

Understanding botanical-drug interactions

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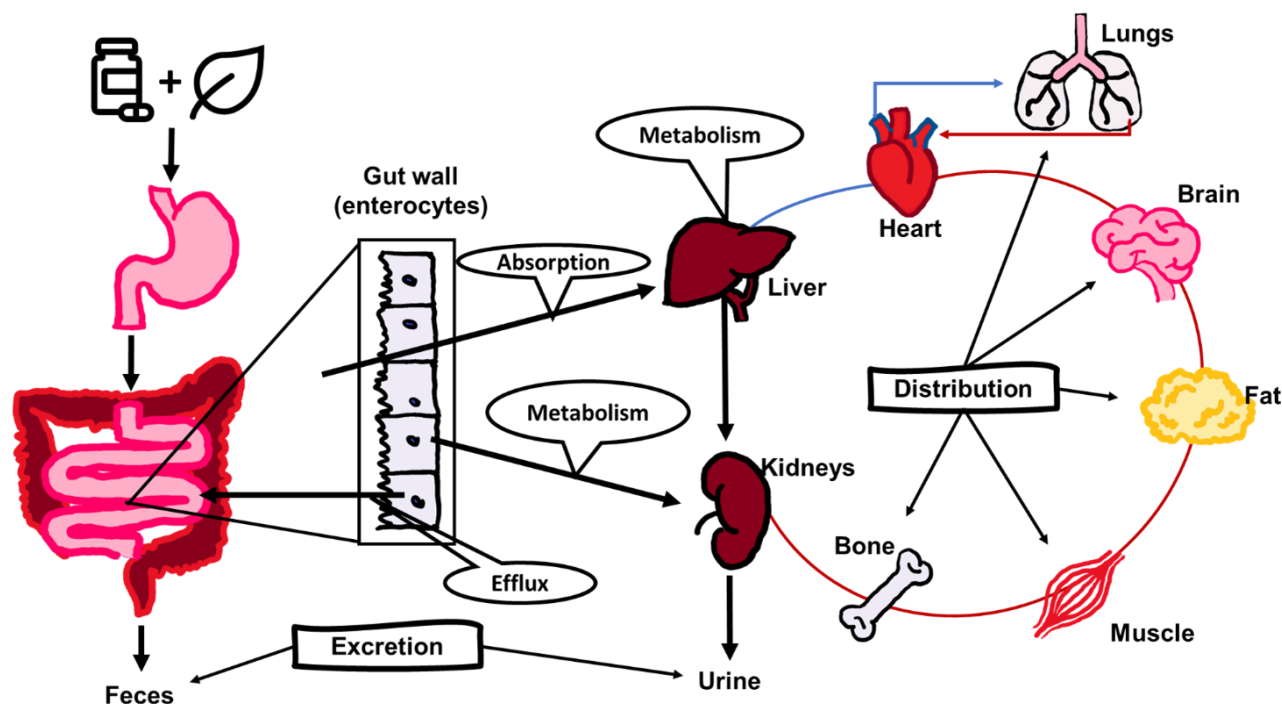


Figure 1: Graphical representation of pharmacokinetic processes. Botanicals taken concurrently with drugs may modify any of these processes.

With a specific focus on pharmacokinetic and pharmacodynamic mechanisms, Dr Erin C Berthold discusses the interactions between botanical and herbal supplements and conventional pharmaceuticals, highlighting the urgent need to examine these interactions for public health and patient safety

When any substance – be it food, a therapeutic drug, an over-the-counter medication, or a botanical supplement – is ingested, it enters a dynamic physiological system. The concurrent ingestion of multiple products creates an opportunity for complex interactions to occur. Given the significant global rise in the self-administration of [botanical and herbal supplements](#) alongside conventional pharmaceuticals, there is an urgent and critical need to thoroughly examine and document the precise effects these natural compounds may have on co-administered medications. This undertaking is not merely academic; it is a fundamental concern for public health and patient safety that demands regulatory and clinical attention. Interactions are broadly categorized into two major areas that govern the ultimate impact and efficacy of a drug: pharmacokinetic and pharmacodynamic interactions.

