# Chapter 4
# Toxicokinetics of Herbal Products

**Olavi Pelkonen and Jorma T. Ahokas**

**Abstract** Pharmacokinetics (PK) and toxicokinetics (TK) mean essentially the same thing, only the final effect of the studied substance differs. In this chapter, the abbreviation "TK" is usually used to acknowledge the title of the book (toxicology), but also the abbreviation "PK" is used, depending on the context. TK is an essential part of the characterization of a conventional pharmaceutical and, besides its "intrinsic scientific" value, TK constitutes a backdrop for understanding and delineating a substance's in vivo potency, potential toxicities, and particular clinical conditions. The same TK principles should apply to herbal medicinal products; however, these products are complex chemical mixtures, with tens or hundreds of major and minor components belonging to a variety of chemical groups and classes, making it rather difficult to study their TK, both in theory and in practice. The TK of an herbal product should address both the time course of its active constituents, and the impact of the various components on the TK processing (metabolism and transport) of its own constituents and simultaneously administered pharmaceuticals.

This chapter describes some of the major areas that should be addressed when investigating the PK/TK of herbal medicinal products. Appropriate analytical methods exist to address major TK issues, despite the complex composition of herbal products. However, the success of these studies depends on pharmacodynamic and mechanistic studies to decide which of the many components should be targeted for the ADME (absorption, distribution, metabolism, and excretion) characterization. The prevailing tenet in the area of herbal products is that the "whole product" is responsible for the therapeutic action. However, such a statement is scientifically inadequate and therefore not really helpful. The dissection of contributing components and their interactions with respect to both therapeutic effects and potential toxicities requires the application of advanced analytical and high-content

O. Pelkonen (✉)
Department of Pharmacology and Toxicology, Institute of Biomedicine,
University of Oulu, Aapistie 5 B, FIN-90014 Oulu, Finland
e-mail: olavi.pelkonen@oulu.fi

J.T. Ahokas
School of Medical Sciences, RMIT-University,
Bundoora Campus, PO Box 71, Bundoora, VIC 3083, Australia
e-mail: Jorma.Ahokas@rmit.edu.au



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technologies, including “omics” methods, computational modelling and simulation approaches, and, most of all, systems biological thinking.

**Keywords** Toxicokinetics • ADME • Absorption distribution • Metabolism • Excretion

## Basic Concepts and Processes of Toxicokinetics of Single Substances

### *Toxicokinetic Processes*

The primary reason for pharmacokinetic studies of pharmaceutical agents is to enable their rational use. The clinical use of drugs depends on knowing the bioavailability of the drug and its absorption, distribution, and elimination characteristics. The elimination characteristics are only fully understood with adequate knowledge of the metabolism of the active constituents. Metabolic characterization also includes the identification of active and/or possibly toxic metabolic products or intermediates.

The very cornerstone of pharmacology and toxicology is that there is a direct relationship between the concentration of an active constituent of a therapeutic product at the site of action and the extent of the effect. However, after a given dose, the concentration at the site of action is extensively modulated by several pharmacokinetic factors (Fig. 4.1). With therapeutically used drugs, the pharmacokinetic principles are well developed and the predictions of concentration at the site of action are good. Similarly, the factors contributing to the inter-individual variability are well established. The most significant sources of variability stem from formulation, body build, and metabolism and/or excretion (Fig. 4.1). These factors affect the ultimate concentration at the active site resulting from a given administered dose.

With a therapeutically used drug, the problem setting is relatively clear-cut, in that one is dealing with a very well characterized active constituent and its metabolites. The information regarding every therapeutically used compound is obtained by a systematic study of absorption, distribution, and elimination kinetics of the active constituent(s). As well as the kinetic parameters, the metabolism of the compound is determined. This characterization includes determining the metabolite pattern and assignment of the enzymes (CYP and conjugating enzymes) responsible for the metabolism. Further studies involve determination of active transport of the compound and its metabolites in and out of various organs.

