a polyherbal blend for genitourinary infections.

▶ Active Compound → Effect

There are two entirely different stories here, depending on whether you use the leaf or the fruit:

LEAF — the key compound is arbutin (about 4% in dried leaves). Arbutin is a beta-glucoside of hydroquinone with proven antimicrobial, antioxidant, and anti-inflammatory properties, used in treating urological infections. Lingonberry leaves contain arbutin and other hydroquinone derivatives and can be used for their antiseptic properties. Mechanism: arbutin is hydrolyzed in the urine to free hydroquinone, which acts as a urinary antiseptic — but only in alkaline urine, an important caveat.

FRUIT — dominated by type-A proanthocyanidins, anthocyanins (cyanidin-3-galactoside), quercetin glycosides, and catechins. Lingonberry fruit contains no arbutin or hydroquinone derivatives — so the fruit's mechanism of action is entirely different from the leaf's: bacterial adhesion to the bladder wall is physically hindered (similar to cranberry, V. macrocarpon), and the anti-inflammatory action works through modulation of the immune response. Trimeric and dimeric proanthocyanidins from the leaves and fruit have shown the strongest antimicrobial, antioxidant, and anti-inflammatory potential.

▶ What the Science Actually Says (Proven vs. Anecdotal)

Most research describes results from in vitro experiments. The situation by level of evidence:

In vitro (laboratory, cell cultures): solid evidence for the antimicrobial, antioxidant, and anti-inflammatory action of extracts.

In animals: lingonberry supplementation significantly prevents metabolic and inflammatory changes in a mouse model of obesity.

Human clinical studies: results suggest that more studies in humans are needed.

▶ Preparation and Dosage (Specifics)

> **| Form | Amount | Frequency | Note |**
> |---|---|---|---|

> **| Dried leaf tea | 2–3 g of leaf / 150 ml boiling water, steep 10–15 min | 3–4 times daily | Standard pharmacopoeial recommendation |**
> | Fresh fruit / jam | Free consumption as food | — | No time limit |

> **| Fruit juice (unsweetened) | 100–200 ml | 1–2x daily | Moderate data |**
> | Standardized leaf extracts | As directed by the manufacturer | — | Watch the arbutin content |

> **Critical distinction: A teaspoon of dried leaf ≠ a high-dose extract. Pharmacopoeial use of the leaf is limited to a maximum of 2–4 weeks because of the potential accumulation of hydroquinone with long-term use.**
>
> There is no dedicated EU/EMA/HMPC herbal monograph for Vaccinium vitis-idaea, folium (lingonberry leaf) — a search of the official list of EMA herbal monographs does not confirm one. Regulatory guidance and safety assessment therefore rely on analogy with Arctostaphylos uva-ursi (bearberry), which has an established EMA/HMPC monograph and an identical mechanism of action (arbutin).

▶ Contraindications (Who Should NOT Use It)

Pregnancy and breastfeeding — insufficient safety data for the leaf; consuming the fruit as food is probably safe, but leaf extracts are not recommended.

Kidney disease (chronic renal insufficiency) — hydroquinone is excreted by the kidneys; impaired function means a risk of accumulation.

Children under 12 — no established safety for leaf extracts.

Known allergy to plants of the family Ericaceae (blueberry, bearberry, heather).

▶ Drug Interactions (+ Why)

> **This is the most important part — two different pathways depending on which part of the plant:**

1. Anticoagulants (warfarin, heparin) — ⚠ caution:

Bilberry (Vaccinium myrtillus) and horse chestnut increase the risk of bleeding with warfarin. The same mechanism is likely for lingonberry: proanthocyanidins and flavonoids from the genus Vaccinium may inhibit platelet aggregation and modulate CYP2C9 (the enzyme that breaks down warfarin), which could raise the drug's blood level and increase the INR. Direct clinical data specific to V. vitis-idaea and warfarin are weak — the conclusion is extrapolated from related species in the same genus, not from clinical studies on lingonberry itself.

2. Lithium and diuretics:

Lingonberry has a mild diuretic effect. Increased fluid excretion can reduce lithium clearance and increase toxicity. The same applies to combination with thiazide diuretics — cumulative electrolyte loss.

3. Drugs that acidify/alkalinize the urine:

Arbutin from the leaf works only in an alkaline environment (urine pH > 7). Taking vitamin C (ascorbic acid), which acidifies the urine, directly blocks arbutin's antimicrobial effect. The paradox: many UTI preparations combine these two components.

4. Nephrotoxic drugs (NSAIDs, aminoglycosides, cyclosporine):

Hydroquinone formed from the breakdown of arbutin is potentially nephrotoxic at high doses. Combining it with drugs that already burden the kidneys is not advisable with long-term use of the leaf.

▶ Pharmacist's Note (Unexpected)

The compounds that actually reach the bloodstream after oral use of lingonberry leaf extract are arbutin and fraxin — both present in the plant in their original form. Fraxin (a coumarin glycoside) has anti-inflammatory and antitussive effects, but is rarely mentioned in the popular literature. Another unexpected fact: there is active scientific interest in the neuroprotective effects of lingonberry extracts and their anti-cytokine and antiapoptotic activity — a potential not mentioned at all in traditional use.

Red Yeast Rice *(Monascus purpureus)*

● **HIGH RISK** the active compound is chemically identical to a prescription drug (lovastatin); EU regulation classified it as a restricted substance in 2022, and in 2025 EFSA concluded that no safe dose threshold exists for supplements.

> *The label says "natural supplement for cholesterol" — but what you're buying may be the pharmacological equivalent of a drug that cannot legally be dispensed without a prescription. In 2025, the European Food Safety Authority announced that no dose is safe.*

▶ Traditional Use

Used for more than 1,000 years in Chinese medicine and cuisine (as a coloring and preservative in tofu and meat). In China it was used to improve circulation and digestion and as a "tonic for the blood" — but in culinary, non-concentrated amounts. Modern supplements are concentrated extracts, which is a fundamental difference.

▶ Active Compound → Effect

Monacolin K is the key substance. It is chemically identical to lovastatin — a drug prescribed in Serbia

and the EU for lowering cholesterol. The mechanism is the same: it inhibits the enzyme HMG-CoA reductase in the liver, which controls cholesterol synthesis. Besides monacolin, red yeast rice also contains pigments, flavonoids, lignans, terpenoids, and polysaccharides that may contribute to the overall effect, but their individual contributions are poorly studied.

▶ What the Science Actually Says (Proven vs. Anecdotal)

Clinically proven:

Research shows that red yeast rice containing larger amounts of monacolin K can lower total cholesterol as well as LDL cholesterol.

Clinical trials show reductions in LDL cholesterol of roughly 15–34%, with effects comparable to low-dose statins.

One multicenter study of 5,000 patients showed that long-term therapy with a purified red yeast rice extract significantly reduced cardiovascular events and overall mortality by 30% and 33%. [To verify: this is the Lu et al. 2008 study, conducted in China with a specific formulation; reproducibility in Western populations and with commercial supplements has not been confirmed with the same strength of evidence.]

Critical problem — product variability:

The monacolin K content of commercial supplements varies drastically between brands, and this is not

always stated on the label. The same name on the box can conceal a tenfold difference in the dose of active substance.

Regulatory warning (current):

EU Regulation 2022/860 limits the monacolin content of supplements to less than 3 mg per daily dose and restricts use to people between 18 and 70 years old. EFSA in 2025 concluded that exposure to monacolin K from red yeast rice, even at doses of 3 mg/day, can cause serious adverse effects on the muscular system, including rhabdomyolysis, and on the liver. EFSA concluded that there is insufficient evidence to establish a safe daily intake of monacolin, and a complete EU-wide ban is the most likely scenario going forward.

▶ Preparation and Dosage (Specifics)

> **| Form | Typical dose used in studies | Note |**
> |---|---|---|

> **| Extract capsules/tablets | 1,200–2,400 mg/day (= 10 mg monacolin K) | This is a pharmacological dose — equal to a therapeutic dose of lovastatin |**
> | EU supplements (post-2022) | Max < 3 mg monacolin K/day | Effectiveness at this level is not proven |

> **| Culinary use (coloring in dishes) | Negligible dose of active substance | Safe as a seasoning |**
> Key distinction: A teaspoon of red yeast rice in a recipe and capsules of concentrated extract are not the same

> thing. There is no "natural" and "harmless" version of the supplement — the compound that acts is the very same one found in the drug.

▶ Contraindications (Who Should NOT Use It)

People already taking statins (simvastatin, atorvastatin, rosuvastatin, etc.) — absolute contraindication

Pregnant and breastfeeding women

People with liver disease or elevated liver enzymes

People with kidney disease

Children and adolescents (under 18)

Adults over 70 (EU restriction)

People with a history of myopathy or rhabdomyolysis

▶ Drug Interactions (+ Why)

> **This is the most important part — treat it as a drug, not as a tea.**
>
> 1. Statins (lovastatin, atorvastatin, simvastatin, rosuvastatin)

> **→ Danger: high. Combining red yeast rice with prescription statins effectively doubles statin exposure and significantly raises the risk of myopathy and rhabdomyolysis. Mechanism: additive inhibition of the same enzyme (HMG-CoA reductase) — the body does not distinguish between a "natural" and a synthetic source.**

2. CYP3A4 inhibitors (clarithromycin, erythromycin, itraconazole, ketoconazole, diltiazem, verapamil)

→ Danger: moderate to high. These drugs inhibit liver enzymes (CYP450, especially CYP3A4) that break down monacolin K — its buildup in the blood increases the risk of adverse effects on the liver and muscles.

3. Gemfibrozil and fibrates

→ Combining with these cholesterol drugs increases the risk of muscle problems. Mechanism: pharmacodynamic synergy — fibrates carry their own risk of myopathy, which adds to monacolin's statin-like effect.

4. Warfarin (anticoagulant)

→ Red yeast rice may potentiate warfarin's anticoagulant effect, requiring INR monitoring. [The mechanism is not fully understood — a possible interaction at the level of CYP enzymes or a direct effect on clotting factors. To verify: the evidence is weaker here — mostly case reports, not randomized trials.]

5. Grapefruit juice

→ Grapefruit is a potent CYP3A4 inhibitor and should be avoided with red yeast rice — the same mechanism as with statins (slowed breakdown → monacolin buildup).

6. St. John's Wort (Hypericum perforatum)

→ The opposite problem: St. John's Wort speeds up CYP3A4 and may reduce monacolin's

effectiveness. [Clinical significance uncertain — to verify.]

7. Alcohol

→ Combining alcohol and red yeast rice may increase hepatotoxicity, since both burden the liver.

▶ Pharmacist's Note (Unexpected)

Monacolin K is chemically identical to lovastatin — the main active ingredient of a prescription drug. In the US, the FDA considers products containing more than trace amounts of lovastatin to be unapproved drugs, not supplements. In the EU, despite a proven effect on LDL, EFSA in 2025 could not establish a safe dose threshold even at the lowest available concentrations.

Another unexpected risk: the presence of citrinin — a nephrotoxic mycotoxin that some strains of Monascus purpureus can produce. EU regulation sets a maximum citrinin level (100 µg/kg), but quality control varies between brands.

Third: monacolins also block the synthesis of coenzyme Q10 (CoQ10), which is important for muscle function — just like pharmaceutical statins. Some experts recommend supplemental CoQ10 intake, though the evidence for this is not strong. [To verify.]

Horse Chestnut *(Aesculus hippocastanum)*

● **MODERATE RISK** interactions with anticoagulants and diuretics; toxicity of raw seeds

> *The same chestnut tree whose seeds children collect in the park is the source of a standardized extract that has been included in chronic venous insufficiency guidelines since 2002 — but only if you take the right form and the right dose. The raw seed is poisonous.*

▶ Traditional Use

Folk medicine across Europe has used horse chestnut bark, seed, and leaf for centuries for "heavy legs," veins that ache and swell in the evening, hemorrhoids, and bruises. The seed was crushed into a powder to make a poultice for sprains and swelling; the bark was used as a tea against fever and diarrhea (due to its tannins). Today, the only application with real scientific grounding is the standardized seed extract for chronic venous insufficiency.

▶ Active Compound → Effect

Aescin (escin) — a mixture of triterpene saponins from the seed — is the main carrier of the effect.

Mechanism: it reduces capillary permeability and boosts venous wall tone (likely via prostaglandins and by reducing the activity of enzymes that break down proteoglycans in the vein wall), which decreases fluid leakage into surrounding tissue.

Simply put:

Aescin "seals" leaky leg veins, so less fluid escapes into the tissue — hence less swelling and heaviness in the legs by evening.

The raw seed and leaf also contain aesculin (a coumarin glycoside) — a compound structurally similar to warfarin but with a much weaker effect; aesculin is precisely why the raw seed is considered toxic and why standardized extracts must be purified to remove it.

▶ What the Science Actually Says (Proven vs. Anecdotal)

✔ Proven (Cochrane review, multiple RCTs): The standardized seed extract (16–20% aescin) reduces the symptoms of chronic venous insufficiency (pain, itching, swelling, leg heaviness) better than placebo, with efficacy comparable to compression stockings in some trials.

⚠ More weakly supported: Use for hemorrhoids — small studies show a positive signal, but they are not large enough to be considered confirmed.

 Not proven: Any effect on varicose veins as a structural change (the extract does not "cure" veins, it only relieves symptoms), nor the claims about "cleansing blood vessels" or antitumor effects that circulate in popular literature.

▶ Preparation and Dosage (Specifics)

> **| Form | Preparation | Dose | Note |**
> |---|---|---|---|

> **| Standardized seed extract (16–20% aescin) | Ready-made pharmaceutical preparation, capsules/tablets | 100 mg aescin daily (usually split into 2 doses) | The only form with clinical evidence; sold as "Venostat," "Aescin," and similar |**
> | Bark tea (traditional) | 1 teaspoon finely chopped bark per 250 ml water, boil 10 min | Up to 2 cups daily, short-term | Weak evidence for efficacy; contains aesculin |

> **| Raw seed / leaf | — | NEVER for internal use | Toxic — contains aesculin and glycosides, causes nausea, vomiting, and in severe cases paralysis |**
> | Topical gel/cream (aescin) | Ready-made pharmaceutical preparation | As directed by manufacturer | For local application to swollen areas |

> Key distinction: the standardized pharmaceutical extract has been tested and the aescin is purified of toxic accompanying compounds; the raw seed/fruit (the "chestnut" children collect) is NOT the same thing

and is not for eating or brewing as tea in any significant amount.

▶ Contraindications (Who Should NOT Use It)

Pregnant and breastfeeding women — insufficient safety data on the standardized extract during pregnancy; traditionally avoided.

Renal or hepatic insufficiency — aescin is metabolized and excreted via these organs; caution and lower doses advised.

Coagulation disorders or anticoagulant therapy — due to aesculin (a coumarin derivative) and a theoretical additive effect on coagulation.

Children — the raw seed is extremely toxic (cases of poisoning have been reported in children who swallowed the seeds); the standardized extract is not recommended without pediatric supervision.

Allergy to Aesculus species or latex (possible cross-reactivity, poorly documented [low level of evidence]).

▶ Drug Interactions (+ Why)

> **This is the most important part — and the part where the data are mixed.**
>
> 1. Anticoagulants (warfarin, heparin, NOACs) — ⚠ moderate to high risk

> **Aesculin (in the raw form) is structurally similar to coumarins; standardized extracts are purified**

of aesculin, so the risk is significantly lower, but manufacturers still recommend caution and INR monitoring in patients on anticoagulant therapy.

2. Antiplatelet drugs (aspirin, clopidogrel) — ⚠ moderate risk, [weak evidence]

A theoretical additive effect on hemostasis; clinical significance is not well established, but it is described in product safety summaries.

3. Drugs metabolized via the kidneys (e.g., aminoglycoside antibiotics) — ⚠ low to moderate risk

There are isolated reports of aescin nephrotoxicity at high intravenous doses (historically, in hospital use); relevance to oral standardized doses is low, but it is mentioned in the literature.

4. Lithium and diuretics — ⚠ low risk, [theoretical]

There is no direct clinical evidence, but general caution is recommended when combining any preparation with a mild effect on fluids/electrolytes with lithium therapy.

▶ Pharmacist's Note (Unexpected)

The standardized horse chestnut seed extract (also known as Aescin/Venostat/Reparil) is one of the few herbal preparations for venous insufficiency to have a complete EMA/ESCOP herbal monograph with "well-established use" status — meaning clinical documentation comparable to conventional drugs is available for it, a rarity in phytotherapy.

Another unexpected fact: horse chestnut is not eaten (unlike the sweet chestnut, Castanea sativa) — the seeds are bitter and toxic raw due to saponins and glycosides, even though they look almost identical to the edible chestnut, which is a common source of confusion and accidental poisoning in children and pets.

Dong Quai *(Angelica sinensis)*

● **MODERATE RISK** interactions with anticoagulants, phototoxicity, dose-dependent hormonal effect

> *In traditional Chinese medicine it's called "female ginseng" — but unlike ginseng, it can seriously disrupt blood clotting in someone taking warfarin. On pharmacy shelves it's sold as "natural hormonal support," yet its active substance doesn't resemble any of the plant hormones usually expected.*

▶ Traditional Use

In TCM (traditional Chinese medicine) it has been used for at least 2,000 years as a tonic for the female reproductive system — to regulate the menstrual cycle, ease dysmenorrhea (painful periods), and relieve menopausal symptoms. It is also used to "tonify the blood" (blood deficiency in TCM terminology), relieve constipation, and as an analgesic for arthritic pain. In Japan it is registered as Toki and is a component of complex formulas (Kampo medicine). The root is the primary part used, and it is traditionally simmered into a decoction with other herbs.

▶ Active Compound → Effect

Z-ligustilide — the main active compound (a phthalide, an aliphatic compound). It relaxes the smooth muscle

of the uterus and blood vessels (a spasmolytic effect), acts as an antiplatelet agent, and has anti-inflammatory properties. This is not a phytoestrogen in the classic sense — Z-ligustilide is neither an isoflavone nor a lignan.

Ferulic acid — an antioxidant that inhibits platelet aggregation (thinning the blood slightly at the biochemical level). This is key to understanding the interactions.

Polysaccharides (ASP) — immunomodulatory effect in preclinical studies. weak evidence in humans

Coumarins (osthole) — phototoxic potential with topical use or high doses; vasodilatory effect.

Phytoestrogenic activity: controversial — the extract shows a weak estrogenic effect in vitro on the ER-α receptor, but clinical significance in humans has not been clearly confirmed. It is not equivalent in potency to red clover or soy. [This is an area of active scientific debate — recommend verification.]

▶ What the Science Actually Says (Proven vs. Anecdotal)

partially proven Dysmenorrhea and menstrual cramping — clinical data (mostly from Chinese studies) support a spasmolytic effect; the methodological quality of the studies is moderate. A Cochrane review of combined TCM formulas offers limited conclusions because dong quai is rarely studied alone.

anecdotal / weak evidence Menopause and hot flashes — RCTs using an isolated dong quai extract have not shown superiority over placebo in reducing hot flashes. Effects seen in combination formulas are harder to attribute to this plant specifically.

preclinical Immunomodulation, antitumor effect — in vitro and animal models exist, but there is no robust clinical evidence in humans. [Should check whether anything new has been published since 2023.]

proven Antiplatelet effect — ferulic acid and Z-ligustilide show measurable inhibition of platelet aggregation, including in human studies. This is not disputed — which is why the interactions are real.

▶ Preparation and Dosage (Specifics)

Dried root (decoction / tea): 3–15 g daily, simmered 20–30 min, divided into 2–3 doses. This is the traditional TCM range — bioavailability varies, and dose depends on the combination with other herbs

Standardized extract (capsules/tablets, 4:1 or 5:1): 200–600 mg daily standardized to 0.8–1% ligustilide; typically 1–2 capsules with a meal. This is 4–5x more concentrated than the raw root — a pinch of raw root ≠ an extract capsule.

Tincture (1:5, 45% ethanol): 2–3 ml, 3x daily. [Standardization varies between manufacturers — check the CoA.]

Duration: TCM tradition does not recommend continuous use beyond 3 months without a break. Do

not take during menstruation (may increase bleeding). [There are no firm clinical guidelines for optimal duration — this is empirical.]

▶ Contraindications (Who Should NOT Use It)

Pregnancy — an absolute contraindication. It stimulates uterine contractions (a uterotonic effect). Risk of miscarriage.

Hormone-dependent tumors — breast, endometrial, ovarian, or uterine cancer — due to the potential estrogenic effect. [The actual degree of risk is uncertain given the weak phytoestrogen data, but the precautionary principle calls for avoidance.]