Pharmacokinetics

Pharmacokinetics (PK) focuses on the quantitative study of the rate of change of a compound's concentration within a living system. It involves the four core processes of absorption, distribution, metabolism, and excretion. When the ingested substance is a formulated dosage form, the initial step also involves the liberation of the active compounds from that form. Botanical compounds possess the potential to modify any and all of these core processes, thereby altering the concentration of the co-ingested drug at its site of action (Figure 1).

The initial gateway for drug entry is the gastrointestinal (GI) tract, where botanicals can significantly alter the environment and impact absorption and liberation. Compounds within supplements may alter the gastric pH or modify gastric emptying time, which subsequently affects the rate at which a drug is released from its dosage form. Once liberated, absorption across the gut wall can be impacted, as botanical constituents may alter gut permeability, interfere with efflux and influx transporters, or chemically bind with co-administered drugs to form large or insoluble complexes that effectively reduce the amount of the drug that can dissolve and enter systemic circulation.

Once a drug enters the bloodstream, its distribution to target tissues can be altered by botanicals through several mechanisms. Many drugs bind reversibly to plasma proteins, and botanical compounds may compete for these same binding sites, displacing the pharmaceutical drug and causing a temporary spike in the concentration of unbound, active drug, which can increase its immediate effect or toxicity. Further, botanicals may alter the permeability of tissue membranes, including the critical blood-brain barrier, or continue to interfere with the same influx and efflux transporters encountered in the gut, but now at the level of tissue capillaries and cellular membranes.

Drug metabolism is the most widely studied area of botanical-drug interactions. Due to their inherent chemical complexity, botanicals frequently modify the body's primary detoxification and breakdown pathways. The cytochrome P450 (CYP450) enzyme system is responsible for the breakdown of the majority of drugs. Botanical compounds have been found to act as either inhibitors or inducers of these enzymes.⁽¹⁾ Beyond the CYP450 system, botanicals can also modify Phase II metabolic pathways, such as glucuronidation and sulfation, thereby further compounding the potential for clinical alterations in drug levels.

The final stage, excretion or elimination, is primarily mediated by the kidneys. Botanicals can impact this process by altering the pH of the urine, which in turn changes the reabsorption or excretion rate of certain drugs, or by competing for active tubular transport mechanisms in the renal tubules, which are responsible for actively secreting drugs into the urine.