Once a detailed pharmacokinetic database has been established for a pharmaceutical agent, it is possible to extend the studies to predict most drug-drug and drug-food interactions, or interactions with any other agent. The most prominent cause of significant interactions involves CYP-based interactions. Nevertheless, PK may be non-linear (e.g., saturable enzymatic or transport systems) and so may not reliably indicate the TK at supra-pharmacological dosages. Also, some genetic outliers may

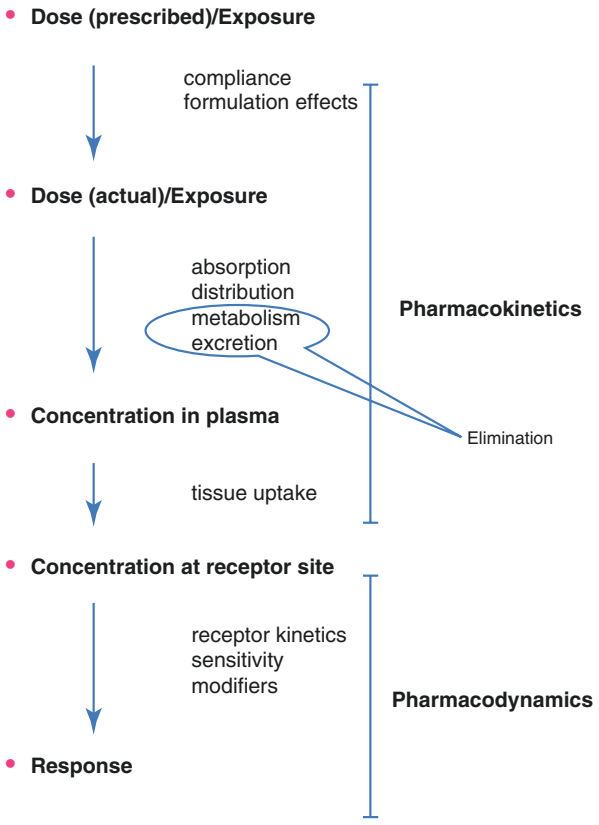


**Fig. 4.1** A schematic view to delineate processes between dose/exposure and the ultimate response (therapeutic or toxicological)

be missed by preclinical and clinical studies, resulting in unexpected (idiosyncratic) toxicities or interactions.

Inter-individual variability of pharmacokinetics is an important cause of concern in therapeutic failure or adverse effects caused by excessive concentration. Such variability can be caused by genetic differences or various organ-specific diseases.

## What Is Pharmacokinetics/Toxicokinetics of Herbal Medicinal Preparations?

While pharmacokinetic studies of therapeutically used drugs can be conducted with relative ease, the difficulties with complementary preparations are significant. The difficulties do not stem from lack of available methodology, but from the nature of the herbal products and the basic philosophy of using herbal products in health care. If the whole product in its entirety is considered to be the active "medicine," then what is the meaning of pharmacokinetics? However, current systems pharmacology thinking assumes that there are several active components in the whole preparation,

targeting various processes in a therapeutically meaningful manner. As the active constituents are often not characterized or even known, how could pharmacokinetics then be studied? Furthermore, the composition of crude herbal products is highly variable and their standardization cannot be easily effected, resulting in variable doses and ratios of (possibly) active components. One is faced with so many unanswered and unanswerable questions that problems seem almost unsurmountable.

As described above, the study of pharmacokinetics/toxicokinetics of a single identifiable substance is very clear, whereas with crude or partially processed plant products, the concept becomes complex and in some aspects meaningless. Especially with ill-defined products and products with questionable efficacy, it becomes a question of kinetics of "what," and consequently kinetic studies are without a clear purpose. In the next section, an attempt is made to categorize various possibilities to define pharmaco/toxicokinetics of an herbal medicinal substance.

## Which Components of an Herbal Medicinal Substance Should Be Analyzed Regarding TK?

### *General Considerations*

Commercial stakeholders of herbal medicinal products usually state that the whole herbal substance is the active principle of herbal medicinal product (Lu et al. 2015). This statement is often used to downgrade the significance of toxicities of isolated ingredients or as a hypothetical claim that the whole is more than the sum of its parts (or in the case of toxicity, less than the sum of the parts). In the area of TK, this statement has been used as an excuse NOT to perform kinetic studies of isolated ingredients, because the results of such studies cannot be extrapolated to the situation in which the whole herbal medicinal product is being used.