Coagulopathies and upcoming surgery — discontinue at least 2 weeks before surgery due to the antiplatelet effect.

Active bleeding or heavy menstruation.

Children — no safety data available.

Allergy to Apiaceae (carrot, celery, parsley, dill) — possible cross-reactivity.

▶ Drug Interactions (+ Why)

MOST IMPORTANT

WARFARIN and anticoagulants — High risk. Ferulic acid and Z-ligustilide inhibit platelet aggregation and potentially inhibit CYP2C9 (the enzyme that breaks down warfarin). Combined effect: prolonged clotting

time, elevated INR, risk of bleeding. Clinical cases of potentiated warfarin effect have been documented.

Aspirin, clopidogrel, ticagrelor — additive antiplatelet effect (both inhibit platelets, each by a different mechanism, but the sum is cumulative). Risk of spontaneous bleeding.

NSAIDs (ibuprofen, naproxen) — mildly increased risk of gastrointestinal bleeding from the combined antiplatelet effects.

Hormonal contraception and HRT — potential modulation of estrogen receptors. Clinical significance unknown, but the interaction is biologically plausible. [Clinical studies are lacking — a precautionary recommendation.]

Tamoxifen — a theoretical conflict at the level of estrogen receptors. Avoid the combination. [Preclinical data, not clinical — flagged as unconfirmed.]

Immunosuppressants (cyclosporine, tacrolimus) — possible CYP3A4 inhibition [weak preclinical signal — check for updated data].

Mechanism in one sentence: dong quai "thins the blood" in two ways at once (antiplatelet action + potential CYP2C9 enzyme inhibition), which amplifies the effect of any drug that already slows clotting on its own.

▶ Pharmacist's Note (Unexpected)

Phototoxicity: The coumarin content can increase skin sensitivity to UV rays (photodermatitis). Especially

relevant for topical use or high oral doses combined with prolonged sun exposure.

Smell and taste are reliable quality indicators: Authentic root has a strong, distinctive aroma similar to Maggi seasoning. Odorless or faintly scented preparations indicate poor quality or adulteration.

Different chemotypes: Multiple chemotypes of the plant exist depending on the growing region (Gansu, Yunnan). Z-ligustilide content can vary by up to 3-fold. This is a pharmaceutically relevant issue — the same "standardized" extract from different sources can have a substantially different activity profile.

Do not confuse with A. archangelica (European angelica) — a completely different chemical profile and indications, despite the similar Latin name.

Devil's Claw *(Harpagophytum procumbens)*

● **MODERATE RISK** mostly safe at recommended doses, but a documented interaction with anticoagulants and a contraindication in ulcers/ gallstones make it unsuitable for self-treatment without consultation

> *In pharmacies across southern African cities this plant is so popular that root exports have sparked debates about threats to wild populations — all because of a crooked, hook-covered fruit that looks like an instrument of torture.*

▶ Traditional Use

The San peoples of southern Africa used devil's claw root for joint pain, digestive complaints, and as a bitter tonic. It arrived in Europe in the early 20th century and quickly became a standard herbal medicine for rheumatic pain.

▶ Active Compound → Effect

The key compound is harpagoside (an iridoid glycoside from the secondary tuberous roots). It acts in two ways: it curbs prostaglandin synthesis and inhibits the NF-κB signaling pathway — two major "amplifiers" of inflammation in tissue. Result: reduced pain and

stiffness in the joints. The secondary tuberous roots contain twice as much harpagoside as the primary root, so the origin of the part used matters for the quality of the preparation.

▶ What the Science Actually Says (Proven vs. Anecdotal)

Clinically supported:

Clinical trials using extracts with 50–60 mg of harpagoside daily have produced the most reliable data for lower back and joint pain — this is the only indication for which the EMA (2016) recognizes "well-established use," a higher standard than mere "traditional use."

The EMA recommends use for at least 2–3 months to see an effect in osteoarthritis.

Anecdotal / insufficiently studied:

Use as a digestive tonic has a long tradition, but there are no robust clinical studies.

An antidiabetic effect and an effect on blood pressure are mentioned in preclinical research — [there are not enough human studies; this should not be presented as proven].

▶ Preparation and Dosage (Specifics)

> | **Form** | **Harpagoside Dose** | **Note** |
> |---|---|---|

| Dry extract (capsules/tablets) | 50–100 mg harpagoside/day | Standardized extracts are most reliable |

| Dried root (tea/decoction) | 0.6–7.5 g dried tuberous root daily | Bitter taste; lower bioavailability |

| Tincture | [Dosing varies by manufacturer — always check the harpagoside percentage on the label] | — |

⚠ Key distinction: a "pinch of dried root" in tea does not have the same harpagoside concentration as a standardized extract capsule — they cannot be swapped for one another by feel.

▶ Contraindications (Who Should NOT Use It)

Gastroduodenal ulcer — the plant increases gastric acid secretion (bitter tonic)

Gallstones — stimulates bile secretion, may trigger colic

Pregnancy — [in vitro data suggest a uterotonic effect; clinical relevance is unclear, but caution is necessary — *[weak evidence, but a reason for strict avoidance]]

Children under 18 — no data available

▶ Drug Interactions (+ Why)

(+ why) — ⚠ MOST IMPORTANT PART:

1. Warfarin and anticoagulants — HIGH risk of bleeding

> **Devil's claw is documented as a plant that potentiates warfarin's anticoagulant effect. In vitro, the extract moderately inhibits CYP2C8, CYP2C9, CYP2C19, and CYP3A4 — and CYP2C9 is precisely the main enzyme that breaks down warfarin in the liver. Less breakdown = more warfarin in the blood = higher INR = greater risk of bleeding. Reported cases include purpura (bruise-like bleeding spots on the skin) as a sign of a potentiated effect.**
>
> 2. Antidiabetics (insulin, metformin)

> **[Preclinical data suggest a hypoglycemic effect — [the mechanism is not sufficiently clarified in humans; the combination calls for glucose monitoring, but the strength of the evidence is weak]]**
>
> 3. Antihypertensives

> **[There are indications it may mildly lower blood pressure — [insufficient human studies; caution when combining, especially with calcium channel blockers]]**
>
> 4. Drugs metabolized by the CYP450 system

Due to the CYP enzyme inhibition mentioned above, it may theoretically slow the breakdown and raise the levels of other narrow-therapeutic-index drugs (e.g., certain antiarrhythmics, immunosuppressants) — [in vitro evidence; clinical significance at standard doses has not been sufficiently confirmed].

▶ Pharmacist's Note (Unexpected)

Whole-plant extracts show a better therapeutic effect than extracts of isolated components — meaning that concentrating harpagoside alone is not necessarily a superior strategy. This runs counter to the intuition that "more active substance = better," and suggests that synergy between constituents likely plays a role. The quality of standardized products on the market varies considerably.

Echinacea *(Echinacea purpurea)*

● **MODERATE RISK** autoimmune diseases and interactions with immunosuppressants can be serious; short-term use in a healthy adult is relatively safe

> *It's sold in almost every pharmacy as an "immune booster" — but most people don't realize they're taking it in doses that are either too weak to do anything, or at the wrong point in the illness.*

▶ Traditional Use

North American peoples (chiefly the 19th-century Eclectic medicine movement, but also Indigenous communities such as the Lakota and Cheyenne) used the root and aerial parts of the plant for wounds, snakebite, throat infections, and "bad blood." It arrived in Europe in the late 19th century and quickly became one of the best-selling herbal drugs in the world.

▶ Active Compound → Effect

There is no single "main" compound — Echinacea acts through the synergy of several groups:

Alkylamides (especially in E. purpurea aerial parts and root) → bind to CB2 cannabinoid receptors and

modulate macrophage activity; considered the primary carriers of immunomodulatory activity

Polysaccharides (arabinogalactans) → stimulate phagocytosis and cytokine production

Caffeoyl derivatives (chicoric acid, echinacoside) → antioxidant and antiviral effect in vitro [the strength of evidence for isolated compounds is weak outside the laboratory]

Glycoproteins → immunostimulation [evidence mostly from older studies, methodologically weaker]

▶ What the Science Actually Says (Proven vs. Anecdotal)

actually says:

Clinically supported (moderately):

A Cochrane review (Karsch-Völk M. et al., published February 20, 2014, CD000530.pub3 — 24 controlled trials, 4,631 participants) suggests that E. purpurea may modestly shorten the duration of the common cold and reduce the likelihood of catching one if taken preventively or at the first sign of symptoms — almost all preventive trials point toward a small positive effect. The effect is modest and clinically borderline, not strong. [An earlier version of this text incorrectly gave the review's year as 2015 — the correct year is 2014.]

⚠ **Insufficient or contradictory:**

The optimal species (purpurea vs. angustifolia vs. pallida), plant part, and formulation differ between studies — direct comparison is nearly impossible

Long-term prevention lacks well-designed evidence

Severe respiratory infections, influenza, COVID — no solid evidence of efficacy

□ Anecdotal (without clinically acceptable evidence):

Lyme disease, chronic fatigue, "boosting immunity" as a general concept

▶ Preparation and Dosage (Specifics)

> **⚠ Key distinction: a handful of dried plant material ≠ a standardized extract. Echinacea tea and 4:1 extract capsules have completely different bioavailability.**

| Form | Dose | Frequency | Duration |

> **|---|---|---|---|**

| Tea (aerial part, dried) | 1–2 g plant material / 150 ml water | 3x daily | Max. 7–10 days, acute use |

> **| Liquid extract (1:1) | 2–4 ml | 3x daily | Max. 7–10 days |**

| Standardized dry extract (4% alkylamides) | 300–500 mg | 2–3x daily | Max. 7–10 days |

> **| Juice (E. purpurea, e.g., Echinacin) | 6–9 ml | 1x daily | Up to 4 weeks (preventive) |**

> □ Echinacea essential oil: not in standard use and has no dosing recommendations — do NOT use without professional supervision.

Preventive use: can be used continuously for up to 8 weeks, then a break [EMA recommendation — but long-term safety has not been rigorously studied].

▶ Contraindications (Who Should NOT Use It)

Autoimmune diseases (MS, lupus, RA, Crohn's disease, psoriasis) — theoretical risk of worsening due to immune stimulation [not directly proven in RCTs, but a mechanistically justified contraindication]

Allergy to the Asteraceae/Compositae family (ragweed, chrysanthemum, chamomile) — cross-reactivity, potential anaphylactic response

Progressive systemic diseases: HIV/AIDS, tuberculosis, leukemia [an older contraindication based on theoretical considerations; evidence is scarce]

Pregnancy and breastfeeding: insufficient data — avoid [the EMA places this in the "insufficient data" category]

Children under 12: not without pediatrician consultation

▶ Drug Interactions (+ Why)

> ***(MOST IMPORTANT PART)*:**

| Drug / Class | Interaction Type | Mechanism |

|---|---|---|

| Immunosuppressants (cyclosporine, tacrolimus, corticosteroids, azathioprine, methotrexate) | ⚠ Antagonism — DANGEROUS | Echinacea stimulates the immune system (↑ cytokines, ↑ phagocytosis); directly opposite to what immunosuppressants do — can lead to transplant rejection or worsening of autoimmune disease |

| CYP3A4 substrates (midazolam, cyclosporine, some statins, oral contraceptives) | ⚠ Inhibition/ induction | Alkylamides and caffeoyl derivatives may inhibit hepatic CYP3A4 in vitro → potentially elevated levels of drugs metabolized via this pathway [clinical significance mostly weak, but may be individually relevant] |

| CYP1A2 substrates (caffeine, theophylline, clozapine, olanzapine) | ⚠ Possible inhibition | Same mechanism — slowed elimination, possible toxic levels at high doses [in vitro evidence; clinical data scarce] |

| Hepatotoxic drugs (methotrexate, amiodarone, high-dose statins) | ⚠ Additive risk | Isolated cases of hepatotoxicity with echinacea; combination with drugs that already burden the liver requires caution |

| Antiviral drugs (e.g., efavirenz, ritonavir in HIV patients) | ⚠ Double problem | Both pharmacological antagonism (immunosuppressive protocol in HIV) and possible CYP interactions |

▶ Pharmacist's Note (Unexpected)

Most products on the market are not standardized to the same marker compound — one product may be standardized to echinacoside, another to alkylamides, a third to polysaccharides, and all three have a different mechanism and bioavailability. The label "Echinacea 400 mg" tells you almost nothing about clinical efficacy without information on the species, plant part, and standardization marker. Always ask for a CoA (Certificate of Analysis) or a pharmacopoeia-compliant preparation.

Ginkgo *(Ginkgo biloba)*

● **MODERATE RISK** serious interactions with anticoagulants and antiplatelet drugs

> *The tree that survived Hiroshima yields an extract that has been sold for decades as a "memory drug" — but what have the meta-analyses actually shown, and why should every cardiologist know whether a patient is taking ginkgo?*

▶ Traditional Use

Used in Chinese medicine for more than 2,000 years — leaves and seeds against cough, asthma, and urinary complaints. In the West only since the 1960s, when German pharmaceutical companies developed standardized leaf extracts, mainly for cerebral insufficiency and tinnitus.

▶ Active Compound → Effect

Ginkgolides and bilobalide (terpene lactones, ~6%) — block platelet-activating factor (PAF), thereby reducing platelet aggregation and bronchoconstriction.

Flavonol glycosides (quercetin, kaempferol, ~24%) — antioxidant activity, vasodilation, mild monoamine oxidase (MAO) inhibition.

The standardized extract (EGb 761) used in studies contains exactly 24% flavonoids and 6% terpene lactones. The leaves you buy at an herbal pharmacy are not the same preparation.

▶ What the Science Actually Says (Proven vs. Anecdotal)

Proven Symptomatic dementia / Alzheimer's disease — meta-analyses (Cochrane, 2009; several updates) show a moderate, short-term benefit on cognition and daily functioning in already-diagnosed patients, with EGb 761 240 mg/day.

Proven Peripheral arterial disease — the EMA accepts its use for symptomatic treatment of peripheral occlusive arterial disease (stage II).

Weak evidence Prevention of dementia in healthy individuals — the large GEM study (USA, 3,069 participants, 2008) showed no difference in dementia incidence vs. placebo.

Anecdotal Improved concentration and memory in healthy young adults — evidence is contradictory and generally negative in rigorous studies.

Moderate evidence Tinnitus and vertigo — some studies are positive, but methodological quality varies significantly.

▶ Preparation and Dosage (Specifics)

Standardized dry extract (EGb 761 or similar, 50:1):

120–240 mg daily, divided into 2 doses, with a meal. At least 4–6 weeks minimum before assessing effect; studies have run up to 6 months.

Leaf tea:

1–2 g dried leaf / 150 ml boiling water, 10 min. — the therapeutic concentration of active substances is inconsistent and far lower. Not a substitute for the standardized extract.

⚠ Raw ginkgo seeds are toxic (4'-O-methylpyridoxine). Roasted, they are traditionally edible in small amounts, but should not be used as a source of active principles.

▶ Contraindications (Who Should NOT Use It)

Pregnancy and breastfeeding — insufficient safety data; avoid.

Known allergy to plants of the Ginkgoaceae family or cross-reactivity with Anacardiaceae nuts (mango, cashew).

Epilepsy — ginkgolides may lower the seizure threshold [evidence mostly from case reports; mechanism unclear].

Before surgery — discontinue at least 36–48 hours prior due to the antiplatelet effect.

▶ Drug Interactions (+ Why)

(most important part)

Warfarin, acenocoumarol High risk

Ginkgolides inhibit PAF and platelet aggregation → additive effect with anticoagulants → increased risk of bleeding. Cases of intracranial hemorrhage have been reported. Monitor INR more frequently or avoid the combination.

Aspirin, clopidogrel, ticlopidine High risk

Double inhibition of platelet aggregation — ginkgo (PAF pathway) + antiplatelet drug (TXA2/ ADP pathway) = a synergistic, not merely additive, bleeding risk.

SSRIs, SNRIs (sertraline, fluoxetine…) Moderate risk

Weak MAO inhibition by flavonoids + serotonergic drugs → theoretical risk of serotonin syndrome [mostly theoretical; case reports, not RCTs].

Drugs metabolized by CYP3A4 / CYP2C9 Moderate risk

Ginkgo can either induce or inhibit CYP enzymes depending on the dose and preparation → altered plasma concentrations of cyclosporine, tacrolimus, and some antiretroviral drugs. [In vitro data; clinical relevance at standard doses is moderate, but individually variable].

Insulin, oral antidiabetics Moderate risk

Ginkgo may modulate insulin signaling → possible mild reduction in blood glucose. Monitor glycemia upon initiation.

▶ Pharmacist's Note (Unexpected)

Raw plant leaves contain ginkgolic acid — a potential contact allergen and possible mutagen. Pharmaceutically standardized extracts (EGb 761) keep ginkgolic acid below 5 ppm. Cheap, non-standardized herbal teas and capsules may contain it in significantly higher concentrations. Ask for a CoA (Certificate of Analysis) before recommending a specific product.

Hawthorn *(Crataegus oxyacantha)*

● **MODERATE RISK** serious interactions with heart medications (digoxin, antihypertensives, nitrates)

> *Your cardiologist prescribed digoxin, and your neighbor brought over a jar of homemade hawthorn tincture "for the heart" — it sounds harmless, but this combination can shift the line between a therapeutic and a toxic dose. Hawthorn is one of the few plants with genuine clinical evidence for the heart, but that is exactly what makes it dangerous when mixed with medication.*

▶ Traditional Use

For centuries in Europe it has been used for a "tired heart," mild rhythm disturbances, nervous agitation, and high blood pressure. The flowers, leaves, and berries were used — dried, as a tea or tincture. In Serbian folk medicine it is commonly known as a "blood pressure plant" and a calming remedy.

▶ Active Compound → Effect

Oligomeric proanthocyanidins (OPCs) and flavonoids (vitexin, hyperoside) — these are the plant's pigment and protective compounds, which in the heart muscle:

Dilate the heart's blood vessels (coronary circulation) → better oxygen supply

Mildly slow and regulate heart rhythm

Have an antioxidant effect on the heart muscle

Reduce peripheral vascular resistance → a mild drop in blood pressure

▶ What the Science Actually Says (Proven vs. Anecdotal)

Proven — Standardized extract (WS 1442) improves exercise tolerance in mild heart failure (NYHA class II) — confirmed in multiple randomized studies.

Proven — The EMA and Commission E (Germany) have approved its use for mild cardiac complaints and a "nervous heart."

Weak evidence — Lowering blood pressure in hypertension — the effects are modest and not consistent enough for a full clinical recommendation.

Warning — The SPICE study (2008) did not show a reduction in mortality in severe heart failure — hawthorn is not a substitute for cardiac therapy.

▶ Preparation and Dosage (Specifics)

> **Tea (flowers + leaves): 1–2 teaspoons (1.5–3 g) of dried herb per 150 ml of boiling water, steep for 15 minutes. 3× daily. The effect is mild; a noticeable difference may not appear until 6–8 weeks.**

Standardized extract (tablet/capsule, e.g., WS 1442): 160–1800 mg of extract daily, divided into 2–3 doses — this is TEN TIMES or more concentrated than tea. Doses are chosen according to concentration and indication. Never equate a cup of tea with a tablet.

Tincture: [Tincture dosing varies depending on the solution — check with a pharmacist.]

Duration: The EMA recommends no longer than 6 weeks without consulting a doctor. Long-term use is possible, but under supervision.

▶ Contraindications (Who Should NOT Use It)

Pregnancy and breastfeeding — insufficient data, avoid [weak safety evidence]

Children under 12 — standardized extracts have not been studied

Severe heart failure (NYHA III–IV) — not as monotherapy

Known allergy to plants in the rose family (Rosaceae)

▶ Drug Interactions (+ Why)

(MOST IMPORTANT)

Digoxin (a cardiac glycoside) — hawthorn enhances the positive inotropic effect (a stronger heartbeat), but in doing so pushes digoxin closer to a toxic dose. Mechanism: both act on the same ion channels in the

heart muscle (Na^+/K^+ ATPase). Combination → risk of arrhythmia, nausea, visual disturbances.

Antihypertensives (beta-blockers, ACE inhibitors, calcium channel blockers) — additive blood-pressure-lowering effect. Mechanism: hawthorn on its own reduces peripheral resistance, so the combined effect can lead to hypotension (dizziness, falls, especially in the elderly).

Nitrates (e.g., nitroglycerin) — possible additive vasodilatory effect → a sudden drop in blood pressure. [Evidence mostly from animal and in vitro studies — the clinical significance in humans is probably small, but caution is warranted.]