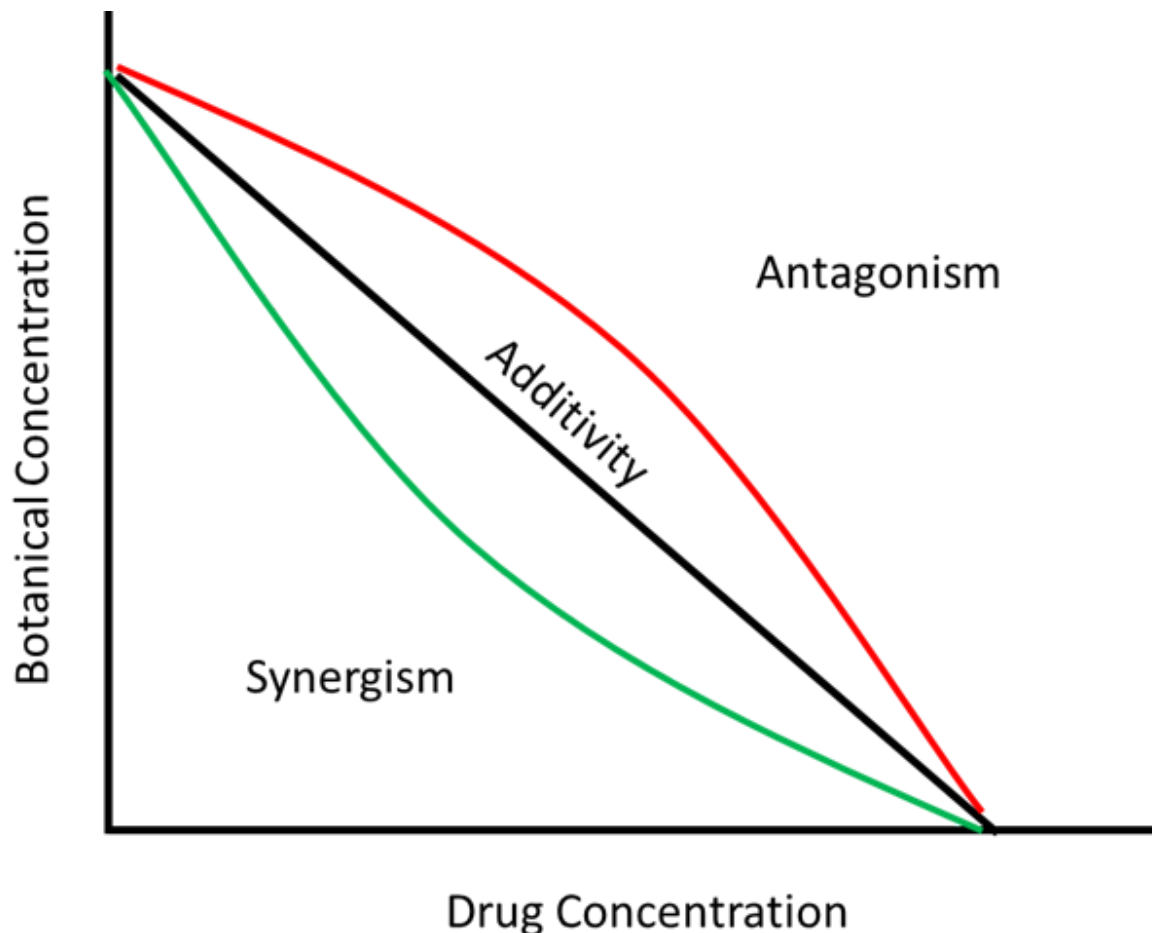


Figure 2: Isobologram of pharmacodynamic interactions. The additive effect line is when the effects of each substance, when taken concurrently, are the same as if each were taken separately. Synergism occurs when a lower dose of the compounds is needed to get an effect, and antagonism is when a higher concentration of the drug or botanical is needed to get an effect.

Pharmacodynamics

Pharmacodynamics is concerned with how a compound affects the body, specifically focusing on its mechanism of action. These interactions occur when a botanical and a drug act on the same physiological target, receptor, or pathway, leading to an effect on the body that is different from that of either substance taken alone. Botanicals can potentiate or diminish the desired or adverse effects of a drug. The resulting interactions are typically classified into three categories (Figure 2). When the total impact of the two co-ingested substances is simply the sum of the effects achieved when the compounds are taken alone, this is termed additivity. When the combined effect is greater than would be expected from the sum of the individual effects, this is known as synergism, meaning a lower dose of one or both compounds achieves the desired clinical effect. Conversely, when the combined effect is less than additive, the interaction is called antagonism, where one substance actively counteracts the action of the other, potentially leading to a loss of therapeutic efficacy for the pharmaceutical drug.

Interactions are only deemed clinically significant if the degree to which the botanical alters the drug response causes the drug concentration to fall outside of its established therapeutic index or induces adverse effects. Given the complexities outlined, it is essential that individuals taking prescription medications, as well as those frequently using over-the-counter drugs, are

fully aware of the potential for botanical supplements to alter the effectiveness or safety of their therapeutic regimen. Healthcare providers must adopt a comprehensive approach, inquiring about all supplements, teas, and natural products patients consume, as this information is vital for optimising treatment outcomes and ensuring patient safety in an era of increasing self-medication.

References

1. Gilani B, Cassagnol M. Biochemistry, Cytochrome P450. [Updated 2023 Apr 24]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK557698/diligently>.

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