It is fair to say that recent developments in "omics" approaches and network or systems pharmacology and toxicology have given at least some credibility to those earlier concepts that the whole is more than the sum of its parts. In particular, studies of traditional Chinese medicines (TCM) have started to produce, even if it is still very tentative, credible data to justify systems views on complex medicinal preparations (see, for example, reviews of Wang et al. 2009; Xu et al. 2012). These systems views are based on detailed studies of comprehensive analytical techniques, medium-throughput bioassays, target interactions, and integrated computational tools – i.e., actual experimental and computational approaches (see this chapter and Chap. 5).

### *Pharmacodynamic and Toxicodynamic Considerations*

In order to overcome the fundamental questions about which components to measure, pharmacodynamic studies and efficacy trials of complementary medicines should precede extensive kinetic studies. These studies should be performed with

adequate knowledge of the composition of the product and the preclinical screen of pharmacodynamics in order to provide a preliminary understanding of which components may or may not be linked with the therapeutic responses or adverse outcomes observed during the clinical studies. Products with proven efficacy and/or observed adverse effects should be automatically considered for pharmacokinetic studies. With respect to these products, it is within our scientific capability to identify active constituents that can be characterized with respect to their pharmacokinetic behavior. The modern metabolomic approach may offer an alternative or additional way of tackling the behavior and pharmacokinetic impact of complex mixtures.

Thus, it seems reasonable to state that clinically or experimentally observed beneficial or adverse effects and their tentative linkages with identified components of the mixture should be a prerequisite and starting point for kinetic studies. Without the pharmaco(toxico)dynamic background knowledge, it is useless to embark on kinetic studies. However, since many herbal medicinal products are on the market and are being used without proof of efficacy, it may still be necessary to conduct certain TK studies to address selected safety concerns with these products. Such concerns include interference with pharmacokinetics of concurrently administered drugs.

## *Analytical and Biomarker Considerations*

Quality control is naturally a *sine qua non* consideration for herbal medicinal products, because the composition and pharmaceutical properties of a product have to be within certain pre-determined tolerances. For quality control purposes, usually one or several major components are selected and their concentrations in the finished product have to be determined on a routine basis (see Chap. 3). If a component is a toxic one, the concentration should be under a certain limit value, as is the case with aconite alkaloids.

A totally different question is whether there is a need to measure a reference constituent (a marker substance used for quality control) in the body just for bioavailability or therapeutic monitoring reasons? Obviously this matter needs further elaboration.

## *Toxicological Considerations*

Often safety concerns arise from a known presence of a toxic substance in the product. Table 4.1 lists some examples of plant-derived substances known to elicit various toxicities. An obvious problem is that these substances are present in greatly varied amounts, together with greatly varied compositions of other constituents in plant-derived products. It is clear that if there is a strong suspicion of toxicological potential of a component, its risks should be adequately evaluated. However, risk assessment of a single component may be a tricky task because of potential interactions with other components, either in the product or in the body.

**Table 4.1** Examples of substances as constituents in plant-derived products that have been linked with adverse effects

| Substance (typical plant) | Adverse effect | Relevant toxicokinetic characteristics | References |
|---|---|---|---|
| Aristolochic acid (*Aristolochia* genus) | Nephrotoxic, carcinogenic | metabolic activation to DNA-reactive metabolites | See Chaps. 9 and 13 |
| Pulegone/menthofuran (*Mentha pulegium* L.) | Hepatotoxic, carcinogenic (animals) | Glutathione conjugation; metabolic activation in the liver | Nelson (1995) |
| Estragole (*Foeniculum vulgare* Mill.) | Hepatotoxic, carcinogenic (animals) | Metabolic activation by oxidation and sulphate conjugation | Rietjens et al (2005) |
| Thujone (*Artemisia absinthium* L.) | Neurotoxic | Metabolic detoxification | Pelkonen et al (2013) |
| Rhein (*Polygonum multiflorum* Thunb.[a]) | Cytotoxic, mutagenic | Metabolic fate in the colon and the body | Lin et al (2015) |
| Aconitine (*Aconitum sp*) | High acute toxicity | Metabolic detoxification | Singhuber et al (2009) |