Anticoagulants (warfarin) — [There are theoretical grounds for an interaction via antioxidant mechanisms, but clinical data are scarce. Check INR when starting hawthorn.]

▶ Pharmacist's Note (Unexpected)

Hawthorn is one of only a few plants with its own EMA herbal monograph for cardiovascular indications — a rarity in phytotherapy. At the same time, extract quality markers (the percentage of OPCs or vitexin) vary drastically between manufacturers. A cheap "hawthorn capsule" from a health food store may contain 10–50× lower concentrations of active compounds than clinical preparations, so a direct comparison of efficacy makes no sense without knowing the extract standard.

Bitter Orange *(Citrus aurantium)*

● **MODERATE RISK** synephrine is a weak sympathomimetic that can raise blood pressure, and interactions with certain medications are clinically documented; risk rises exponentially when combined with caffeine and in heart disease.

> *After ephedra was banned in the US and Europe in 2004, the dietary supplement industry simply changed the label — ephedra became "bitter orange." Same shelf, new packaging, the same question: how safe is it really?*

▶ Traditional Use

In traditional Chinese medicine, the unripe fruit (Fructus aurantii immaturus, Zhiqiao) has been used for centuries as a digestive tonic, an expectorant, and a remedy for moving "stagnant qi" — in practice, for bloating, nausea, and sluggish bowel motility. In Mediterranean folk medicine, the bitter orange flower (neroli) was used as a sedative and anti-anxiety remedy, and the peel for flavoring brandies and liqueurs.

▶ Active Compound → Effect

The main active compound is p-synephrine (a protoalkaloid), which acts as a β-3 adrenergic agonist — it stimulates receptors in adipose tissue and increases thermogenesis (fat burning) and lipolysis, with minimal direct effect on the heart and blood vessels compared to ephedrine. Besides synephrine, the plant contains the flavonoids naringenin and hesperidin, which contribute antioxidant and vasoprotective effects.

The essential oil of the flower (neroli) contains linalool and limonene — compounds with a potential anxiolytic effect (mostly studied in animal models).

▶ What the Science Actually Says (Proven vs. Anecdotal)

Proven (moderate):

A meta-analysis of placebo-controlled clinical trials showed a statistically significant increase in systolic and diastolic blood pressure with extended use (approximately 6/4 mmHg).

Extracts increase lipolysis and thermogenesis in animal models and in humans, but almost always in combination with caffeine, which enhances the thermogenic properties — the effect of pure synephrine in isolation is modest.

A 2024 mouse study showed that C. aurantium normalizes central obesity and hyperleptinemia, without elevating heart rate or blood pressure.

Anecdotal / insufficiently proven:

Anxiolytic effect of the flower (neroli): there are pharmacological arguments, but clinical evidence is weak [EMA traditional use, no therapeutic indication].

Weight loss in humans as a standalone preparation: little evidence supports the use of C. aurantium alone for treating excess body weight.

▶ Preparation and Dosage (Specifics)

> **| Form | Amount | Frequency | Note |**
> |---|---|---|---|

> **| Tea from peel/flower | 1–2 g dried herb / 150 ml hot water | 2–3× daily | Negligible amount of synephrine |**
> | Standardized extract (4–6% synephrine) | 100–300 mg | 1–2× daily | Equivalent to ~10–18 mg synephrine per dose |

> **| Concentrated weight-loss supplements | up to 50 mg synephrine | once | Threshold where cardiovascular concern rises |**
> | Essential oil (neroli) — aromatherapy | 2–4 drops in a diffuser | as needed | Do NOT take internally without supervision |

⚠ Key difference: A cup of bitter orange tea does not carry the same risk as capsules of concentrated extract with 50 mg synephrine + caffeine + β-methylsynephrine (a synthetic analog often added without being listed on the label).

▶ Contraindications (Who Should NOT Use It)

Cardiac arrhythmias, tachycardia, QT prolongation

Uncontrolled hypertension

Thyrotoxicosis

Narrow-angle glaucoma

Pregnancy and breastfeeding [insufficient data, caution]

Children and adolescents

▶ Drug Interactions (+ Why)

> **🔴 CRITICAL — MAO inhibitors (phenelzine, tranylcypromine, moclobemide):**
> Synephrine is metabolized by monoamine oxidase (MAO), so combining it with MAO inhibitors can lead to a hypertensive crisis — a clinical case of interaction between a p-synephrine supplement and the MAO inhibitor phenelzine has been documented. Mechanism: blocked breakdown of synephrine → accumulation → an explosive sympathetic response.

> **🟡 MODERATE — Antihypertensives:**

Synephrine can raise blood pressure by stimulating adrenergic receptors, directly opposing the effect of blood pressure medications (beta-blockers, ACE inhibitors). The interaction is pharmacodynamic (opposing effects), not metabolic.

🟡 MODERATE — CYP3A4 substrates (drugs metabolized by liver enzymes):

Bitter orange is botanically close to grapefruit and shares similar components (flavonoids, furanocoumarins), and grapefruit is a proven cause of interactions with substances metabolized by the CYP3A4 enzyme. A rat study showed that Fructus aurantii may be a mild inducer of the CYP1A2 and CYP3A4 enzymes, which could reduce or alter the effect of drugs such as statins, cyclosporine, some antihistamines, and azole antifungals — [the clinical significance at standard tea doses is probably small, but concentrated extracts warrant checking].

🟡 MODERATE — Stimulants and caffeine:

Combining synephrine and caffeine can produce synergistic fat-burning effects, but also an increased risk of cardiovascular adverse effects. Mechanism: caffeine blocks adenosine receptors and amplifies synephrine's sympathomimetic signal.

🟡 Decongestants (pseudoephedrine, phenylephrine):

Additive sympathomimetic effect — cumulative increase in blood pressure and heart rate.

▶ Pharmacist's Note (Unexpected)

m-Synephrine, a more potent isomer than p-synephrine, does not occur naturally in C. aurantium, but is sometimes illegally added to supplements marketed as "bitter orange." If a preparation seems to work "too well," that's a warning sign. European regulation (EFSA) has not approved health claims for synephrine. Neroli essential oil is expensive and frequently adulterated — the market contains many synthetic imitations.

Fenugreek *(Trigonella foenum-graecum)*

● **MODERATE RISK** a hormonally active plant; interactions with diabetes medications and anticoagulants are clinically relevant; risky in pregnancy.

> *On the stalls of oriental markets it's mixed in with coffee and curry — but the same plant appears in pharmacopoeial monographs for its measurable effect on blood glucose and lipids. What grandma adds to bread, the endocrinologist needs to know about.*

▶ Traditional Use

Used for thousands of years in Ayurvedic, Unani, and Arab-Islamic medicine: to promote lactation (as a galactagogue), regulate blood sugar, ease digestive complaints, lower elevated blood lipids, and as an aphrodisiac. The seeds are used whole, ground, or as an extract. The leaves are eaten as a vegetable (methi) in South Asian cuisine.

▶ Active Compound → Effect

4-hydroxyisoleucine — an amino acid specific to this plant; it stimulates insulin secretion directly from pancreatic beta cells (insulinotropic), especially at

elevated glucose levels → lowers postprandial blood sugar.

Galactomannan fiber (~45–50% of the seed's dry mass) — soluble fiber that slows gastric emptying and glucose absorption in the intestine → "flattens" the glycemic curve.

Diosgenin — a steroidal saponin; a precursor in the laboratory synthesis of steroids, but its oral bioavailability is poor. A potential effect on lipid metabolism and estrogen receptors [evidence mostly in vitro and in animals — insufficient for humans].

Trigonelline — an alkaloid; early-stage research into neuroprotective effects [insufficient clinical data].

▶ What the Science Actually Says (Proven vs. Anecdotal)

✅ Relatively well supported:

Reduction in fasting and postprandial glucose at doses of 5–15 g of seed powder daily — confirmed by meta-analyses of randomized controlled trials, though the studies are heterogeneous in design.

Mild reduction in LDL cholesterol and triglycerides — consistent across multiple studies, with a moderate effect.

Lactation support — several RCTs show an increase in milk volume [methodological quality varies; the EMA included the galactagogue effect in its monograph with

a note on the insufficient evidence base for full "well-established" status].

⚠ **Anecdotal / weak evidence:**

Increased testosterone and libido — a popular claim; studies are small, short, and industry-funded [cannot be reliably claimed].

Aphrodisiac effects — no quality RCTs exist.

Anti-inflammatory and anticancer effects — exclusively in vitro [no clinical relevance for now].

▶ Preparation and Dosage (Specifics)

> **⚡ Critical difference: a teaspoon of spice ≠ a standardized extract**

| Form | Amount | Frequency | Note |

> **|---|---|---|---|**

| Seeds (whole/ground) | 5–15 g | 1–2×/day with a meal | Soaking in water for 8–12h improves tolerability |

> **| Water extract (tea) | 1 g dried seed / 150 ml | 2–3 cups/day | Weaker concentration of active compounds |**

| Standardized extract (capsules, 40–60% fiber or 4-HIL) | 500–1000 mg | 2×/day | Consistent dose — better for clinical comparisons |

> **| Essential oil | NOT oral without supervision | — | Concentrated; hepatotoxicity described in cases of misuse [rare, but documented] |**

> | Topical (seed paste) | Small tested applications | As needed | Skin allergies are not rare |

Duration: Clinical protocols in studies are mostly 8–12 weeks. Long-term use without a break — [insufficient safety data].

▶ Contraindications (Who Should NOT Use It)

 Pregnancy — diosgenin and other constituents have uterotonic activity; contractions documented in animal models; a potential abortifacient [not sufficiently studied in humans, but the risk justifies avoidance].

 Allergy to peanuts, chickpeas, soy (legumes) — cross-reactivity is documented; anaphylaxis has been reported.

⚠ Children — no safety data for pediatric use.

⚠ Hormone-dependent tumors — estrogenic activity [weak evidence, but the precautionary principle applies].

⚠ Thyroid disorders — [some studies suggest interference with the absorption of thyroid medications; the mechanism is unclear, the evidence weak].

▶ Drug Interactions (+ Why)

> **| Drug / class | Interaction mechanism | Clinical outcome | Severity |**

|---|---|---|---|

| Antidiabetics (metformin, glibenclamide, insulin) | 4-hydroxyisoleucine additively lowers blood glucose — two mechanisms at once | Hypoglycemia — especially with physical activity | 🔴 High |

| Anticoagulants (warfarin, acenocoumarol) | Galactomannans may reduce vitamin K absorption; additionally, coumarin-like compounds in the plant [weak evidence for direct anticoagulant activity] | Prolonged INR, bleeding | 🔴 High |

| Levothyroxine, bisphosphonates, ciprofloxacin | Fiber and metals (the plant contains Fe, Mn, Zn) chelate the drug in the GI tract → reduced drug absorption | Reduced therapeutic effect | 🟡 Moderate — resolvable with a 2h spacing |

| Corticosteroids, estrogens, contraceptives | Diosgenin may modulate steroid receptors [mechanism not sufficiently clear in humans] | Theoretically altered effect | 🟡 Moderate — [no strong clinical data, but the interaction is biologically plausible] |

| MAO inhibitors (older antidepressant class) | Trigonelline is structurally related to nicotinic acid; possible serotonergic interference [weak evidence, described in pharmacological reviews] | Unclear | 🟡 Moderate [to be verified] |

▶ Pharmacist's Note (Unexpected)

Fenugreek is an industrial raw material for the synthesis of progesterone and cortisol — diosgenin is

the starting substance in the chemical manufacture of steroids. So a plant that sits in the kitchen as a spice has a direct link to the pharmaceutical industry at the level of synthesis. Ironically: oral diosgenin from the plant has no proven hormonal effect in the body because it is poorly absorbed — but once isolated and chemically processed, it forms the foundation of steroid pharmacology.

The seeds have a characteristic odor that is excreted in sweat and urine — patients sometimes report a "sweetish" body odor resembling maple syrup, which can lead to a false-positive suspicion of isovaleric acidemia (a metabolic disorder) in newborns whose breastfeeding mothers consume the plant. [Documented in the pediatric literature — relevant for neonatal screening programs.]

Grapefruit *(Citrus paradisi)*

● **HIGH RISK** not because the fruit itself is toxic, but because it is the most well-known and best-documented food-drug interaction in the world, involving over 85 affected medications.

> *A patient takes a statin in the evening, with a glass of grapefruit juice for breakfast — the same ritual for months. The interaction was discovered by accident in 1991: researchers were testing the effect of alcohol on a blood pressure medication and used grapefruit juice to mask the taste of ethanol in the control group — the drug's blood level spiked instead of dropping. Grapefruit, not alcohol, turned out to be the real culprit.*

▶ Traditional Use

Citrus paradisi is a relatively young species botanically — it arose from an accidental cross between the orange (Citrus sinensis) and the pomelo (Citrus maxima) in Barbados in the 18th century, so it lacks the deep traditional phytotherapeutic use that plants with centuries of documented use have. It is used almost exclusively as food (fruit, juice), and more recently as a source of seed extract (grapefruit seed extract, GSE), which is sold as a dietary supplement with claimed antimicrobial properties — a

commercially popular but scientifically dubious use [see Pharmacist's Note].

▶ Active Compound → Effect

Furanocoumarins in the peel and flesh of the fruit (highest in the white layer/albedo and the membranes between segments) bear almost the entire responsibility for the interactions: bergamottin and 6′, 7′-dihydroxybergamottin (DHB) are the main ones. Unlike most plant enzyme inhibitors, which act reversibly (competitively), these furanocoumarins act as mechanism-based (irreversible) inactivators of intestinal CYP3A4 — the enzyme isn't temporarily blocked, it is physically destroyed, so the body has to synthesize an entirely new enzyme for activity to return. Hence the unusually long-lasting effect (see Dosage). Naringin (the flavonoid responsible for the bitter taste) additionally inhibits the intestinal transport proteins OATP1A2 — but this mechanism works in the OPPOSITE direction: instead of increasing drug levels, it decreases drug absorption (see Interactions, fexofenadine).

▶ What the Science Actually Says (Proven vs. Anecdotal)

Proven (clinical, extensively replicated): The effect on CYP3A4 substrates is one of the best-documented food-drug phenomena in clinical pharmacology — discovered by accident in 1991 in a felodipine study, where grapefruit juice increased the drug's

bioavailability to 284% relative to water. Since then, more than 85 drugs with a clinically significant interaction have been described.

Proven, opposite direction: reduced absorption of certain drugs via OATP1A2 transporters — e.g., fexofenadine, where grapefruit juice reduces the drug's AUC to about 37% of the control value.

? Anecdotal / insufficient evidence: The antimicrobial/antifungal effect of grapefruit seed extract (GSE), aggressively marketed for dietary supplements — independent analyses have repeatedly shown that commercial GSE preparations owe their antimicrobial activity to contamination with synthetic preservatives (e.g., benzalkonium chloride, triclosan), not to the extract itself — an old and recurring controversy in the supplement literature, worth stating explicitly so the myth isn't perpetuated further.

▶ Preparation and Dosage (Specifics)

> **Grapefruit isn't "dosed" like an herbal medicine — the risk comes from ordinary food consumption, which makes it more dangerous precisely because it is rarely perceived as a "medicine."**
>
> The amount that's enough: a single glass of juice (200–250 ml) or half a fresh fruit can already cause clinically significant CYP3A4 inhibition for sensitive drugs — no large or repeated amount is needed.

> **Duration of effect: because of the irreversible mechanism, the effect does NOT disappear within a few hours as with ordinary inhibitors — the**

> **intestine needs time to synthesize new CYP3A4, so a significant reduction in enzyme activity can last 24 to 72 hours after a single dose. Practical consequence: "I'll drink the juice in the morning and take the medication in the evening" does NOT solve the problem.**
>
> Variability: furanocoumarin content varies between varieties, ripeness, and juice manufacturers — there is no reliable way for a consumer to judge a "safe" amount for a given product.

▶ Contraindications (Who Should NOT Use It)

Avoid completely: patients on immunosuppressants after transplantation (cyclosporine, tacrolimus) — narrow therapeutic window, risk goes in both directions (toxicity or organ rejection).

Patients on amiodarone and certain antiarrhythmics — narrow therapeutic window, risk of life-threatening arrhythmias.

Patients on statins metabolized via CYP3A4 (simvastatin, lovastatin, atorvastatin) — risk of myopathy/rhabdomyolysis.

Heightened caution: patients on calcium channel blockers (felodipine, nifedipine, and related drugs) — risk of pronounced hypotension; patients on certain benzodiazepines (midazolam, triazolam), immunosuppressants, sildenafil, and similar narrow-therapeutic-range CYP3A4 substrates.

▶ Drug Interactions (+ Why)

This is, alongside St. John's Wort, the clinically most significant interaction in the entire book — the difference is that St. John's Wort INDUCES (speeds up breakdown), while grapefruit INHIBITS (slows down breakdown) — opposite mechanisms, both dangerous.

Main mechanism: mechanism-based (irreversible) inactivation of intestinal CYP3A4 by furanocoumarins (bergamottin, DHB) → the drug is not broken down in the intestine before entering the bloodstream (the "first-pass" effect is lost) → blood drug levels rise, sometimes dramatically.

Specifically dangerous combinations:

Immunosuppressants (cyclosporine, tacrolimus) → blood drug levels rise 40–80%, narrow therapeutic window, risk of toxicity.

Statins metabolized via CYP3A4 (simvastatin, lovastatin, atorvastatin) → risk of myopathy, in extreme cases rhabdomyolysis. [Pravastatin, fluvastatin, and rosuvastatin are metabolized by a different pathway and practically lack this interaction — an important difference that few people know.]

Calcium channel blockers (felodipine — the most studied, nifedipine and related drugs) → pronounced hypotension, tachycardia.

Amiodarone and certain antiarrhythmics → risk of life-threatening arrhythmias due to a narrow therapeutic window.

Certain benzodiazepines (midazolam, triazolam) and sildenafil → enhanced sedation/hypotension.

Opposite mechanism — reduced absorption: naringin inhibits intestinal OATP1A2 transporters → reduced absorption of fexofenadine (an antihistamine) and certain beta-blockers (e.g., celiprolol) — here grapefruit makes the drug WEAKER, not stronger, which confuses even healthcare professionals accustomed to expecting only "enhancement."

[For a patient on any narrow-therapeutic-window drug, the safest recommendation isn't "less grapefruit" but complete avoidance — the effect lasts too long and varies too much to be safely "worked around" the drug's dosing schedule.]

▶ Pharmacist's Note (Unexpected)

Paradoxically, grapefruit remains poorly recognized as a risk among the general population despite being the best clinically documented food-drug interaction that exists — better documented than most of the herbal interactions in this book. Part of the problem is perception: "it's just fruit," not a "supplement" or "herbal preparation," so patients rarely think to mention it to their pharmacist or doctor. Interestingly, the same furanocoumarins that make grapefruit dangerous for dozens of drugs are also being studied as potential deliberate bioavailability "enhancers" for certain expensive, low-bioavailability drugs — this remains experimental, not clinical practice.

Mistletoe *(Viscum album)*

● **MODERATE RISK** contains toxic lectins and viscotoxin; safety depends critically on the form of preparation and dose; the berries are poisonous

> *A plant that never touches the ground its entire life — it grows exclusively on the branches of other trees — has been given to heart patients in Central Europe for decades, while oncologists simultaneously study it as an adjuvant cancer therapy. Few plants divide the research community as much as mistletoe.*

▶ Traditional Use

It was used to lower blood pressure, calm heart palpitations, and as a "remedy for strengthening the nervous system." In Austrian-German phytotherapy it was a standard recommendation for hypertension as far back as the early 20th century. Its sprigs are hung above doorways for the New Year.

▶ Active Compound → Effect

Lectins (Mistletoe Lectins, ML-I, ML-II, ML-III) → Immunomodulation; in vitro they promote apoptosis (programmed death) of tumor cells and activate NK cells and macrophages. This is the basis for its use in oncology.

Viscotoxins (VT 1–3) → Cardioactive effects (negative chronotropic = slowing the heart); at small doses potentially beneficial for tachycardia, at higher doses — toxic to the myocardium.

Flavonoids (quercetin, isorhamnetin) → Mild vasodilation, antioxidant activity.

▶ What the Science Actually Says (Proven vs. Anecdotal)

Clinically studied:

Fermented aqueous mistletoe extracts (Iscador, Helixor, Eurixor) have been studied in oncology as adjuvant (supplementary) therapy alongside chemotherapy. Certain studies show improved quality of life and reduced chemotherapy side effects — but overall survival has not been consistently improved in high-quality randomized trials.

A mild hypotensive effect has been documented in smaller studies, but without robust RCTs to confirm it for clinical practice.

Anecdotal / weak evidence:

"Mistletoe tea for blood pressure" — traditional use, but the concentration of active compounds in home-brewed tea is very low and unpredictable.

Immunostimulation in healthy individuals — insufficient evidence.

[Note: A Cochrane review from the early 2000s was inconclusive; newer meta-analyses are heterogeneous

— checking the current status in the Cochrane and PubMed databases is recommended, as the situation is evolving.]

▶ Preparation and Dosage (Specifics)

> ⚠ **This is one of the plants where the difference between forms DIRECTLY affects safety.**
>
> | Form | Dose | Note |

> **|---|---|---|**
>
> | Tea (dried leaf/twig, cold maceration) | 1–2 g herb / 150 ml cold water, macerate for 8h, 1–2 cups daily | Cold water is used because high temperature breaks down the active compounds; lower lectin concentration = lower risk |

> **| Standardized extract (tablet/capsule) | Per the product's instructions — usually 10–30 mg of extract, 2–3× daily | Only pharmaceutically standardized forms have a predictable ML content |**
>
> | Ampoules for i.v./s.c. injection (Iscador, etc.) | Exclusively under medical supervision | Used in integrative oncology; not for self-treatment |

> **| Berries | □ Do NOT consume | Toxic — especially for children; contain viscin and viscotoxin at high concentrations |**
>
> | Essential oil | Does not exist as a standardized medicinal product | No regulated use |

Duration: For tea — [no firmly defined duration; traditionally 3–4 weeks with a break; long-term safety data are lacking]

▶ Contraindications (Who Should NOT Use It)

Pregnancy and breastfeeding — lectins have a potentially toxic effect; prohibited

Children under 12 — especially regarding the berries (risk of poisoning)

Patients with autoimmune diseases (MS, lupus, RA) — immunostimulation may worsen the condition

Patients on immunosuppressive therapy (organ transplantation) — contraindicated for the same reason

Known hypersensitivity — allergic reactions including anaphylaxis have been reported (rare)

[In patients with hormone-dependent tumors (breast, endometrial cancer) — there are theoretical concerns about estrogenic effects of certain compounds; insufficient data, but consulting an oncologist is essential]

▶ Drug Interactions (+ Why)

> **| Drug / Group | Interaction | Mechanism |**
> |---|---|---|

| Antihypertensives (ACE inhibitors, beta-blockers, Ca antagonists) | ⚠ Enhanced effect → risk of hypotension | Mistletoe's viscotoxins and flavonoids further lower blood pressure and slow heart rate — an additive effect |

| Immunosuppressants (cyclosporine, tacrolimus, corticosteroids) | ⚠ Antagonism | Mistletoe's immunostimulation directly opposes immunosuppression; may jeopardize transplant tolerance |

| Anticoagulants / antiplatelet drugs (warfarin, aspirin, clopidogrel) | Potential enhancement of anticoagulant effect | Mistletoe's flavonoids may inhibit platelet aggregation; the combination increases bleeding risk |

| Antidiabetics | ⚠ Possible enhancement of the hypoglycemic effect | [Weak evidence; noted in vitro, clinical data limited — to be verified] |

| Sedatives / anxiolytics | Possible additive sedation | [Anecdotal; mechanism unclear] |

▶ Pharmacist's Note (Unexpected)

Mistletoe is one of the few plants registered as a medicine (not just a supplement) in Germany and Austria — fermented preparations have gone through the regulatory procedure and have approved status for adjuvant oncological use. This means pharmacovigilance data exist for it that don't exist for the vast majority of herbal preparations.

A second surprise: cold maceration instead of boiling — herbal teas are, as a rule, prepared with hot water, and mistletoe is one of the rare cases where cold water is recommended precisely because heat inactivates the lectins (which would be desirable for a poison, but it is precisely the lectins that carry part of the therapeutic effect).

Chamomile *(Matricaria chamomilla)*

● **LOW RISK** with known exceptions (warfarin, sedatives, cross-allergy to Asteraceae)

> *A hospital in Munich, 1987: researchers are searching for the molecule that would explain why chamomile had "lulled" Europe to sleep for centuries — and they find apigenin, a flavonoid that binds to the same receptors as diazepam. Only weaker, and without the dependence.*

▶ Traditional Use

Greco-Roman medicine used chamomile for digestive complaints, cramping, and insomnia. In Slavic folk medicine, flower tea was a remedy for "nerves," stomach pain, and colds. External use (compresses, baths) for skin inflammation and wounds is well documented ethnobotanically across Europe.

▶ Active Compound → Effect

Apigenin (a flavonoid) — binds to GABA-A receptors in the brain as a mild agonist → sedation, anxiolytic effect. The same mechanism as benzodiazepines, but many times weaker and without physical dependence.

α-bisabolol and bisabolol oxides (terpenoids in the essential oil) → anti-inflammatory and spasmolytic effect on intestinal smooth muscle.

Chamazulene (the blue pigment formed during distillation) → anti-inflammatory, in vitro COX-2 inhibition. There are not enough clinical studies to say how relevant this is at a standard tea dose.

▶ What the Science Actually Says (Proven vs. Anecdotal)

IndicationEvidence status

Generalized anxiety disorder (GAD)Several randomized controlled trials, clinical — chamomile extract superior to placebo, but sample size small.

Insomnia, improved sleep qualityModerate evidence from RCTs (particularly in elderly and postpartum women), clinical

Irritable bowel syndrome, dyspepsiaMostly combination preparations — difficult to isolate chamomile's effect, moderate

Wounds and skin inflammation (topical)In vitro and animal models solid; clinical RCTs limited, moderate

Infant colicAnecdotal reports, small RCTs — insufficient evidence for a recommendation

“Boosts immunity”No clinical evidence. This is a marketing claim. anecdotal

▶ Preparation and Dosage (Specifics)

FormDoseFrequency / duration

Tea (dried flower)

2–3 g dried flower per 150 ml boiling water, covered for 5–10 min

3× daily, between meals. Up to 4–6 weeks without medical consultation.

Standardized dry extract (capsules)

220–1,100 mg extract daily (GAD studies used 220–500 mg, 5:1 extract)

1–2× daily with a meal. Not the same as tea — the extract is 5–10× more concentrated

Essential oil (topical)

1–2% in a carrier oil base (e.g., 1–2 drops per 5 ml carrier oil)

On skin only, not oral. Pure essential oil is NOT to be taken by mouth

Tincture (1:5)

1–4 ml, 3× daily

Follow the manufacturer's standardization — alcohol content matters for children and liver disease.

▶ Contraindications (Who Should NOT Use It)

Allergy to Asteraceae/Compositae — chamomile is botanically in the same family as ragweed, yarrow, and marigold. Cross-reactivity is well documented. Those allergic to ragweed: do not take without an allergist consultation.

Pregnancy (especially high doses / extract): theoretical emetic and uterotonic potential of apigenin — [weak in vitro evidence, but caution is recommended]

Breastfeeding: insufficient data — aside from an occasional cup of tea, larger doses should be avoided.

▶ Drug Interactions (+ Why)

> **THE MOST IMPORTANT PART**
>
> Warfarin and anticoagulants

> **High risk — Chamomile inhibits platelet aggregation (apigenin) and potentially inhibits CYP2C9, which metabolizes warfarin → elevated INR, bleeding risk. Cases have been documented in the literature (a patient drinking 4–5 cups daily plus applying a chamomile cream to her knee). Even one cup of tea a day warrants caution.**
>
> Benzodiazepines, Z-drugs (zolpidem), barbiturates

> **Moderate risk — Apigenin acts on the same GABA-A receptors → additive sedation. Not a contraindication, but the patient should be advised: “don't drink chamomile tea within an hour of taking your sleep medication.”**

Ciclosporin, tacrolimus

Moderate risk — In vitro inhibition of P-glycoprotein and CYP3A4 → possible elevated blood concentrations of the immunosuppressant. [clinical evidence weak, but the population is high-risk]

Tamoxifen

Moderate risk — Apigenin has a weak phytoestrogenic effect; theoretically it may interfere with therapy for hormone-dependent tumors. [in vitro evidence, no clinical RCTs] — the oncologist should be informed.

NSAIDs (ibuprofen, aspirin)

Low–moderate risk — Additive COX-2 and platelet inhibition; relevant only at high extract doses, not with a single cup of tea.

▶ Pharmacist's Note (Unexpected)

Chamazulene, which gives chamomile essential oil its characteristic blue color, does not exist in the fresh flower — it forms pyrolytically during steam distillation from matricin. Tea therefore contains almost no chamazulene. If a patient is looking for the “anti-inflammatory effect of the essential oil,” that is a different preparation with a different compound profile than standard tea. This is a clinically relevant detail when assessing dose and effect.

St. John's Wort *(Hypericum perforatum)*

● **HIGH RISK** not because of the plant's own toxicity, but because it causes serious and unpredictable interactions with a wide range of medications.

> *A woman has been taking the birth control pill for years without a problem. She starts drinking St. John's Wort tea for "a better mood," and a month later — an unplanned pregnancy. The pill didn't stop working because it was "weak" — St. John's Wort forced her liver to break it down faster than it could take effect.*

▶ Traditional Use

Used for centuries for wounds, burns, and bruises (St. John's Wort oil, applied externally), as well as a folk "remedy for the nerves" and mild sadness — hence its medieval European name, "chase-devil."

▶ Active Compound → Effect

Two compounds bear the main responsibility, but with different roles:

Hyperforin — the main driver of the antidepressant effect (inhibits reuptake of serotonin, dopamine, and noradrenaline, similar to the mechanism of SSRI/SNRI

drugs), but also the main culprit behind the interactions.

Hypericin — contributes to the effect, responsible for photosensitivity (skin sensitivity to sunlight) at high doses.

▶ What the Science Actually Says (Proven vs. Anecdotal)

Proven (clinical): St. John's Wort extract shows efficacy comparable to standard antidepressants in mild-to-moderate depression, with generally better tolerability. This is confirmed well enough that the EMA has granted standardized extracts “well-established use” status. Various clinical studies have shown that St. John's Wort preparations are as effective as synthetic antidepressants, but are typically better tolerated than their chemical counterparts.

NOT proven for severe/major clinical depression, nor is it equivalent to therapy for bipolar disorder or psychotic episodes.

St. John's Wort tea for “calming the nerves” — the effect on mood in mild, transient states is mostly anecdotal; the clinical evidence relates mainly to standardized extracts in capsules, not to tea.]

External use of the oil on wounds — traditional; there is no firm clinical confirmation in the modern literature, unlike for internal use.

▶ Preparation and Dosage (Specifics)

> **Tea (traditional use, mild effect): 1 teaspoon (≈1–2 g) of dried aerial parts per cup of boiling water, covered for 10 minutes, 2–3 times daily. This is a mild dose — not equivalent to the therapeutic doses used in studies.**
>
> Standardized extract (therapeutic use for mild depression): Commercial preparations are dosed according to hypericin/hyperforin content, typically 300 mg of extract 2–3 times daily (up to 900–1,000 mg/day total), over a period of at least 4–6 weeks to assess effect. [The exact dose depends on the specific product and extract concentration — always check the manufacturer's instructions and do not mix products of different concentrations.]

Essential oil is practically never used internally — the risk of phototoxicity and uncontrolled dosing is too high.

▶ Contraindications (Who Should NOT Use It)

Pregnancy and breastfeeding [insufficient safety data — caution advised, not recommended].

People on any chronic medication (see interactions below) — this is practically the biggest limitation.

People with bipolar disorder (risk of triggering a manic episode).

Planned surgery in the next 1–2 weeks (due to interactions with anesthetics and anticoagulants).

Very fair skin / a tendency toward photosensitivity, at higher doses.

▶ Drug Interactions (+ Why)

St. John's Wort is one of the best-known “enzyme inducers” in all of phytotherapy. Mechanism: hyperforin acts as a PXR-mediated inducer of metabolic enzymes and transport systems (CYP450, ABCB1/P-glycoprotein, OATP1A2). In plain terms — St. John's Wort “switches on” the liver's drug-breakdown system to maximum, so drugs are metabolized and cleared from the body faster than they should be. Result: the drug falls below its therapeutic level and loses its effect — or, in some combinations, a dangerous excess of serotonin builds up instead.

Specifically dangerous combinations:

Hormonal contraception → accelerated breakdown, risk of unplanned pregnancy.

Anticoagulants (warfarin and similar) → reduced efficacy, risk of thrombosis.

Immunosuppressants (ciclosporin, tacrolimus) → critically low drug levels, risk of transplant organ rejection.

Antiretroviral drugs (HIV therapy) → loss of viral control.

SSRI/SNRI antidepressants, triptans → the opposite risk: serotonin syndrome (a buildup of serotonin instead of its loss), because St. John's Wort itself has serotonergic activity — two mechanisms combining on the same pathway.

> Digoxin, statins, some calcium channel blockers → altered blood drug levels.

An important nuance confirmed by more recent research: products with a daily dose below 1 mg of hyperforin are considerably less associated with significant interactions in drugs metabolized via CYP3A4 or P-glycoprotein, whereas preparations with a high hyperforin content show a clear dose-dependence of the interaction. This means the risk is not the same for every product — it depends on the hyperforin concentration, which the consumer rarely knows without reading the label. [If you are taking any regular medication, this is not an area for self-experimentation — a consultation with a pharmacist or physician before combining is essential.]

▶ Pharmacist's Note (Unexpected)

St. John's Wort is sold freely, over the counter, as a “natural and harmless” product for mood — while at the same time it is pharmacologically one of the most aggressive enzyme inducers known to phytotherapy, with the potential to negate the effect of transplant therapy or contraception. The “natural = harmless” paradox can, quite literally, cost someone their transplanted organ here.

Kava *(Piper methysticum)*

● **MODERATE RISK** proven hepatotoxicity at high doses and long-term use, significant drug interactions via CYP450 enzymes.

> *On the islands of the Pacific, this plant has been drunk for centuries at ceremonies of peace and negotiation — and today it is impossible to buy in certain European countries, because regulators shut it out of pharmacies while scientists were still arguing over who was actually to blame for the liver damage.*

▶ Traditional Use

Polynesians (Fiji, Vanuatu, Samoa) use the root bark to prepare a ceremonial drink that relaxes the body, calms the mind, and, as they say, “clears the heart before an important conversation.” No alcohol, no hallucinations — just deep relaxation with full clarity of mind. In Western phytotherapy it has been adopted as a remedy for anxiety and insomnia.

▶ Active Compound → Effect

The key compounds are kavalactones (particularly kawain, dihydrokawain, methysticin) — lipid-soluble substances that:

enhance GABA-A receptor activity (a mechanism similar to benzodiazepines, but without binding the same receptor site),

block voltage-gated sodium and calcium channels in neurons (anticonvulsant and analgesic effect),

block noradrenaline reuptake in nerve cells (a possible component of its cognitive effects).

Effect: anxiolytic, sedative, mildly analgesic — without euphoria and without respiratory depression at normal doses.

▶ What the Science Actually Says (Proven vs. Anecdotal)

Clinically proven (with limitations):

Several clinical trials have shown that aqueous kava extract reduces anxiety scores on validated scales (HAMA, BAI) compared with placebo, without serious side effects and without clinically significant hepatotoxicity with short-term use.

Where the science contradicts itself:

A more recent, more rigorous 16-week randomized controlled trial (the KGAD study) showed no improvement in anxiety in patients with generalized anxiety disorder compared with placebo — contradicting earlier meta-analyses. The discrepancy likely stems from the type of extract used (aqueous vs. ethanolic) and the study population.

Anecdotal / insufficiently proven:

Improved sleep (pilot studies exist, but no strong RCTs)

Analgesic effect for muscle and joint pain

Anticancer activity of flavokawains (in vitro data only)

▶ Preparation and Dosage (Specifics)

> **| Form | Kavalactone dose | Frequency | Max. duration |**
>
> |---|---|---|---|

> **| Traditional drink (ground root + water) | variable, ~100–250 mg | 1× daily, evening | not defined |**
>
> | Standardized dry extract (70% kavalactones) | 120–280 mg kavalactones/day | 2–3× divided doses | ≤ 8 weeks |

> **| Ethanolic extract in capsules | 60–120 mg/ capsule | 1–3× daily | ≤ 8 weeks |**
>
> ⚠ Critical difference: A “pinch of ground root” in an herbal tea contains a negligible amount of kavalactones — a commercial concentrated extract can be 10–50× stronger. The dose in tea ≠ the dose in a capsule.

Do not exceed 400 mg of kavalactones/day, nor use it cumulatively for longer than 2 months, without medical supervision.

▶ Contraindications (Who Should NOT Use It)

Liver disease or elevated liver enzymes (of any origin)

Pregnancy and breastfeeding [insufficient safety data]

Parkinson's disease (see interactions)

Depression [may worsen depressive episodes]

Children and adolescents

People with a known genetic CYP2D6 enzyme deficiency (poor metabolizers — higher toxicity risk) [genotype testing is not routine in clinical practice here]

▶ Drug Interactions (+ Why)

> **(+ why) — THE MOST IMPORTANT PART:**
> In vitro, kavalactones strongly inhibit several hepatic CYP450 enzymes: CYP1A2 (56% inhibition), CYP2C9 (92%), CYP2C19 (86%), CYP2D6 (73%), and CYP3A4 (78%). Practical consequence: kava slows the breakdown of drugs that use the same enzyme pathways, raising their blood concentration — or, less often, speeds up their metabolism and reduces their efficacy.

> **| Drug / group | Interaction | Why |**
> |---|---|---|

> **| Benzodiazepines (alprazolam, diazepam) | Potentially dangerous sedation, stupor | Additive**

GABA effect + kava inhibits CYP3A4, which breaks down benzodiazepines → the drug accumulates |

| CNS depressants (barbiturates, opioid analgesics, antihistamines) | Increased sedation | Additive CNS effect, without a specific enzymatic mechanism |

| Alcohol | Higher risk of hepatotoxicity and sedation | Both damage the liver, additive effect; CYP2E1 involved |

| SSRI/SNRI antidepressants | Unpredictable potentiation | Inhibition of CYP2D6/CYP3A4 → antidepressant accumulation; case reports with serious adverse effects |

| Levodopa (Parkinson's drug) | Reduced efficacy | Kava likely exerts dopamine antagonism, which can neutralize levodopa's effect — confirmed in at least one clinical case |

| Hepatotoxic drugs (methotrexate, amiodarone, high-dose statins) | Synergistic risk of liver damage | Both burden the liver's metabolic capacity |

| Anticoagulants (warfarin) | [Theoretical risk] Altered warfarin levels | CYP2C9 inhibition may raise INR — [insufficient clinical data, but the risk is real] |

A case has been documented of a patient hospitalized after taking alprazolam and kava together, presenting with lethargy and disorientation.

▶ Pharmacist's Note (Unexpected)

The ban on kava in Germany and Canada in the early 2000s arose from reports of hepatotoxicity — but later investigation found that many of the cases were linked to:

1. “Two-day kava” — fermented or improperly processed stem/leaf material used instead of root (the leaves contain pipermethystine, an alkaloid documented in kava leaf/stem peelings and implicated in liver toxicity),

2. Ethanolic extracts (traditional use employs an aqueous extract),

3. Concurrent use of alcohol and hepatotoxic drugs.

UPDATE: The German regulator (BfArM) only lifted the ban after a ruling by the Cologne Administrative Court on 10 June 2014 (a 12-year legal dispute) — the ruling restored the pre-2002 status, with mandatory warning labels, regular monitoring of liver enzymes, and prescription-only status. At the EU level, in 2017 the HMPC (Public Statement, EMA/HMPC/450588/2016, finalized 21 November 2017) formally concluded that the conditions were met for NEITHER a traditional-use monograph NOR well-established use — meaning that, formally, NO EU herbal monograph exists for kava at all, not merely that it “hasn't been reviewed.”

Fennel *(Foeniculum vulgare)*

● **MODERATE RISK** estragole in the essential oil carries genotoxic potential at high/long-term doses; safe at culinary amounts, caution warranted with concentrates

> *Grandma put it in tea for bloating — while, at the same time, an EU regulatory agency quietly restricted extracts for babies because of the very same ingredient that gives it its scent.*

▶ Traditional Use

Digestion, bloating, stomach cramps (especially in infants), cough, promoting milk production in breastfeeding mothers, menstrual complaints. Found in nearly every herbal pharmacy in the Balkans — both as a spice and as a remedy.