[a]Is in fact a synonym of *Reynoutria multiflora* (Thunb.) Moldenke

## Matrix-Derived Effect

Within a complex herbal substance or preparation, there is a large number of potential components that may affect the toxicity of other components. For example, the induction or inhibition of metabolic or transport processes by a "perpetrator" component may drastically change the concentration of a target (also referred to as "victim") component. Plant products also often contain various antioxidant or pro-oxidant compounds that may affect the in vivo effects of other components in the same product, if they reach sufficient concentrations in the body compartments. However, it is clear that toxicological characteristics of single substances cannot be neglected even if they are in a complex mixture. There are many past examples of toxicological effects of single components administered as constituents of an herbal product. Usually the actual harmful effects of most toxic compounds have been detected in humans as sporadic or epidemic case reports (Table 4.1). It can be easily agreed that there may be various interactions between components of complex mixtures; these interactions can be inhibitory, additive, or synergistic in nature and should be taken into consideration if such effects have been observed or demonstrated. It is also clear that the toxicity study of a well-characterized mixture itself provides the most reliable results when it comes to most adverse outcomes. However, genotoxicity or carcinogenicity, for example, are two outcomes that are difficult to detect in conventional toxicity tests (or by pharmacovigilance), and they can have severe adverse outcomes that must be addressed even if the evidence is based on a single component study.

Toxicology of complex mixtures has been a topic of recent reviews (Meek et al. 2011). Furthermore, these reviews specifically addressed the matrix-derived combination effects, although a fair number of examples have come from food and environmental research (Rietjens et al. 2015; van der Berg et al. 2013).

## *Mechanisms Behind Matrix-Derived Effects*

Matrix-derived effects may be detected, impacting at all levels of ADME processes, with some examples listed in Table 4.2. It seems obvious that a comprehensive evaluation of matrix effects of herbal products will become an important topic in future studies of herbal medicinal products (see below for methods).

Considering gastrointestinal absorption, the rate and the extent of release of a substance from the herbal matrix may be highly variable as adsorbents, tensioactive

**Table 4.2** Examples of potential sites and mechanisms of matrix-derived effects on ADME characteristics and systemic exposure of components of herbal medicinal products. For background reviews, see Wagner and Ulrich-Merzenich (2009) and Rietjens et al (2015)

| Site/mechanism | Consequence of interaction | Example | Reference |
|---|---|---|---|
| Release from matrix and solubilization in water | Potentially improved bioavailability | Hypericin by procyanidins | Nahrstedt and Butterweck (2010) |
| | | | See Chap. 3 for other examples |
| Inhibition of transporters (P-glycoprotein) in the gut wall | Enhanced basolateral transport (enhanced bioavailability) | Hypericin by flavonoid glycosides and proanthocyanidins | Nahrstedt and Butterweck (2010), Yang et al (2014), and Sevior (2012) |
| Metabolism in the gut wall | Increased/decreased bioavailability | Potentially e.g., mutual interactions of CYP3A4 substrates and inhibitors | Ajazuddin et al (2014) and Yang et al (2014) |
| | | | See Chap. 3 for other examples |
| Metabolism in the liver | Inhibition of metabolic activation | Estragole and methyleugenol by nevadensin | van den Berg et al (2013) |
| | | | Alhusainy et al (2014) |
| Metabolism in the liver | Induction/inhibition of metabolic activation or detoxication | Potentially e.g., mutual interactions of CYP3A4 substrates and inhibitors | Sevior (2012) and Rietjens et al (2015) |
| Excretion into the bile | Inhibition of biliary transporters | Isorhamnetin (Gingko component) on MATE1 | Kawasaki et al (2014) |
| Binding to plasma proteins | Displacement from binding sites | Potentially, e.g., albumin and alpha-1-acid glycoprotein | Sevior (2012) |
| Excretion in the kidney | Inhibition of tubular transporters | Isorhamnetin (Gingko component) on MATE1 | Kawasaki et al (2014) |

or dispersing agents may accompany the studied substance. Transporters in the gut wall may be inhibited, which may lead to increased bioavailability when efflux transporters such as P-glycoprotein at the apical membrane are inhibited. The consequences of transporter modifications depend on both their localization in the cell, i.e., whether they are apical or baso-lateral, and their function, i.e., whether the herbal constituents are ligands or modulators of influx or efflux transporters. The same type of interaction can be seen for biliary transport affecting excretion and entero-hepatic cycling. Xenobiotic-metabolizing enzymes in the gut wall may also affect the bioavailability of various components of herbal medicines.