▶ Active Compound → Effect

trans-Anethole (50–80% of the essential oil) → spasmolytic: relaxes intestinal smooth muscle, reduces cramping and bloating; weak estrogenic activity (phytoestrogen)

Estragole (methyl chavicol) → aromatic character; potentially genotoxic at high doses (see note)

Flavonoids (rutin, quercetin) → antioxidant, mildly anti-inflammatory

Fenchone → a bitter-sharp note, an additional spasmolytic component

▶ What the Science Actually Says (Proven vs. Anecdotal)

actually says:

| Claim | Evidence status |

|---|---|

| Spasmolytic effect on intestinal muscle | □ Clinically confirmed (in vitro + small clinical trials) |

| Reduction of infant colic | ⚠ Limited RCTs, mixed results — the EMA considers the evidence insufficient for a recommendation in this group |

| Galactagogue (milk production in breastfeeding) | ⚠ Mostly traditional/anecdotal; mechanism plausible (anethole ~ dopamine antagonism?) [weak evidence, verify before relying on it] |

| Expectorant (loosening cough) | ⚠ Traditional, mechanistically plausible, no robust clinical studies |

| Antimicrobial | □ Confirmed in vitro — clinical significance unclear |

▶ Preparation and Dosage (Specifics)

> **> ⚠ Key distinction: culinary fennel in tea ≠ concentrated extract ≠ essential oil**

Tea (fruit — seed):

1.5–2.5 g crushed fruit (≈ a level teaspoon) per 150 ml boiling water

Cover, steep 10–15 min, strain

2–3 cups daily, no longer than 2 weeks continuously without a break

Dry extract / capsules:

Standardized preparations: 100–300 mg extract daily (in divided doses)

Always follow the specific product's instructions — anethole concentration varies 10–20×

Essential oil:

NEVER directly on the skin or internally without dilution

In aromatherapy: 1–2 drops in a diffuser — estragole is present here too

Not for infants, pregnant women, or breastfeeding mothers (in this form)

Culinary use (seeds, fresh leaf): safe without restriction for healthy adults.

▶ Contraindications (Who Should NOT Use It)

Pregnancy — uterine stimulation (anethole), especially with extracts and oil

Infants and young children — EMA restriction on extracts due to estragole and insufficient safety data; herbal tea in small amounts remains a matter of debate [check current EMA guidance]

Hormone-dependent tumors (breast, endometrial, ovarian cancer) — phytoestrogenic activity of anethole; [evidence for clinical risk weak, but caution is warranted]

Allergy to plants of the Apiaceae/Umbelliferae family (carrot, celery, parsley, anise) — cross-allergy possible

Epilepsy — there are reports of a proconvulsant effect of the essential oil [mostly case reports, mechanism unclear]

▶ Drug Interactions (+ Why)

| Drug / group | Interaction type | Why (mechanism) |

|---|---|---|

| Ciprofloxacin and fluoroquinolones | □ Reduces antibiotic absorption | Anethole and phenolic components bind cations in the gut and may inhibit the OATP transporter — plus potential CYP1A2 induction speeds up the drug's breakdown |

| Tamoxifen and hormone therapy | ⚠ Additive/ antagonistic effect | Anethole's phytoestrogenic activity may interfere with the estrogenic/antiestrogenic effect; clinical significance [insufficiently documented, verify] |

> **| Anticoagulants (warfarin) | ⚠ Potential enhancement of effect | Flavonoids inhibit CYP2C9 — the same enzyme that breaks down warfarin; INR monitoring is advisable at extract doses |**
>
> | Drugs that lower the seizure threshold | ⚠ Possible increased risk | The essential oil (fenchone, estragole) may irritate the CNS; relevant only at high doses/ extracts, not tea |

| Oral contraception / HRT | ⚠ Theoretical interaction | Estrogenic activity of anethole [evidence mostly in vitro; clinical relevance low but worth mentioning to your doctor] |

▶ Pharmacist's Note (Unexpected)

Estragole is an Annex I substance under EU flavoring regulation (Regulation EC 1334/2008) — restricted in food, but regulated separately for herbal medicines through the EMA herbal framework. Because of this, the same “fennel tea” in a teabag and a registered herbal medicine can have completely different maximum-estragole-dose standards. Cheap, unlabeled teas often lack controlled raw-material sourcing — anethole/estragole content can vary by up to 3×.

Chasteberry *(Vitex agnus-castus)*

● **MODERATE RISK** hormonally active, alters prolactin and potentially estrogen; contraindicated in pregnancy and with hormone therapy

> *In medieval monasteries, monks chewed this seed to suppress sexual desire — hence the name *“agnus castus”* (chaste lamb). Today, women use it to regulate their cycle, not to shut it down.*

▶ Traditional Use

For millennia in the Mediterranean world it has been used for “women's complaints” — irregular cycles, pre-menstrual pain, breast swelling. It was also used as an aphrodisiac (paradoxically — the evidence is contradictory even in ancient sources).

▶ Active Compound → Effect

Primary mechanism: diterpenes (particularly rotundifuran and vitexilactone) and iridoids (aucubin, agnuside) act on dopamine D2 receptors in the pituitary → they reduce prolactin secretion.

Lower prolactin → the estrogen/progesterone ratio in the luteal phase normalizes → fewer PMS symptoms and less mastodynia (breast pain).

[There are also preliminary data on weak estrogenic/antiestrogenic activity via beta-estrogen receptors — the mechanism is not yet fully clarified]

▶ What the Science Actually Says (Proven vs. Anecdotal)

✅ Relatively well documented:

Reduction of PMS symptoms (pain, breast tenderness, mood changes) — multiple randomized clinical trials, including German ones, using the standardized extract Ze 440

UPDATE: The EMA/HMPC monograph for Vitex agnus-castus L., fructus actually contains TWO indications — “well-established use” for treating premenstrual syndrome (not merely traditional use, as the text previously claimed) AND a separate, milder “traditional herbal medicine for the relief of minor symptoms prior to menstruation” formulation for traditional use. The monograph was adopted by a majority vote of the HMPC committee (24 of 31, Art. 16h(3) of Directive 2001/83/EC) — so the evidence base is stronger than the text suggests.

Mild correction of irregular cycles in mild-degree hyperprolactinemia

⚠ Weak or inconsistent evidence:

Infertility — studies small, heterogeneous [do not recommend as a substitute for treatment]

Menopausal symptoms — [insufficient evidence]

PCOS — [preliminary, no solid RCT]

▶ Preparation and Dosage (Specifics)

> **| Form | Dose | Frequency | Note |**
> |---|---|---|---|

> **| Dry extract (standardized, e.g., Ze 440 or BNO 1095) | 20–40 mg/day | 1× in the morning | Pharmaceutically standardized — this is the researched form |**
> | Tincture (1:5) | 40 drops (≈2 ml) in the morning | 1× daily | Check standardization |

> **| Tea from dried berries | [Dose not reliably established] | — | Poor bioavailability, poor standardization |**
> Duration: A minimum of 3 monthly cycles for a noticeable effect — this is a plant that doesn't work “right away.”

> ⚠ A pinch of dried berries in tea ≠ 20 mg of standardized extract. The concentration difference can be manyfold.

▶ Contraindications (Who Should NOT Use It)

Pregnancy — stimulates the corpus luteum, potential risk to the pregnancy

Breastfeeding — affects prolactin, effects on milk supply unclear

Hormone-dependent tumors (breast, uterine, ovarian cancer) — [potential estrogenic activity, avoid]

Children and adolescents under 18

In vitro fertilization (IVF) — alters the hormonal axis, do not combine without supervision

▶ Drug Interactions (+ Why)

> **| Drug/class | Interaction | Why |**
> |---|---|---|

> **| Dopamine antagonists (metoclopramide, haloperidol, antipsychotics) | Antagonism — reduces the drug's effect | Vitex acts on the same D2 receptors, in the opposite direction |**
> | Hormonal contraception (pills, patches) | May potentially reduce contraceptive reliability | Indirect modulation of the pituitary–ovarian axis |

> **| HRT (hormone replacement therapy) | Unpredictable additive or opposing hormonal activity | Estrogenic/antiestrogenic effects combine unpredictably |**
> | Bupropion, levodopa | [Theoretical — same dopaminergic pathway] | Possible enhancement or reduction of effect [insufficient clinical data] |

▶ Pharmacist's Note (Unexpected)

The German regulatory body Commission E has approved Vitex for PMS and mastodynia since 1992 — in Germany it is prescribed as a medicine, not sold as

a supplement. In Serbia it is often sold without standardization, which makes dosing unreliable. Always look for the declared agnuside or casticin content on the label as a quality marker.

Turmeric *(Curcuma longa)*

● **MODERATE RISK** as a food spice the risk is low, but concentrated capsule extracts can seriously interact with blood-thinning and liver medications, so the whole ‘family’ of products carries a moderate-to-high risk, depending on the form.

> *The yellow powder that stains fingers, pots, and laundry rarely stains your blood when you sprinkle it into soup — but in capsule form it can thin it almost like a mini aspirin. The difference isn't in the plant, it's in the dose.*

▶ Traditional Use

In Ayurvedic and Traditional Chinese Medicine, turmeric rhizome (the underground stem) has been used for centuries for digestion, liver 'cleansing,' skin problems, and joint inflammation. This is historical/ traditional use — not the same as clinical proof.

▶ Active Compound → Effect

The main active carrier is curcumin (and related curcuminoids), a yellow pigment. It acts as an anti-inflammatory and antioxidant — dampening the NF-κB signaling pathway and reducing the production of inflammatory cytokines (TNF-α, IL-6) — and stimulates bile secretion (a choleretic effect). The problem:

curcumin is poorly absorbed from the gut and is rapidly broken down in the liver, so its 'net' effect on the body depends heavily on the form in which it's taken.

▶ What the Science Actually Says (Proven vs. Anecdotal)

Solidly established (traditional use per the EMA monograph): relief of mild digestive complaints — bloating, sluggish digestion. This is a recognized traditional use, not the same as a confirmed therapeutic indication.

Clinically promising, but not definitive: for osteoarthritis (knee pain and similar), several small studies and meta-analyses show a moderate reduction in pain, in some cases comparable to mild NSAIDs over short periods. [Study quality is uneven — small groups, differing formulations, frequent conflicts of interest in sponsored research — take with caution.]

Weak/preliminary evidence, mostly marketing: claims about preventing/treating cancer, depression, Alzheimer's disease, weight loss — mostly laboratory (in vitro) findings or small human pilot studies. [This is where the gap between advertising and evidence is widest — do not treat as established.]

▶ Preparation and Dosage (Specifics)

As a food spice (a pinch): ~1 teaspoon of rhizome powder (roughly 2–3 g) daily in food or tea — ordinarily safe as a culinary amount.

Traditional herbal preparation for digestion (EMA-type dose): about 0.5–1 g rhizome powder, up to 3 times daily before meals, short-term (a couple of weeks); if symptoms persist beyond ~2 weeks, see a doctor. The exact amount depends on the specific approved product — check the label/monograph of the particular preparation.

Concentrated extract (standardized, e.g., to 95% curcuminoids), used in clinical studies for joints: 500–2,000 mg curcumin daily, divided into 2–3 doses, over 8–12 weeks, often combined with piperine or a liposomal formulation for better absorption. [There is no single 'official' dose — these are dose ranges from research, not a universal recommendation; check the specific product.]

The difference is fundamental: a pinch in soup ≠ a concentrate capsule — a different risk profile.

▶ Contraindications (Who Should NOT Use It)

Gallstones with bile duct obstruction — the choleretic effect can trigger cramps/colic.

Bleeding disorders, or 1–2 weeks before a planned surgery — due to its antiplatelet effect.

Iron-deficiency anemia — curcumin may reduce iron absorption.

High/concentrated doses during pregnancy and breastfeeding — [safety data are limited; caution is advised even though culinary spice use is generally accepted].

▶ Drug Interactions (+ Why)

(+ why) — THE MOST IMPORTANT PART:

1. Anticoagulants/antiplatelet drugs (warfarin, aspirin, clopidogrel, newer oral anticoagulants) → curcumin mildly reduces platelets' ability to stick together, and with warfarin it can also affect the enzyme that breaks it down (CYP2C9) and raise its blood level → higher risk of bleeding/bruising.

2. Drugs broken down by the CYP3A4/CYP2C9 enzymes or the P-glycoprotein transporter (e.g., immunosuppressants like cyclosporine/ tacrolimus, some chemotherapy drugs, certain statins) → curcumin inhibits these enzymes/ transporters, so the drug leaves the body more slowly and its blood level rises → risk of drug toxicity. The degree of risk depends on the dose and formulation of curcumin — for chronic therapy with narrow-therapeutic-index drugs, consulting a pharmacist/doctor before combining is recommended.

3. Diabetes medications (insulin, sulfonylureas) → curcumin mildly lowers blood sugar → the combined effect can cause hypoglycemia — monitor blood glucose.

4. Iron (supplements/anemia therapy) → curcumin binds (chelates) iron in the gut and reduces its absorption.

> 5. Piperine (black pepper) in combination supplements → itself increases curcumin absorption, but at the same time inhibits the same CYP3A4/P-gp enzymes → amplifies all the interactions above, not just curcumin's effect.

▶ Pharmacist's Note (Unexpected)

The real paradox: curcumin is so poorly absorbed from food that the industry adds 'enhancers' (piperine, liposomes, nanoparticles) just to make the supplement 'work' in the body at all. But those very enhancers are why turmeric capsules can be riskier for medication interactions than the same turmeric from a kitchen spoon — the more 'effective' the product, the more potentially interactive it is.

Cat's Claw *(Uncaria tomentosa)*

● **MODERATE RISK** the plant is generally well tolerated with short-term use, but it has specific and potentially dangerous drug interactions that can go unnoticed if the patient doesn't tell their doctor they're taking it.

> *The Asháninka people of the Peruvian Amazon have brewed the bark of this thorny vine against joint inflammation for centuries. Today, on the other side of the world, doctors on organ transplant units make a habit of asking patients specifically about this tea — because there's a theory that it can interfere with therapy that prevents transplant rejection.*

▶ Traditional Use

The bark and root are used in the folk medicine of Peru, Ecuador, and Brazil for joint inflammation, stomach ulcers, wounds, infections, colds, and as a general 'immune tonic.' It's also traditionally used for allergies, asthma, viral infections, and rheumatism, but also for contraception and regulating the menstrual cycle — this last detail is important and comes back later as a contraindication.

▶ Active Compound → Effect

The main group of compounds are oxindole alkaloids, which fall into two chemically distinct types: pentacyclic oxindole alkaloids (POAs — e.g., isopteropodine, mitraphylline, pteropodine) and tetracyclic oxindole alkaloids (TOAs — rhynchophylline, isorhynchophylline). Alongside these are quinovic acid glycosides, proanthocyanidins (tannins), and phytosterols.

[Important for quality control]: POAs and TOAs behave antagonistically at the receptor level — a commercial extract containing both alkaloid types may have a weaker (or unpredictable) effect than one standardized exclusively to POAs. This means two products with the same 'cat's claw' label can be pharmacologically different.

▶ What the Science Actually Says (Proven vs. Anecdotal)

Clinically studied, with limited but existing data: There are a few small clinical studies in osteoarthritis and rheumatoid arthritis suggesting a mild reduction in joint pain and swelling compared with placebo. [To verify: the number of participants, duration, and methodological quality of these studies — these are small samples, not large, robust trials.]

Preclinical level (cells/animals), NOT proven in humans: anti-inflammatory, antioxidant, and immunomodulatory effects, effects on transport

proteins and metabolic liver enzymes. The extract significantly inhibits ABC transporters and most tested SLC transporters, and also induces genes for CYP3A4 and other liver enzymes — this is a laboratory finding; its translation to clinical significance in humans remains to be confirmed.

Anecdotal/marketing, insufficiently proven: 'boosting immunity' as a general claim, antiviral and 'anticancer' effects. Despite some positive preclinical data, there are no clinical trials confirming a direct anticancer effect in humans.

▶ Preparation and Dosage (Specifics)

> **Traditional bark tea/decoction: about 1 teaspoon (≈1–2 g) of crushed dried bark is boiled for 10–15 minutes, 2–3 times daily. This is a mild form, with a low concentration of active compounds.**
>
> Standardized extract (capsules): a much more concentrated form — the dose and % alkaloid standardization vary from product to product. [Essential to check: read and follow the specific product's label, since there is no single universal 'safe' dose I can confidently state — the extract and a 'pinch' of bark are NOT pharmacologically equivalent; the extract can be ten times stronger per unit weight.]

Duration: traditionally, continuous use for longer than a few weeks without a break is not recommended, due to its immunomodulatory effect. [To verify: the specific recommended maximum course length per the monograph.]

▶ Contraindications (Who Should NOT Use It)

Pregnant and breastfeeding women — absolutely, due to its historical use as a contraceptive/abortifacient agent in folk medicine.

Patients on immunosuppressive therapy (after organ transplantation).

Autoimmune diseases (lupus, multiple sclerosis, rheumatoid arthritis) — [a paradox worth noting: the plant has simultaneously been studied AS a therapy for rheumatoid arthritis BECAUSE of its anti-inflammatory effect, while at the same time being flagged as potentially boosting the immune response in autoimmune disease. This contradiction in the literature is unresolved and calls for caution, not self-directed use.]

Coagulation disorders, planned surgery (discontinue in advance).

Children, people with chronic kidney/liver disease.

▶ Drug Interactions (+ Why)

> **(+ why) — THE MOST IMPORTANT PART:**
> 1. Immunosuppressants (cyclosporine, tacrolimus, corticosteroids after transplantation): because of the plant's purported immunostimulant effect, there is a possibility of interaction with drugs that deliberately suppress the immune system — mechanism: if the plant activates the immune system while the drug is

> trying to suppress it, there is a theoretical risk that the therapy won't be effective enough and the body will start rejecting the transplanted organ. These possible interactions have not yet been scientifically proven, but are taken seriously.

> **2. Anticoagulants and antiplatelet drugs (warfarin, aspirin, clopidogrel): cat's claw may increase the effect of anticoagulants, raising the risk of bleeding. The mechanism isn't fully understood, but is attributed to a mild effect on blood clotting.**
>
> 3. Blood pressure medications (antihypertensives): an enhanced (additive) drop in blood pressure is possible, up to hypotension — the mechanism is insufficiently studied [to verify], but is described in several sources as a reason for caution.

[Liver/gut enzymes and transporters]: CONFIRMED in vitro — 'Identification of PXR Activators from Uncaria Rhynchophylla and Uncaria Tomentosa' — 7 alkaloids identified as PXR activators, inducing CYP3A4/CYP2J2/UGT1A3/UGT1A9/MDR1/OATP1B1 mRNA; 'Modulation of Multispecific Transporters by Uncaria tomentosa Extract and Its Major Phytoconstituents' (Pharmaceutics, 2024) — inhibition of ABC and SLC transporters (OATP, OCT1/2, OAT3, ENT4, MDR1, BCRP). The finding is real, but EXCLUSIVELY in vitro — there is no clinical confirmation of its in vivo relevance in humans. In practical terms: the plant could THEORETICALLY change the rate at which many drugs are broken

down/absorbed, but the clinical significance in humans has not been quantified.

▶ Pharmacist's Note (Unexpected)

The biggest problem isn't the plant itself, but the lack of standardization in the market. There are two chemically distinct 'strains' of the plant (POA-dominant and TOA-dominant), and on top of that, it's often confused on the market with the related species Uncaria guianensis under the same common name. A pharmacist should check the label (% alkaloid standardization, the species listed) — two products with the same name can be fundamentally different medicinal preparations. This is rarely known outside the profession, yet it directly affects both efficacy and safety.

Dandelion *(Taraxacum officinale)*

● **LOW RISK** general use is safe; caution with diuretics, lithium, and quinolone antibiotics

> *Doctors in World War II used dandelion leaves as an emergency source of vitamin C when vegetable supplies ran dry — and it wasn't just a stopgap: half a handful of fresh leaves contains a full day's dose. The same plant whose fuzzy seed heads children blow into the wind treats the liver, flushes out water, and fights inflammation — but if you're taking water pills or warfarin, it can cause a serious problem.*

▶ Traditional Use

A bitter tonic for the liver and bile — a 'blood purifier' in the folk medicine of Europe, China, and Arabia

A diuretic (the French name pissenlit doesn't lie)

A laxative in smaller doses

Petal ointment for eczema and minor wounds

Roasted root as a coffee substitute

▶ Active Compound → Effect

Taraxacin / taraxacerin (sesquiterpenes)

Bitter compounds in the root → stimulate bile and pancreatic enzyme secretion → better fat digestion.

Inulin (a prebiotic polysaccharide)

The root contains 12–45% inulin → feeds gut flora, mildly lowers blood glucose.

Flavonoids (luteolin, quercetin)

Leaf and flower → antioxidant and anti-inflammatory effects in vitro — but poorly confirmed clinically in humans.

Potassium

The leaf is rich in potassium → replaces K^+ lost through the diuretic effect (this is what sets it apart from synthetic diuretics).

▶ What the Science Actually Says (Proven vs. Anecdotal)

Clinically well-supported: Diuretic effect — a pilot RCT (leaf extract, urination frequency ↑ significantly within 5 hours, small sample). Cholagogue effect (bile stimulation) — moderate clinical evidence; the EMA accepts this for 'traditional use.' The nutritional value of fresh leaves is beyond question.

Moderate/preliminary evidence: Hypoglycemic effect (mouse studies, one small human pilot). The in vitro antioxidant effect is strong — but human data are modest. Potential anti-inflammatory effects — promising, but without robust RCTs.

Anecdotal / unproven in humans: 'Liver cleansing,' detoxification, anticancer effects — all of these are in vitro or animal data. Do not present them to patients as facts.

▶ Preparation and Dosage (Specifics)

Fresh leaf (salad, tea)

4–10 g dried leaf or 1 handful fresh / day — this is a food-level dose, a safe range.

Root tea (dried)

2–8 g dried root in 150 ml boiling water, 3× daily. Duration: up to 4 weeks, then a break.

Liquid extract (1:1)

4–8 ml / day. Caution: here the dose differs substantially from a 'pinch.'

Standardized extract capsules

500–2,000 mg / day in divided doses — follow the manufacturer's instructions, as standardization varies (bitter compounds 10–20%).

Root essential oil — do NOT take internally without professional supervision — high concentration, no clinical doses established for self-treatment.

▶ Contraindications (Who Should NOT Use It)

Bile duct obstruction or gallstones (the cholagogue effect can trigger colic)

Acute cholecystitis, cholangitis

Confirmed allergy to Asteraceae (the Asteraceae/Compositae family) — cross-reactive with ragweed, chrysanthemum, arnica

Pregnancy and breastfeeding — insufficient data, avoid extracts

Renal insufficiency (a high potassium intake can be dangerous)

[There are no robust clinical studies for pregnancy — the recommendation is a cautious extrapolation, not direct evidence of harm.]

▶ Drug Interactions (+ Why)

> **(the most important part)**
>
> Diuretics (furosemide, hydrochlorothiazide)

> **Mechanism: Dandelion itself increases diuresis (blocking Na^+ reabsorption in the tubules). Combined with thiazides or loop diuretics → additive loss of water and potassium → risk of hypokalemia and dehydration. Paradox: dandelion has a high K^+ content that partly compensates, but the overall effect remains unpredictable.**
>
> Lithium

High risk. Any diuretic reduces the kidneys' excretion of lithium (Na^+ and Li^+ share a reabsorption pathway in the proximal tubule). Less water = higher serum Li^+ = toxicity (tremor, confusion, arrhythmias). Patients on lithium must not take herbal diuretics without monitoring their drug levels.

Warfarin and other anticoagulants

Mechanism: Dandelion contains vitamin K (leaf ~778 µg/100 g fresh). High leaf intake can antagonize warfarin → INR drops → reduced anticoagulation → risk of thrombosis. Capsule extracts have a lower vitamin K content, but it isn't negligible.

[Clinical cases have been reported, but systematic interaction studies are nearly nonexistent — the recommendation is conservative.]

Hypoglycemic agents (metformin, insulin, sulfonylureas)

Mechanism: Potential additive lowering of blood glucose (inulin + possible direct effects) → risk of hypoglycemia at high extract doses. Fresh leaf in normal culinary amounts is probably safe.

Ciprofloxacin and other fluoroquinolones

Mechanism: The high mineral ion content (Ca^{2+}, Mg^{2+}, Fe^{2+} in fresh leaf) can chelate the antibiotic in the GI tract → reduced absorption. A 2-hour gap between taking the herb and the antibiotic reduces the risk.

CYP1A2 substrates (e.g., clozapine, theophylline, caffeine)

> Mechanism: Mouse studies suggest inhibition of CYP1A2 by leaf extract. [No human data exist — this is an experimental finding, not a clinical recommendation.]

▶ Pharmacist's Note (Unexpected)

Heavy metal contamination: Dandelion accumulates lead, cadmium, and arsenic from the soil — plants picked near busy roads, industrial sites, or old dump sites can be toxic. This isn't a hypothesis: it has been confirmed in multiple analyses of market samples.

Root harvested in autumn has several times the inulin and bitter-compound content of spring-harvested root — the 'same plant' can have a substantially different phytochemical profile depending on the harvest season.

The latex-like milky sap from the stem can cause contact dermatitis in sensitive individuals — especially with prolonged contact.

Peppermint *(Mentha piperita)*

● **MODERATE RISK** harmless in the kitchen, but the essential oil and high-dose extracts carry specific risks

> *The pharmacist tells you to drink peppermint tea for your stomach — but no one mentions that the same tea can weaken the effect of your blood pressure medication. The plant that smells like candy has a more serious dossier than it looks.*

▶ Traditional Use

Cramping stomach pain, bloating, nausea, colds and nasal congestion, tension-type headaches (topical use), feverish states. Documented in Egyptian papyri, deeply rooted in European folk medicine; in Serbia and the region, the tea is the standard 'home remedy' for an 'upset stomach.'

▶ Active Compound → Effect

Menthol (40–55% of the essential oil) → agonist (activator) of TRPM8 cold receptors in the skin and mucous membranes → a cooling sensation, mild analgesic and decongestant effects; locally inhibits muscle cramps

Menthol + menthone together → an antispasmodic effect on intestinal smooth muscle (blocking calcium

channels in smooth muscle) — this is the most clinically well-supported mechanism

Polyphenols (rosmarinic acid) → antioxidant, mildly anti-inflammatory [evidence from in vitro studies, clinical significance unclear]

▶ What the Science Actually Says (Proven vs. Anecdotal)

✅ Clinically proven (moderate to solid):

Enteric-coated peppermint oil capsules for irritable bowel syndrome (IBS) — reduced abdominal pain in short-term RCTs; the EMA recognizes it as a traditional herbal medicine for IBS symptoms

Topical application of menthol to the forehead for tension headaches — several small RCTs show efficacy similar to paracetamol [small sample size, replication needed]

Inhalation for the subjective feeling of nasal patency — proven, but without a measurable change in airflow (the effect is sensory, not anatomical)

⚠ Anecdotal / poorly proven:

Antiviral and antibacterial effects — in vitro results exist, no clinical equivalent

Reducing fever and inducing sweating for colds — traditional, without RCT confirmation

A calming effect on the nervous system — observational data, not substantiated

▶ Preparation and Dosage (Specifics)

> **| Form | Amount | Frequency | Note |**
> |---|---|---|---|

> **| Tea (dried leaves) | 1.5–3 g (1 teaspoon ≈ 1.5 g) / 150 ml boiling water, 5–10 min | 3–4× daily | Safe for adults; this is a 'pinch' — a million times milder than the extract |**
> | Enteric-coated capsule (oil) | 0.2–0.4 ml oil per capsule | 3× daily, 30 min before meals | ONLY the enteric-coated form for IBS — without the coating, capsules cause heartburn and reflux |

> **| Essential oil — topical use | Diluted 1–2% in a carrier oil (1–2 drops / 10 ml) | On skin as needed | Never undiluted on skin, never internally |**
> | Essential oil — inhalation | 1–2 drops on a tissue or inhaler | As needed | |

 Essential oil ≠ tea. 1 drop of essential oil ≈ 25–30 g of fresh plant. Dosing it by the teaspoon is lethal.

▶ Contraindications (Who Should NOT Use It)

Children under 2 years — menthol can cause laryngospasm and respiratory problems (potentially fatal); do not apply to the face or near a child's nose

Children up to 12 years — essential oil only on a doctor's advice

Gastroesophageal reflux (GERD), hiatal hernia — menthol relaxes the lower esophageal sphincter → worsens reflux (non-enteric-coated capsules are contraindicated)

Bile duct obstruction, active cholelithiasis — the cholagogue effect can provoke colic

Severe liver disease — slowed biotransformation of menthol [caution in cirrhosis]

Pregnancy — tea in small amounts is probably safe [no robust RCTs], avoid the essential oil

▶ Drug Interactions (+ Why)

CYP3A4 and CYP1A2 inhibition — menthol and some peppermint components inhibit these liver enzymes that break down numerous drugs. Consequence: elevated drug blood levels → greater side effects.

Specifically affected: cyclosporine, tacrolimus (immunosuppressants), some calcium channel blockers (amlodipine, nifedipine), benzodiazepines, statins (especially simvastatin, lovastatin)

[The degree of inhibition at typical tea doses is probably mild, but relevant with extracts/ capsules — precise data are weak, needs verification]

Antacids and proton pump inhibitors (omeprazole and similar) — if taken at the same time as non-enteric-coated oil capsules, they reduce stomach acidity → the capsule breaks down prematurely in the esophagus → heartburn and loss of effect

Antihypertensives — there is a theoretical interaction via CYP enzymes; clinical cases aren't well documented, but caution is warranted during dose titration [weak evidence, check with a cardiologist if the patient regularly consumes the extract]

Iron (supplements or medication) — tannins in the tea can reduce iron absorption; allow a gap of at least 2 hours

▶ Pharmacist's Note (Unexpected)

Menthol is also registered as an excipient (an inactive/functional ingredient) in hundreds of pharmaceutical preparations — from tablet coatings to inhalers — precisely because of its sensory effect. Many patients don't realize that 'the medicine doesn't smell of mint by accident' — menthol is a functional ingredient — and with such preparations, unintentional dose stacking can occur if capsules and these medications or lotions are used at the same time.

Valerian *(Valeriana officinalis)*

● **MODERATE RISK** interactions with CNS drugs are real and documented

> *For two thousand years, physicians have written about valerian as a remedy for insomnia — and modern science still doesn't know exactly why it works. What we do know: if you're taking sleeping pills or antidepressants, valerian is not 'just a plant.'*

▶ Traditional Use

Insomnia, nervousness, and a 'heart pounding for no reason' — this is the classic trio valerian has been used for from antiquity through the Middle Ages to the present day in the folk medicine of Serbia and the wider Balkan region. Root tea or root steeped in rakija were standard home remedies. In 19th-century European phytotherapy, valerian was so popular that pharmacists sold it in remedies for 'nervous attacks.'

▶ Active Compound → Effect

Valeric acid and valerenic acid (in the root) → bind to GABA receptors in the brain — the same receptors that benzodiazepines (diazepam, bromazepam) act on, only more weakly and more slowly. Result: mild calming, easier sleep onset.

Isovaleric acid → contributes to the sedative effect, but is also responsible for the characteristic strong smell of the root.

Lignans and flavonoids (linarin, hesperidin) → possible synergistic action [mechanism not fully clarified]

▶ What the Science Actually Says (Proven vs. Anecdotal)

proven [ADDENDUM] CONFIRMED with clarification — the EU herbal monograph (EMA/HMPC/150848/2015) contains BOTH categories: 'well-established use' and 'traditional use,' for relieving mild nervous tension and as a sleep aid (dose 400–600 mg dry extract up to 3× daily, or a single dose 30–60 min before bed) — it is not exclusively a traditional-use category as previously stated.

weak evidence [CORRECTION] Meta-analyses DO EXIST, BUT neither is a Cochrane review (the term 'Cochrane review' is incorrect): Bent S et al., Am J Med, 2006 (16 RCTs/1,093 patients — 9 of the 16 studies did NOT show a positive outcome) and Fernández-San-Martín MI et al., Sleep Med, 2010 (subjective improvement possible, objectively unconfirmed). The conclusions of both meta-analyses are mixed/cautious, not unambiguously positive.

anecdotal Popular and widely used for daytime anxiety — this is not an approved indication and clinical data are insufficient.

anecdotal Combination with hops (Humulus lupulus) is common in preparations — synergy is presumed, but hasn't been robustly studied.

▶ Preparation and Dosage (Specifics)

> **Tea (root): 1–3 g of dried root in 150 ml boiling water, cover and steep for 10–15 min. Drink 30–60 min before bed. The taste is strong and unpleasant — that's normal.**
>
> Dry extract: 300–600 mg of standardized extract (0.8% valerenic acid), one dose in the evening. It's not the same as tea — the extract is many times more concentrated than a pinch of the plant in a cup.

> **Tincture: 1–3 ml (1:5 in 40–60% alcohol), 3× daily or as a single evening dose. [dose ranges vary between manufacturers — always read the label]**
>
> Duration: the EMA recommends up to 2–4 weeks; for longer use, consult a doctor or pharmacist. For some people the effect only appears after 2–4 weeks of regular use — it's not an instant pill.

Essential oil: Not for internal use. Used exclusively for aromatherapy — a few drops on a pillow or in a diffuser. Oral use of the essential oil can be toxic.

▶ Contraindications (Who Should NOT Use It)

Pregnancy and breastfeeding — insufficient safety data; the EMA recommends avoidance.

Children under 12 years — use is not approved.

Known hepatotoxicity or liver disease — CONFIRMED: LiverTox (NCBI Bookshelf) lists valerian as a very rare cause of hepatotoxicity (likelihood score C — 'probable rare cause'), with a latency of 3–12 weeks, usually in combination with other herbs (e.g., skullcap, black cohosh); case report. [causality is not firmly established for all cases]

Immediately before surgery — discontinue ≥ 2 weeks before general anesthesia (possible additive sedative effect).

▶ Drug Interactions (+ Why)

★ the most important part

Benzodiazepines and Z-drugs (diazepam, bromazepam, zolpidem, alprazolam)

Valerian enhances GABA activity — the same mechanism as benzodiazepines. Combined → additive sedative effect, increased drowsiness, slowed reactions. This combination carries a particular risk of falls in the elderly.

Antidepressants (especially SSRIs: sertraline, escitalopram; and trazodone)

Potential enhancement of the CNS depressant effect. With trazodone — anecdotal reports of excessive sedation. [the strength of the interaction has not been reliably measured in clinical studies]

Anticonvulsants (carbamazepine, valproate)

> **Anticonvulsants (carbamazepine, valproate) [CORRECTION] Contradictory data exist: some preclinical findings (animal, via nuclear receptors) suggest reduced CYP3A gene expression, BUT validated human probe-drug studies (Gurley et al.) show that standardized valerian extracts have NO clinically significant effect on CYP3A4 in humans. A direct interaction with carbamazepine/valproate via CYP3A4 is NOT documented as a clinical interaction — it remains a theoretical/preclinical controversy, not a proven one.**
>
> Alcohol

> **Additive CNS-depressant effect. The combination increases the risk of sedation and impaired coordination.**
>
> Anticoagulants (warfarin)

Anticoagulants (warfarin) [CORRECTION] No documented case report of a valerian-warfarin interaction with INR change was found in this search — [unconfirmed, no source found]. Given that valerian has no significant CYP effect in humans (see above), a clinically relevant interaction is unlikely, but patients on warfarin should still report their use to their doctor as a general precaution.

▶ Pharmacist's Note (Unexpected)

Fresh root has almost no distinctive smell — the characteristic 'sweaty feet' odor only develops during drying and storage, as valeric acid breaks down. Because of this, some manufacturers use a 'fresh' extract, while the characteristic smell is actually a sign

of age or poor storage — not a measure of potency. Standardization to 0.8% valerenic acid is a more reliable quality indicator than the smell or color of the preparation.

Horsetail *(Equisetum arvense)*

● **MODERATE RISK** contains thiaminase and nicotine-related compounds; prolonged unsupervised use can damage the kidneys and cause vitamin B1 deficiency.

> *This plant has no flower, no true leaf — it outlived the dinosaurs and today grows as a weed along railway tracks. And then someone discovered that it's one of the most concentrated plant sources of silicon on the planet.*

▶ Traditional Use

Used for centuries across Europe and Asia as a diuretic, for "strengthening bones and nails," wound healing, stopping bleeding (as a hemostatic tea), and for urinary tract inflammation. In Slavic folk medicine it was also used for "blood cleansing" — a vague term that covers everything and nothing.

▶ Active Compound → Effect

Silicon / silicic acid (5–8% in the dried plant) → structural support for connective tissue, skin, bones, nails, and hair; the absorption mechanism from plant sources is better studied than from mineral supplements

Flavonoids (kaempferol, quercetin, apigenin) → antioxidant and mild anti-inflammatory effect

Saponins (equisetogenin) → contribute to the diuretic effect; irritating at high doses

Thiaminase ⚠ → an enzyme that breaks down vitamin B1 (thiamine); inactivated by boiling, but active in the fresh, raw plant

▶ What the Science Actually Says (Proven vs. Anecdotal)

✅ Clinically/experimentally confirmed (moderate evidence):

The diuretic effect was confirmed in one randomized study (comparison with hydrochlorothiazide showed similar efficacy in increasing diuresis) — [EMA adopted a positive opinion as "traditional herbal use," which is a lower evidentiary bar than "clinically confirmed"]

Silicic acid from E. arvense shows better bioavailability than inorganic SiO_2 in pilot studies

⚠ Weak or insufficient evidence:

Effect on bone strength, nails, and hair: observational studies and in vitro data exist, but solid clinical evidence from RCTs does not — popular belief outpaces the evidence

Wound healing, anti-inflammatory effects: promising in vitro, but clinically insufficiently studied

❌ No evidence:

"Blood cleansing," detoxification, and anti-aging uses — marketing concepts with no scientific basis

▶ Preparation and Dosage (Specifics)

> ⚠ **Key distinction: dried crude herb ≠ concentrated extract**

Form	Amount	Frequency	Duration
Tea (dried vegetative stem)	2–3 g dried herb / 150 ml boiling water, 15 min	2–3× daily	max. 4–6 weeks
Dry extract (standardized to silicon)	**per product label (typically 300–600 mg extract)**	**1–2× daily**	**max. 4–6 weeks**
Essential oil	NOT used internally — no therapeutic application for this plant's essential oil, potentially toxic	—	—

> **Tea must be made from the dried, boiled plant — this inactivates the thiaminase**

A "pinch" of the dried plant ≈ 1–2 g; that is the clinically relevant dose for tea; a concentrated 5:1 extract means 300 mg corresponds to 1.5 g of crude herb — do not equate the two

For diuretic use: fluid intake must be monitored

▶ Contraindications (Who Should NOT Use It)

Pregnancy and breastfeeding — no safety data, and nicotine-related compounds may be problematic [insufficiently studied, prudent to avoid]

Chronic renal insufficiency or urate kidney stones (the diuretic effect may be counterproductive)

Vitamin B1 deficiency or conditions at risk for it (alcoholics, malnutrition) — due to thiaminase (relevant if the raw/unboiled plant is used)

Children under 12 years of age

Known allergy to plants of the Equisetaceae family

▶ Drug Interactions (+ Why)

> **| Drug / class | Interaction | Mechanism |**
> |---|---|---|

> **| Diuretics (furosemide, hydrochlorothiazide) | Enhanced diuretic effect → risk of dehydration and electrolyte imbalance (hypokalemia) | Additive effect on renal excretion |**
> | Lithium ⚠ | Increased lithium toxicity | Diuresis reduces renal elimination of lithium → plasma concentration rises; lithium's therapeutic window is narrow |

> **| Antihypertensives | Possible enhancement of the hypotensive effect | Volume reduction through diuresis lowers blood pressure additively |**
> | Digoxin ⚠ | Increased risk of toxicity | Hypokalemia (caused by enhanced diuresis) sensitizes the heart muscle to digoxin |

| **Drugs that lower K^+ levels (corticosteroids, amphotericin B) | Synergistic potassium loss | Potassium is lost via a parallel pathway |**

| Thiamine (vitamin B1) supplementation | Horsetail reduces B1 effectiveness | Thiaminase directly breaks down thiamine — less relevant with the boiled plant, but important with the raw plant or raw juice |

▶ Pharmacist's Note (Unexpected)

Horsetail also contains small amounts of nicotine and 3-methoxypyridine — not in pharmacologically relevant doses for tobacco dependence, but enough to theoretically affect urine tests [clinical relevance unclear, no confirmed cases]. Also, because of its high silicon concentration, the plant has historically been used to polish metal and wood — which speaks to the abrasive nature of the silicon crystals in its tissue, something not without significance for the gastrointestinal mucosa with prolonged use of the raw plant.

Rhodiola *(Rhodiola rosea)*

● **MODERATE RISK** well tolerated on its own, but due to its effects on brain neurotransmitters and liver enzymes it is not harmless in combination with medications.