Very little is known about the distribution of constituents of herbal medicinal products. It is hypothetically possible that multiple components bind to the same plasma proteins or tissue proteins and thus affect each other's free (i.e., diffusible) concentrations. There are also some examples of displacing concurrently administered drugs by herbal constituents, thus causing an increase in the concentration of the free fraction of a drug (Sevior 2012). In general, such interactions are not clinically relevant as the increase in free fraction is usually compensated for – except in some cases of hepatic or renal failure. Because some organ barriers in the body, such as placenta or blood-brain barriers, contain both influx and efflux transporters, it is possible that the competition of herbal components at those transporters results in changes of barrier penetration, but again these possibilities are mostly hypothetical.

In terms of biotransformation, various hepatic drug metabolizing enzymes provide the principal routes for detoxification and metabolic activation of components of herbal medicines as well as determining the elimination of metabolizable components. Theoretically, matrix effects based on hepatic metabolism are expected to be possibly the most frequent mechanism due to a large number of potentially metabolizable components in any herbal medicinal product. Although examples of matrix effects based on metabolism are increasingly published (Table 4.2), most of them are observed in animal studies and "real-life" examples in human use of herbal medicines are scarce.

### *Interactions Between Components*

Pharmacokinetic interactions (as discussed in Chap. 5) can be studied with herbal products without knowing the chemical composition of the product. Crude extracts/products can be subjected to studies where the induction and inhibition of pharmacokinetic processes are assessed; this involves the study of the effect of herbal products on drug metabolizing enzymes and transporters. Also, displacement of drugs from protein binding sites can be investigated, and, of course, variability in the herbal products is an ongoing problem. Differential variation of constituents that may affect any one of the pharmacokinetic processes is problematic, as it cannot be

compensated for, even by monitoring a single or a few selected marker compounds in the herbal product. However, some benefit can be gained by screening crude herbal products for their impact on pharmacokinetics. It is possible to add some value to this approach if the goal of the studies is to deal with drugs that have a narrow therapeutic index. Matching the therapeutic indications of drugs with the therapeutic indications of herbal products is of substantial value in focusing these studies (this is discussed in detail in Sevior 2012).

## Possibilities for Solving the TK of Herbal Medicinal Products

A frequently expressed claim is that the efficacy and safety of herbal medicines is thought to be due to a number of active components exerting their effects on multiple targets, possibly also acting synergistically or antagonistically. Consequently, it is important to assess how the kinetic behavior is dictated in complex mixtures. Similarly, we need to assess whether there are so-called "matrix effects" and interactions between components affecting the fate and effects of the total mixture. At least at present, it is difficult or practically impossible to elucidate such complex possibilities in clinical studies; consequently, it is advisable to start with in vitro studies, which are routinely used in the pre-clinical ADME studies of conventional pharmaceuticals.

### *Analytical Methods*

As herbal medicinal products are complex plant-derived mixtures, the primary goal – and also the prerequisite for further studies – is to employ analytical methods that can identify the major and minor components and, when necessary, quantitate the components of concern. Various chromatographic separation methods, linked with mass spectrometry, are the methods of choice, because at least a tentative composition and relative quantification of the major components can be achieved relatively easily within a reasonable time frame. Furthermore, the information on components is beneficial for various non-clinical and clinical pharmacodynamics studies. However, these studies have to be conducted according to basic requirements; otherwise, they yield impressive but totally useless and misleading data (Sansone et al. 2007; see also Pelkonen et al. 2012). Indeed the unequivocal identification of a component, as well as absolute quantitation, need additional analytical methods, such as NMR and synthesis of reference compounds. The need for such methods and studies, however, has to be justified by other requirements, such as the elucidation of pharmacodynamic or toxicological characteristics of active components, or the use of a component as an analytical marker or as a biomonitoring marker.