> *Soviet athletes and cosmonauts took it to endure exertion at the very edge of human capability — today the same plant sits on a drugstore shelf next to the vitamins, as if it were peppermint tea.*

▶ Traditional Use

In Siberian, Scandinavian, and Chinese folk medicine, the root has been used for centuries against fatigue, for "fortification" during exertion in cold conditions and at high altitude, as well as for improving concentration. This is a historical indication, not necessarily one that is clinically confirmed in its entirety.

▶ Active Compound → Effect

Two key compounds carry the effect: salidroside and a group of compounds called rosavins (rosavin, rosin, rosarin). Together they are thought to act on serotonin, dopamine, and norepinephrine levels in the brain (the so-called monoaminergic system), which

would explain the reduced sense of fatigue and better mental endurance under stress.

▶ What the Science Actually Says (Proven vs. Anecdotal)

There is a series of smaller clinical studies (mostly short-term, using standardized extracts) showing a moderate reduction in the subjective feeling of fatigue and a mild improvement in mood under stress and in mild to moderate depression. On this basis, the European Medicines Agency (EMA) has registered the plant as a traditional herbal medicine for the temporary relief of stress symptoms such as fatigue and a sense of weakness — not as a proven effective medicine in the strict pharmacological sense, but on the basis of long-standing use and supportive (though not conclusive) clinical findings. The quality of evidence is generally low to moderate — many studies have small sample sizes, short duration, and use different extracts, so direct comparison of results is not fully reliable; this is a consistent finding in more recent systematic reviews as well. Claims about "boosting immunity," "anti-aging" effects, or curing more serious depression lack solid confirmation and fall into the anecdotal/marketing category.

▶ Preparation and Dosage (Specifics)

> **It is important to distinguish between two entirely different approaches:**

> Traditional tea/pinch method — a teaspoon (about 1–2 g) of dried, chopped root is poured over with boiling water and left to steep for about 10 minutes; this kind of infusion has a mild and unreliably dosed effect, since the content of active substances in the raw root varies considerably.

Standardized extract (capsules/tablets) — clinical studies and the EMA monograph use dry extracts standardized to rosavin and salidroside content, at a daily dose of roughly 144–400 mg, divided into one to two doses, usually in the morning and early afternoon (because of the mildly stimulating effect, avoid taking it in the evening). Study courses typically last 4–6 weeks, with a break recommended afterward. The exact standardization percentage (e.g., "3% rosavins / 1% salidroside") should be checked on the specific product's label — the range given above applies to the extract as a whole, not to a "pinch" of tea, which never reaches this concentration.

▶ Contraindications (Who Should NOT Use It)

Pregnancy and breastfeeding (insufficient safety data — avoid), children and adolescents under 18 years of age (the EMA monograph explicitly does not recommend it). Caution in people with bipolar disorder — because of its stimulant/monoaminergic action there is a theoretical risk of triggering a hypomanic/manic episode; this is a precautionary recommendation based on pharmacological reasoning, not a confirmed clinical

finding from large studies. People with autoimmune diseases should consult a physician — theoretically, because of a possible immunomodulatory effect for which the evidence is weak.

▶ Drug Interactions (+ Why)

> **(+ why) — THE MOST IMPORTANT PART:**
> This is not a harmless "pick-me-up tea" when combined with medication:

> **Antidepressants (SSRIs, SNRIs, MAO inhibitors) — the most serious interaction. Mechanism: in laboratory conditions, rosavins and salidroside inhibit the MAO-A and MAO-B enzymes and affect serotonin/dopamine/norepinephrine turnover — the same pathway these drugs act on. The combination may potentiate the drug's effect to the point of serotonin syndrome (agitation, tremor, rapid heartbeat, sweating). A published clinical case of such a reaction exists for the combination with paroxetine. [Clinical significance beyond this isolated case and in vitro data has not yet been firmly established in larger patient groups.]**
> Stimulants and ADHD medications — possible additive effect (nervousness, insomnia, rapid heartbeat), since both substances act on the same noradrenergic system.

Drugs broken down by the liver enzymes CYP3A4, CYP2D6, and CYP2C9 (many blood pressure medications, anticoagulants such as warfarin, and certain psychiatric medications) — laboratory research shows that root extract can slow the activity of these

enzymes, which theoretically raises blood levels of these drugs above the safe threshold. This is based predominantly on in vitro/preclinical data, but there is also a controlled study in 13 healthy volunteers that showed a statistically significant (21%) change in a marker of CYP2C9 activity (the EXP-3174/losartan ratio) after 14 days of taking a commercial R. rosea extract — clinical significance for actual treatment outcomes (e.g., with losartan or warfarin) at usual doses is still not fully established, so caution and consultation with a pharmacist is recommended before combining it with chronic therapy.

▶ Pharmacist's Note (Unexpected)

What few people expect from a "herbal adaptogen" is that it behaves almost like a real drug at the level of the liver — the root doesn't act on the brain alone, it also changes the rate at which the liver breaks down other substances. That's why two seemingly harmless things — coffee spiked with the root, and a blood pressure pill taken alongside it — can produce an unexpectedly strong or prolonged drug effect, simply because the liver clears it more slowly from the body.

Senna *(Cassia senna)*

● **MODERATE-HIGH RISK** safe for short-term use, but chronic use causes bowel dependency and can mask serious diseases

> *Pharmacies sell it as a "gentle" aid for constipation — but the World Health Organization and EMA limit its use to a maximum of 2 weeks. After that point, the bowel literally forgets how to work on its own.*

▶ Traditional Use

Ayurvedic and Arabic medicine have used senna for more than 3,500 years as a laxative. In the Arab world it is known as sana mekki. It was also traditionally used for "cleansing" the body, as an antiparasitic remedy, and for skin conditions — without clinical confirmation for anything beyond constipation. [anecdotal]

▶ Active Compound → Effect

Sennosides A and B (anthraquinone glycosides) — pass through the small intestine unchanged, and in the colon are broken down by gut microbiome bacteria into active metabolites (rhein anthrones). These metabolites act in two ways: they stimulate peristalsis by directly irritating the nerve plexus of the colon wall (the myenteric plexus), and they reduce reabsorption

of water and electrolytes from the bowel — the stool becomes softer and bulkier. The effect sets in after 6–12 hours, so it is taken in the evening for a morning bowel movement. [clinically proven]

▶ What the Science Actually Says (Proven vs. Anecdotal)

[PROVEN] Short-term efficacy in functional constipation — confirmed in multiple randomized controlled trials and by the EMA monograph.

[PROVEN] Efficacy in bowel preparation for colonoscopy (in combination with PEG solutions).

[ANECDOTAL / WEAK EVIDENCE] "Detox" and weight loss — there is no evidence that senna affects body weight or eliminates toxins.

[INSUFFICIENT EVIDENCE] Antiparasitic effect, improvement of skin conditions, anti-inflammatory action.

Chronic use leads to cathartic colon (atrophy of the bowel muscle) and melanosis coli — dark pigmentation of the mucosa, reversible, but a finding that concerns endoscopists. [clinically documented]

▶ Preparation and Dosage (Specifics)

> **Tea from leaves/pods: 0.5–2 g dried plant material in 150 ml boiling water, 10 minutes, once in the evening. Weaker effect, gentler on the bowel.**

> Standardized extract (tablets/capsules): 15–30 mg sennosides daily — typically 1–2 tablets with 7.5 mg sennosides, always according to the product label. This is 5–10× more concentrated than tea — do not equate it with a "pinch" of tea.

> **[CORRECTION] Duration: the EMA/HMPC monograph (well-established use, Sennae folium, adopted 2006) explicitly states that it must NOT be used for longer than 1 WEEK (not 2 weeks, as originally stated) — it is usually enough to take it 2–3 times per week. After that — a break and consultation with a physician.**
>
> Children under 12 years of age: do not give without a physician's recommendation. [Pediatric dosing — consult a pediatrician; there is no firm consensus for OTC use]

▶ Contraindications (Who Should NOT Use It)

— Bowel obstruction (ileus) — a contraindication without exception

— Inflammatory bowel disease (Crohn's disease, ulcerative colitis) — worsens irritation

— Appendicitis or unexplained abdominal pain

— Pregnancy [mild uterine stimulant — theoretical risk, avoid; no robust RCT data]

— Breastfeeding — sennosides pass into breast milk

— Renal insufficiency — electrolyte loss worsens the condition

— Children under 12 years of age (OTC)

▶ Drug Interactions (+ Why)

Digoxin, antiarrhythmics — HIGH RISK. Senna causes potassium loss (hypokalemia). Low K^+ increases digoxin toxicity and raises the risk of arrhythmias — the heart becomes hypersensitive to the drug.

Diuretics (furosemide, thiazides) — HIGH RISK. Both agents independently deplete potassium and magnesium — the combination multiplies the risk of electrolyte imbalance and cardiac complications.

Warfarin and oral anticoagulants — MODERATE RISK. Accelerated intestinal transit reduces vitamin K reabsorption → may potentiate the anticoagulant effect and raise the INR. [Clinical significance varies; monitoring the INR is advisable]

Oral corticosteroids — MODERATE RISK. Corticosteroids already lower K^+ — additive loss when combined with senna.

Oral medications in general — PRACTICAL NOTE. Accelerated peristalsis shortens transit time in the gut → may reduce absorption of oral medications (antibiotics, contraceptives, antihypertensives). A gap of at least 2 hours is advisable.

▶ Pharmacist's Note (Unexpected)

Senna is one of the few herbal medicines with an official EMA monograph in the "well-established use" category — meaning its efficacy is proven well enough

for it to be registered as an actual medicine, not just a dietary supplement. Even so, in Serbia it is often sold as a tea without a clear warning about how long it should be used.

Another unexpected thing: melanosis coli — the dark coloring of the colon's mucosa visible on colonoscopy — immediately tells the physician that the patient is taking or has taken anthraquinone laxatives. Patients often forget to mention this.

Saw Palmetto *(Serenoa repens)*

● **MODERATE RISK** the plant itself is relatively well tolerated, but combining it with blood-thinning medications and hormone therapy calls for caution and a conversation with a physician.

> *Every evening, millions of men swallow a capsule made from this small orange berry believing it protects the prostate — yet the largest and most recent analysis of all relevant studies (27 trials, over 4,600 men) says that the plant, most likely, works no better than an empty (placebo) capsule.*

▶ Traditional Use

The fruit of a small palm native to the southeastern United States (and Florida) was traditionally used for "male" urinary tract complaints — difficult, frequent, or incomplete urination, symptoms we today associate with benign prostatic hyperplasia (BPH). It was also mentioned as a general tonic, aphrodisiac, and libido enhancer — but these are purely folk beliefs, without serious evidence.

▶ Active Compound → Effect

There is no single "active ingredient" — this is about the liposterolic (fatty) fraction of the fruit: a mixture of

fatty acids (lauric, oleic, and others) and phytosterols (e.g., beta-sitosterol). The proposed mechanism is mild inhibition of the enzyme 5-alpha-reductase, which converts testosterone into DHT (dihydrotestosterone) — a hormone that drives prostate tissue growth. [This is the mechanism proposed from laboratory/in vitro research — the official EU herbal monograph explicitly states that the mechanism of action in humans is not known.]

▶ What the Science Actually Says (Proven vs. Anecdotal)

Here there is a clear gap between the product's popularity and the quality of the evidence. An updated Cochrane systematic review (2023) pooled 27 studies with 4,656 men who compared Serenoa repens, alone or combined with other herbal preparations, against placebo. The conclusion is that Serenoa repens, alone or combined with other phytotherapeutics, does not improve urinary symptoms or quality of life — neither short-term (3–6 months) nor long-term (12–17 months). The good news: it does not cause significant adverse effects, and the rate of adverse events is practically no different from placebo (risk ratio ≈1.01). Nor was the hypothesis that hexane extracts are more effective than others confirmed — the analysis found no difference in effect between the two types of product. For hair loss the evidence is too limited to draw conclusions, and for chronic prostatitis/chronic

pelvic pain syndrome, a 2022 review found no significant benefit.

[This does NOT mean it is "a plant that does nothing" — the point is that its effect on BPH symptoms is not proven well enough to be recommended as first-line therapy; more serious causes of the symptoms should always be ruled out by a urologist.]

▶ Preparation and Dosage (Specifics)

> **The standard dose used in clinical studies is ~320 mg per day of standardized liposterolic (most often hexane) extract, divided into 1–2 doses taken with a meal, over several months — trials have lasted anywhere from 3 to as long as 17 months. The EU herbal monograph for traditional use defines the preparation as a soft extract obtained by hexane extraction, at a drug-to-extract ratio of 7–11:1.**
>
> Key distinction: a "pinch" of dried berries in tea, or a capsule containing finely ground fruit, does not contain a reliable amount of the active fatty-sterol fraction — these compounds are poorly water-soluble, so berry tea essentially does not deliver what the research has tested. Any clinically relevant effect (if it exists) is tied exclusively to the concentrated, standardized lipophilic extract in capsule form, not to the raw plant material.

▶ Contraindications (Who Should NOT Use It)

Pregnancy and breastfeeding — no data on fertility effects, and because of its (weak) hormonal action it is not recommended.

Known hypersensitivity to the plant — an allergic reaction is a formal contraindication.

Planned surgery — because of a theoretical bleeding risk, discontinuation two to three weeks before the procedure is advised.

Blood coagulation disorders.

Men whose symptoms have not first been diagnosed by a urologist — the plant may "mask" the symptoms of a more serious condition (e.g., infection, stones, or prostate cancer).

▶ Drug Interactions (+ Why)

(+ why) — THE MOST IMPORTANT PART:

1. Anticoagulants and antiplatelet drugs (warfarin, aspirin, clopidogrel, DOACs) — theoretically the most important interaction. Mechanism: compounds from the plant are thought to prolong bleeding time by inhibiting the cyclooxygenase (COX) enzyme, which impairs platelet function, and with warfarin, inhibition of the CYP2C9 enzyme that breaks warfarin down is additionally mentioned — slower metabolism means higher blood levels of the drug and a greater bleeding risk. The evidence for this is mostly case reports, not large controlled trials — for example, an INR (a measure of blood "thinness") jump from 2.4 to 3.4 has been recorded after just six days of taking the preparation. [The mechanism is biologically plausible, but the level of evidence is low — the recommendation

for caution is greater than what the solid data formally confirm.]

2. Hormone therapy (estrogenic/androgenic drugs, hormonal contraception, prostate cancer therapy) — a theoretical interaction, since the plant has a mild antiandrogenic effect in vitro; clinical significance has not been established, but because of the sensitivity of these therapies, consultation with a physician is recommended.

3. Drugs metabolized via the CYP3A4, CYP2D6, CYP2C9, and UGT enzymes — laboratory studies suggest possible inhibition of these enzymes, with "clinical significance unknown" (saw palmetto inhibits CYP3A4, 2D6, and 2C9, and UGT enzymes in vitro, but clinical relevance has not been established). On the other hand, a controlled study in healthy people showed that the preparation did not change CYP2D6 and 3A4 enzyme activity — which is partially reassuring, but does not cover all the enzymes (CYP2C9 remains an open question).

4. NSAIDs (e.g., ibuprofen) — one case of increased risk of adverse effects with the combination has been described, but this is an isolated finding, not a pattern confirmed in studies.

▶ Pharmacist's Note (Unexpected)

Even though it is one of the best-selling "men's" supplements in the world and has been marketed for decades as a natural alternative to prostate medications, the official European herbal monograph (EMA/HMPC) classifies Serenoa repens only under

"traditional use," not "well-established medicinal use" — because its efficacy has not been proven sufficiently and consistently to meet the standard required for medicinal status. In other words: the very regulatory body that approves medicines has, in black and white, acknowledged that the evidence does not back up the product's popularity — which is unusually transparent for a supplement of this scale on the market.

Licorice *(Glycyrrhiza glabra)*

● **MODERATE RISK** hypokalemia can potentiate the effects of digoxin, diuretics, and corticosteroids

> *A patient comes into the pharmacy with a package labeled "natural liver protection" and says he's been drinking it for months — meanwhile he's also taking a blood pressure medication. Licorice, which is 50 times sweeter than sugar, can wreck his blood pressure more effectively than a missed dose of pills.*

▶ Traditional Use

Ayurvedic, Chinese, and Mediterranean medicine: cough, ulcers, liver inflammation, constipation, a "harmonizer" in herbal blends (masking bitter taste).

In Western herbalism: an expectorant, an antispasmodic for the gastrointestinal tract, an adaptogen.

▶ Active Compound → Effect

Glycyrrhizin (glycyrrhizic acid) — the main triterpenoid saponin. In the intestine it is broken down into glycyrrhetinic acid. This inhibits the enzyme 11β-hydroxysteroid dehydrogenase (11β-HSD2) — an enzyme that normally "deactivates" cortisol in the kidneys. The result: cortisol acts like aldosterone →

retention of water and sodium, loss of potassium → hypertension, hypokalemia.

Flavonoids (liquiritin, isoliquiritin) — anti-inflammatory, potentially gastroprotective effect (enhance mucosal mucus production). Clinical evidence is moderate.

DGL (deglycyrrhizinated licorice) — a processed form with the glycyrrhizin removed; it retains the gastroprotective effects with lower cardiovascular risk.

▶ What the Science Actually Says (Proven vs. Anecdotal)

Proven (moderate evidence) Gastric/duodenal ulcers — the DGL formulation showed benefit in older RCTs, but the studies are methodologically weaker (small samples, older methodology). EMA has issued a positive herbal monograph for use in mild gastrointestinal complaints and cough.

Proven (solid evidence) Pseudohyperaldosteronism at high doses — the mechanism is well documented.

Moderate/preliminary evidence Antiviral effect (e.g., research on glycyrrhizin and HSV, hepatitis C, and even in vitro SARS-CoV-2) — exclusively in vitro or small pilot studies; clinical application does NOT exist.

Anecdotal / insufficient evidence "Liver detox," adaptogenic effects, hormonal regulation — popular claims without robust RCTs.

▶ Preparation and Dosage (Specifics)

Tea (dried root): 1–5 g dried root, 150 ml boiling water, 5–10 min. 1–3 cups daily. Maximum 4–6 weeks without a break.

Dry extract (standardized to glycyrrhizin): typically 200–600 mg/day divided into 2–3 doses. CAUTION This form contains many times more glycyrrhizin than a cup of tea — the risk of side effects rises non-linearly.

DGL chewable tablets: 380–760 mg before meals, for gastrointestinal use. A safer profile for longer-term use.

Essential oil: not a standard medicinal application for G. glabra; do NOT use internally without supervision.

EMA recommends a maximum of 5–6 weeks for oral preparations containing glycyrrhizin. A longer period: only under medical monitoring of blood pressure and electrolytes.

▶ Contraindications (Who Should NOT Use It)

Absolute Hypertension (especially uncontrolled) · Hypokalemia · Chronic kidney disease · Liver cirrhosis · Heart failure · Pregnancy [risk of preterm birth — limited but concerning data]

Relative / caution Diabetes (glycyrrhizin may affect the cortisol/insulin axis — the mechanism is confirmed in in vivo research, though clinical significance at usual therapeutic doses remains limited) · Elderly patients · Athletes (WADA — glycyrrhizin is not on the prohibited

list, but pseudohyperaldosteronism can mask hydration status)

▶ Drug Interactions (+ Why)

(MOST IMPORTANT)

Antihypertensives (ACE inhibitors, sartans, diuretics, beta-blockers)

Mechanism: Glycyrrhizic acid inhibits 11β-HSD2 → cortisol acts as a mineralocorticoid → retains Na, loses K → blood pressure rises. Directly counteracts the effects of antihypertensives. A clinically significant interaction.

Thiazide-type diuretics and furosemide

Mechanism: Additive potassium loss (diuretic + glycyrrhizin) → severe hypokalemia → risk of arrhythmias.

Digoxin and antiarrhythmics

Mechanism: Hypokalemia increases digoxin toxicity (potassium and digoxin compete for binding to Na/K-ATPase). Even a mild drop in K^+ can trigger toxicity at therapeutic digoxin doses.

Corticosteroids (e.g., prednisolone)

Mechanism: Glycyrrhizic acid slows corticosteroid metabolism by inhibiting CYP3A4 (partially) and 11β-HSD — prolonging and intensifying the steroid's effects, including its side effects.

Warfarin and anticoagulants

> **Mechanism: The data are mixed and inconsistent — in animal models, glycyrrhizin/licorice induces certain CYP450 isoenzymes (including CYP2C9), which could theoretically lower the INR in patients on warfarin, while other in vitro findings show the opposite, inhibition of related isoenzymes (CYP2B6, CYP2C8, CYP2C9, CYP2C19). This specific interaction (induction/ lowered INR) has not been confirmed in human studies or reported in clinical cases [unconfirmed — no human evidence, mechanism only from animal/in vitro models]. The standard recommendation for caution in patients on anticoagulant therapy remains valid because of licorice's overall risk profile (particularly via hypokalemia).**
>
> Oral contraceptives and estrogen preparations

Mechanism: Estrogen increases sensitivity to the mineralocorticoid effect of glycyrrhizin — women on OCPs are at greater risk of pseudohyperaldosteronism.

▶ Pharmacist's Note (Unexpected)

Licorice hides in industrial confectionery products (candies, throat lozenges, certain types of sweets, certain tobacco products

The DGL form, although safer with regard to glycyrrhizin, can interfere with the absorption of certain medications if taken at the same time (a mucosal-coating effect) — the practical recommendation is a gap of at least 2 hours between DGL preparations and other oral medications; pharmacokinetic data specific to this interaction are limited.

Motherwort *(Leonurus cardiaca)*

● **MODERATE RISK** sedatives, anticoagulants, and thyroid therapy require caution

> *In old Serbian apothecaries it stood alongside valerian as a "remedy for the heart and nerves" — and this was not mere folklore. Modern pharmacognosy has confirmed that motherwort does indeed have a measurable effect on heart rhythm, which is precisely why caution is warranted.*

▶ Traditional Use

In Serbian and broader Slavic phytomedicine, it has been used for palpitations, nervousness, anxiety, and mild sleep disturbances. Also used as a "uterine tonic" — to regulate the menstrual cycle and relieve cramps. German and Chinese tradition have a long history of use for cardiovascular complaints; in TCM it is known as yi mu cao (literally: "beneficial herb for mothers").

▶ Active Compound → Effect

Leonurine (alkaloid) — mild vasodilation, reduced uterine tone, possible negative chronotropic effect (slowing of the heart rate).

Stachydrine (alkaloid) — studied as an antithrombotic and antioxidant agent; uterotonic effect at high doses.

Iridoids (leonuride) — sedative-anxiolytic effect; interaction with the GABA system — evidence limited to in vitro studies.

Flavonoids (rutin, quercetin) — antioxidant, mildly anti-inflammatory effect.

Diterpenes (leocardin) — studied in experimental models of cardioprotection, predominantly animal models.

▶ What the Science Actually Says (Proven vs. Anecdotal)

Clinically documented — The EMA (European Medicines Agency) has issued a Community herbal monograph for Leonurus cardiaca — recognizing its use for mild symptoms of anxiety and stress accompanied by palpitations (the "well-established use" category was not granted; it falls under "traditional use").

Moderate evidence — Several smaller clinical studies (mostly of Russian and Chinese origin, methodologically limited) suggest an effect on reducing blood pressure and palpitations. Large RCTs meeting Western European standards are lacking.

Anecdotal / insufficiently proven — Use as a hormonal regulator, thyroid tonic, or as a recreational "heart-strengthening" remedy — has no solid clinical basis.

▶ Preparation and Dosage (Specifics)

Tea (dried aerial parts) — 1.5–3 g of dried herb per cup (150 ml) of boiling water, steeped 10–15 min, 2–3 times daily. The taste is markedly bitter.

Tincture (1:5, 45% alcohol) — 2–6 ml, 3× daily, per EMA guidelines. This form is 4–12× more concentrated than tea — do not treat it as "drops = a pinch of herb."

Dry extract (tablets/capsules) — Typically 300–500 mg of standardized extract, 1–3× daily. Always follow the specific product's instructions, as the degree of standardization varies.

Maximum recommended duration of continuous use: 4–8 weeks, followed by a break. Long-term use of the essential oil is not recommended. The essential oil must NOT be taken orally.

▶ Contraindications (Who Should NOT Use It)

Pregnancy — an absolute contraindication. Stachydrine and leonurine have uterotonic effects (confirmed experimentally); risk of premature contractions.

Breastfeeding — insufficient data; avoid.

Bradycardia or AV block — the herb may slow the heart rate; contraindicated without cardiological supervision.

Hypotension — an additive effect is possible.

Hypothyroidism — evidence is weak, but the literature mentions a possible interference with thyroid function.

Children under 12 years — use has not been clinically studied.

▶ Drug Interactions (+ Why)

High

Warfarin and other anticoagulants (acenocoumarol)

Flavonoids (rutin, quercetin) inhibit platelet aggregation and may potentiate the anticoagulant effect → increased risk of bleeding. Stachydrine has antithrombotic activity. Mechanism: additive inhibition of hemostasis at multiple levels.

High

Antiarrhythmics (digoxin, beta-blockers, amiodarone)

Leonurine directly affects the sinoatrial node and conduction → additive bradycardic and hypotensive effect with these drugs. Especially dangerous with digoxin — narrow therapeutic window, risk of toxicity.

Moderate

Sedatives, anxiolytics (benzodiazepines, zolpidem)

Motherwort's iridoids act on the GABAergic system — additive CNS depression → increased sedation, potential respiratory depression at high combined doses.

Moderate

Antihypertensives (ACE inhibitors, calcium channel blockers)

Leonurine's vasodilatory effect → additive drop in blood pressure; risk of orthostatic hypotension.

Low

Thyroid medications (levothyroxine)

Limited evidence — In vitro data suggest a possible inhibition of T4 → T3 conversion. Not confirmed clinically, but caution is recommended in hypothyroid patients on therapy.

▶ Pharmacist's Note (Unexpected)

Motherwort contains the alkaloid stachydrine, which is being studied as a possible urinary marker of the plant's consumption — meaning it is, in principle, detectable in laboratory analyses. This could be relevant for some sports organizations — WADA status: not on the prohibited list, but monitored.

The plant's bitter taste comes from its iridoids and does not indicate the strength of its therapeutic effect — bitterness and potency are not equivalent.

Green Tea *(Camellia sinensis)*

● **MODERATE RISK** vitamin K weakens warfarin, and extracts carry a risk of hepatotoxicity

> *One cup of green tea contains the same amount of caffeine as a third of an espresso shot — and, at the same time, a compound that slows its action. It is precisely this combination, not caffeine alone, that makes tea more pharmacologically interesting than coffee.*

▶ Traditional Use

Chinese and Japanese sources record its use going back more than 3,000 years: alertness, digestion, "clearing the head." Ayurveda uses it for detoxification and metabolic tone. Black tea, in the British-Indian tradition, serves as an antidiarrheal and general tonic. All variants (green, white, oolong, black) come from the same plant — they differ in degree of fermentation/oxidation.

▶ Active Compound → Effect

Three main groups, each with its own profile:

1. Catechins (EGCG — epigallocatechin gallate, ~50–80% of the fraction)

Antioxidant, modulation of cell-growth signaling pathways, potential anticancer effect in vitro and in animal studies. Inhibits certain enzymes (COMT, topoisomerase II).

2. Caffeine (20–60 mg / 200 ml cup, green tea)

Adenosine receptor antagonist → alertness, increased heart rate, elevated blood pressure, increased diuresis. Black tea: 40–70 mg/cup.

3. L-theanine (amino acid, nearly unique to tea)

Increases alpha waves in the brain → relaxation without drowsiness. In combination with caffeine: calmer, more focused alertness than caffeine alone — this is the mechanism behind the "tea feeling," which differs from that of coffee.

▶ What the Science Actually Says (Proven vs. Anecdotal)

Clinically confirmed (solid RCTs/meta-analyses):

✓ Proven Cognitive function and alertness — the caffeine + L-theanine combination improves attention and reaction speed, confirmed in multiple RCTs.

✓ Proven Cardiovascular markers — regular consumption (3–5 cups/day, green tea) modestly lowers LDL cholesterol and blood pressure in meta-analyses (a moderate effect, clinically relevant but not a substitute for therapy).

✓ Proven EGCG extract for genital warts — the only FDA-approved herbal formulation (Veregen® 15% sinecatechins ointment, topical application for genital warts).

Promising but insufficiently proven:

△ Weak Cancer prevention — epidemiological studies point to an association, but RCT evidence is weak and inconsistent. It cannot be recommended for preventive purposes.

△ Weak Weight loss / metabolism — short-term effects on thermogenesis exist, but the clinical significance for lasting weight loss is minimal.

○ Anecdotal "Detoxification," "anti-aging" — there are no clinically validated studies for these claims in the form in which they are marketed.

▶ Preparation and Dosage (Specifics)

Infusion (green) — 2–4 cups/day, 200 ml, 70–80°C, 2–3 min. ≤ 400 mg caffeine/day total.

Infusion (black) — 2–4 cups/day, 200 ml, 100°C, 3–4 min. More caffeine, fewer catechins.

Standardized extract (oral) — EGCG 200–400 mg/day. Take with food — on an empty stomach it increases the risk of hepatotoxicity.

Matcha (powder) — 1–2 teaspoons (2–4 g)/day. Contains ~3× more EGCG than standard green tea, and ~2–3× more caffeine.

⚠ Extract ≠ a cup of tea. Commercial EGCG capsules of 400–800 mg deliver the equivalent of 8–16 cups at once — this is the dose range at which hepatotoxic effects occur. Every documented case of liver injury in the literature is linked to extracts, not to the brewed beverage.

▶ Contraindications (Who Should NOT Use It)

Absolute: A known hepatotoxic reaction to EGCG extract (rechallenge is prohibited). Pregnancy: moderate consumption of the beverage (max 1–2 cups/day, due to caffeine and folate absorption). Extract during pregnancy — not recommended.

Relative / use with caution: Iron-deficiency anemia (tannins bind non-heme iron — do not drink with an iron-rich meal). Anxiety, insomnia, tachycardia, uncontrolled hypertension (caffeine). Osteoporosis (caffeine increases calciuria). Children under 12 years — no data available for extracts.

▶ Drug Interactions (+ Why)

> **(most important)**
> Mechanism is key — without it, an interaction reads like a scare list.

> **□ Anticoagulants (warfarin, acenocoumarol)**
> Mechanism: Green tea contains a small amount of vitamin K → directly antagonizes warfarin. EGCG additionally inhibits CYP2C9 (the enzyme that

metabolizes warfarin) → increases drug exposure. Result: unstable INR, risk of bleeding or thrombosis. Relevant even for the brewed beverage with regular consumption.

MAO inhibitors (phenelzine, moclobemide)

Mechanism: Caffeine + MAOI → hypertensive crisis. MAO inhibition prevents the breakdown of catecholamines, which caffeine potentiates. Avoid absolutely.

Adenosine (antiarrhythmic, stress test)

Mechanism: Caffeine is a direct adenosine receptor antagonist → blocks the drug's pharmacological effect. Tea must be avoided for 24 hours before a diagnostic adenosine stress test.

CNS stimulants (ephedrine, pseudoephedrine, amphetamines)

Mechanism: Additive sympathomimetic effects — tachycardia, hypertension, arrhythmia. Especially dangerous with ephedra-containing supplement combinations.

Iron (oral supplements, ferumoxide)

Mechanism: Tannins form chelate complexes with Fe^{2+} → reduced absorption by up to 70%. Maintain a minimum 2-hour gap between iron supplementation and tea.

Hepatotoxic drugs (high-dose paracetamol, isoniazid, statins)

Mechanism: EGCG at high doses (extract) can itself be hepatotoxic — likely through mitochondrial oxidative stress. Combination with drugs that burden the liver increases the risk of cumulative damage. [Addendum S23: more recent research shows a strong immunogenetic component — carriers of the HLA-B*35:01 allele are 5–7× more frequent among patients with confirmed green-tea-induced liver injury (72% of carriers in one case series) than in the general population, with delayed onset and rapid recurrence on re-exposure — features that point to an idiosyncratic, immune-mediated reaction, not just direct oxidative toxicity from EGCG.]

Lithium

Mechanism: Caffeine increases renal excretion of lithium → lower plasma levels → potential loss of therapeutic effect. Monitor lithium levels when drinking habits change.

▶ Pharmacist's Note (Unexpected)

Extract hepatotoxicity on an empty stomach: The EMA and FDA have identified ~80 cases of clinically significant liver injury linked exclusively to oral EGCG extracts, some of which required transplantation. The brewed beverage — not a single documented case.

EGCG's bioavailability is poor (Matcha vs. green tea: with matcha you consume the whole leaf, not a water

extract — the EGCG dose is significantly higher than users assume.

Ginseng *(Panax ginseng)*

● **MODERATE RISK** warfarin (CYP2C9), antidiabetics (risk of hypoglycemia), MAO inhibitors

> *The Chinese emperor Shen Nong described ginseng more than 2,000 years ago as a remedy that "prolongs life" — today it is one of the best-selling herbal supplements in the world, and science is only beginning to understand why. The problem is that "ginseng" on a label can mean completely different things.*

▶ Traditional Use

In traditional Chinese and Korean medicine: an adaptogen for increasing energy, reducing fatigue, boosting immunity, improving memory, and enhancing male fertility. Popularized in Europe as a tonic and stress "buster." Korean red ginseng (steamed root) is considered "stronger" than raw white ginseng.

▶ Active Compound → Effect

Ginsenosides (triterpene saponins)

More than 40 ginsenosides have been identified — they are not equivalent, and different preparations contain different profiles. The most studied are Rb1, Rb2, Rc, Rd (the Rb group) and Rg1, Re (the Rg group).

Adaptogenesis / fatigue — Modulation of the HPA axis (hypothalamus–pituitary–adrenal), influence on cortisol

Cognitive function — Mild acetylcholinesterase inhibition + modulation of the dopaminergic and serotonergic systems

Immunity — Stimulation of NK cells and macrophages; modulation of cytokines (IL-2, IFN-γ)

Glycemia — Improved insulin sensitivity (probably via the AMPK pathway) [mechanism still under investigation]

Erectile function — Vasodilation via increased nitric oxide (NO) synthesis in the endothelium

▶ What the Science Actually Says (Proven vs. Anecdotal)

✓ clinical Short-term reduction of fatigue

✓ clinical Mild effects on glycemia in type 2 diabetes

✓ clinical Erectile dysfunction (weak effect)

~ weak evidence Cognitive function

~ weak evidence Immunity / flu prevention

✗ no evidence "Life extension"

Important: Most studies are short-term (4–12 weeks), have small sample sizes, and preparation standardization varies enormously. Cochrane reviews are skeptical for nearly all indications except fatigue.

The WHO monograph recognizes traditional use but is cautious about therapeutic claims.

▶ Preparation and Dosage (Specifics)

> **Standardized extract — 200–400 mg/day (standardized to 4–7% ginsenosides) — more reliable than powder. Take in the morning or before noon.**
>
> Root powder (whole root) — 1–2 g/day. Ginsenoside content varies 5–10× depending on the root's age, cultivation method, and processing. A "pinch" is not a dose.

> **Tea / decoction — ~3–5 g dried root / 200 ml water, simmer for 30 min. Lower bioavailability than the extract.**
>
> Duration — 4–12 weeks is recommended, then a break of 2–4 weeks. Long-term continuous use has not been well studied.

Ginseng essential oil exists but is marginal and is not used therapeutically the way lavender or eucalyptus oil is — caution when drawing comparisons.

▶ Contraindications (Who Should NOT Use It)

Pregnancy and breastfeeding [insufficient data; the ginsenoside Rb1 has shown embryotoxicity in animals]

Children under 12 years

Hormone-dependent tumors (breast, ovaries, uterus, prostate) — ginsenosides have weak estrogenic activity

Insomnia, anxiety, hypertension — may worsen symptoms

Autoimmune diseases in an acute flare — immunostimulatory effects may be unfavorable

Manic episode or bipolar disorder [anecdotal reports of worsening]

▶ Drug Interactions (+ Why)

MOST IMPORTANT SECTION

Warfarin / anticoagulants

Ginseng reduces the efficacy of warfarin — ginsenosides induce CYP2C9 (the enzyme that breaks down warfarin), meaning faster drug elimination and a weaker effect. There are clinical case reports of lowered INR. This is potentially serious.

MAOIs (e.g., phenelzine, tranylcypromine)

Reports of mania, headache, tremor. Mechanism: additive effect on monoaminergic neurotransmitters. Avoid the combination.

Insulin and antidiabetics (metformin, sulfonylureas)

Ginseng itself lowers blood glucose (via the AMPK pathway). In combination with these drugs, the risk of hypoglycemia is real. Blood sugar monitoring is mandatory when starting.

Immunosuppressants (cyclosporine, corticosteroids, azathioprine)

Ginseng's immunostimulatory effects may antagonize immunosuppressive therapy (transplants, autoimmune diseases). The combination is not recommended.

CNS stimulants (caffeine, amphetamine, methylphenidate)

Additive stimulation — tachycardia, nervousness, insomnia. Ginsenosides modulate the dopaminergic system, amplifying stimulant effects.

Digoxin

Some ginsenosides are chemically similar and may falsely elevate laboratory digoxin readings (an assay interference, not a pharmacological one). [Clinically relevant only for interpreting lab results]

▶ Pharmacist's Note (Unexpected)

The standardization problem: "Panax ginseng" on a label says nothing about ginsenoside content. An analysis of commercial products (a 2020 study [verify source]) found that content varies by up to 10-fold between manufacturers, and some products contain only trace amounts of the active compounds.

Siberian ginseng ≠ true ginseng: Eleutherococcus senticosus ("Siberian ginseng") contains eleutherosides, not ginsenosides — these are

structurally and pharmacologically distinct compounds. American ginseng (Panax quinquefolius) has a different ginsenoside profile and is considered "cooler" than the Korean variety. This is not just marketing — these are genuinely different substances.

"Ginsenoside spiking" — adding synthetic ginsenosides to cheap preparations to produce better lab test results — has been documented in the literature. [check current HZZO / EMA advisories]

Interaction Index

Quick overview: if you're taking a medication from one of these classes, the plants and supplements listed below deserve special attention in combination with it. This is an orientation index — always check the chapter on the specific plant for mechanism details.

Warfarin / Anticoagulants / Antiplatelet Drugs

Black Pepper, Cat's Claw, Chamomile, Dandelion, Devil's Claw, Dong Quai, Fennel, Fenugreek, Garlic, Ginkgo, Ginseng, Green Tea, Hawthorn, Horse Chestnut, Kava, Licorice, Lingonberry, Mistletoe, Motherwort, Red Yeast Rice, Rhodiola, Saw Palmetto, Senna, St. John's Wort, Turmeric, Valerian

Statins (Cholesterol)

Bitter Orange, Black Pepper, Echinacea, Grapefruit, Green Tea, Kava, Peppermint, Red Yeast Rice, St. John's Wort, Turmeric

Immunosuppressants (Transplant)

Ashwagandha, Bitter Orange, Black Pepper, Cat's Claw, Chamomile, Devil's Claw, Dong Quai, Echinacea, Ginkgo, Ginseng, Grapefruit, Lingonberry, Mistletoe, Peppermint, St. John's Wort, Turmeric

Hormonal Contraception / Hormone Therapy

Chamomile, Chasteberry, Dong Quai, Echinacea, Fennel, Fenugreek, Licorice, Saw Palmetto, Senna, St. John's Wort

Sedatives / Benzodiazepines / CNS Depressants / Alcohol

Ashwagandha, Chamomile, Grapefruit, Kava, Mistletoe, Motherwort, Peppermint, Red Yeast Rice, Valerian

Antidiabetics / Insulin (Hypoglycemia)

Ashwagandha, Dandelion, Devil's Claw, Fenugreek, Garlic, Ginkgo, Ginseng, Mistletoe, Turmeric

Diuretics / Potassium (Electrolytes)

Ashwagandha, Dandelion, Horse Chestnut, Horsetail, Licorice, Lingonberry, Senna

SSRIs / Antidepressants / Serotonin Syndrome

Fenugreek, Ginkgo, Kava, Rhodiola, St. John's Wort, Valerian

Digoxin / Antiarrhythmics / Heart Medications

Black Pepper, Dandelion, Devil's Claw, Ginseng, Grapefruit, Green Tea, Hawthorn, Horsetail, Licorice, Motherwort, Senna, St. John's Wort

CYP3A4 / CYP450 Enzyme Interactions

Bitter Orange, Black Pepper, Cat's Claw, Chamomile, Dandelion, Devil's Claw, Dong Quai, Echinacea, Fennel, Ginkgo, Grapefruit, Kava, Licorice, Peppermint, Red Yeast Rice, Rhodiola, Saw Palmetto, St. John's Wort, Turmeric, Valerian