## *In Vitro and In Vivo Methods for Studying TK*

In Table 4.3, some possibilities for studying TK and ADME processes are presented. Almost all these methods were originally developed and intended for pre-clinical studies during drug development of conventional medicines. However, these methods should be used also to study herbal products and their components, even if modifications are probably required just for the sake of the complexity of herbal products. Firstly, the metabolism and metabolic interactions of complex mixtures and their main components are studied in in vitro systems, preferably human-derived preparations such as subcellular organelles (microsomes) and hepatocytes. In the cellular systems, it is also possible, at least in principle, to study associations between the metabolic and kinetic behavior of an herbal preparation and/or its components and cellular effects and toxic outcomes and markers. These effects and markers include selected in vitro toxicity outcomes (e.g.,, cytotoxicity in hepatocytes) or specific markers of mechanisms of action of toxic compounds (e.g., mitochondrial toxicity, reactive intermediates). Subsequently, the findings and predictions most relevant to clinical investigations in human volunteers or patients and, in selected cases, in vivo experimental animals are carried out. The goal is to develop a viable scheme for elucidating major ADME properties of complex herbal mixtures in in vitro systems so that the results can be extended to in vivo for comparison (see the section on poly-pharmacokinetics). *In vitro* testing systems are already being used to study metabolic interactions between herbal medicines and conventional medicines (see Sevior 2012; Pozadski et al. 2013), but other ADME-associated characteristics have not been extensively studied. It is not currently known to what extent the in vitro approach designed for single drugs can be applied for the studies of herbal products; therefore, the above-mentioned scheme is mostly conjectural, but it is believed to be a feasible starting point for investigations directed towards building an evidence-based scientific and regulatory TK dossier for herbal medicinal products.

## *Poly-pharmacokinetics*

As described earlier in this chapter, determining pharmacokinetics of a complex herbal medicinal product, especially in clinical settings in humans, is a daunting task. Recently, Chinese scientists suggested that the advent of comprehensive profiling technologies offer new opportunities for understanding multicomponent pharmacokinetics (Lan and Jia 2010; Lan et al. 2013; Jia et al. 2015). Firstly, metabolomics, coupled with multivariate statistical tools to study the metabolism of xenobiotics, delineate the complicated variations in multiple metabolites of exogenous origin within the landscape of herbal medicine-dietary exposure-gut microbial-host metabolic

**Table 4.3** *In vitro* and in vivo approaches to studying ADME (absorption, distribution, metabolism, excretion) processes of herbal medicinal products

| Study specifics | Purpose | Methods | Outcome |
|---|---|---|---|
| Herbal substance/ preparation | Identification and quantification of major and minor components | Metabolomics | "Xenometabolome" of the preparation (composition of the preparation; principal 'active' components) |
| Subcellular organelles (microsomes), primary and permanent cells in culture | Metabolism, identification and quantitation of metabolites | Conventional analytics, metabolomics | *In vitro* "xenometabolome" (after metabolism) |
| | | Metabolism of individual principal components | Rate of metabolism (clearance), metabolic profile of individual components |
| Major and minor constituents of the herbal substance | Identification of metabolizing enzymes | Recombinant enzymes, enzyme-selective inhibitors, antibodies | Enzymes catalyzing different pathways (especially of "active" components) |
| Intestinal cells (Caco-2, etc.), hepatocytes in culture | Permeation, transporters, metabolism | LC-MS, inhibitors of transporters | Rate of permeation, contribution of transporters, bioavailability of individual components |
| Cryopreserved primary hepatocytes, HepaRG cells | Metabolism | Metabolomics | Prediction of clearance and metabolic routes of "active" components |
| Experimental animals | "Poly-pharmacokinetics" | Metabolomics | In vivo "xenometabolome" in experimental animals |
| Administration of preparation or components | In vivo kinetics of herbal product and/ or components | Conventional analytics | Bioavailability |
| Volunteers, patients | "Poly-pharmacokinetics" | Metabolomics | In vivo "xenometabolome" in humans |
| Administration of preparation or components | In vivo kinetics of herbal product and/ or components | Conventional analytics | Bioavailability |

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*LC-MS* liquid chromatography-mass spectrometry

machinery interactions, and unravel the underlying mechanisms in terms of systems biology. Secondly, metabolomics of body fluids offer simultaneously a view on endogenous metabolites altered in response to the treatment. Thirdly, integration of the bioavailable ("systemic") PK profile of the herbal product with an endogenous metabolomic profile may indicate herbal-target-effect relationships of clinical and treatment outcomes. In the words of the authors (Lan et al. 2013): "Acquisition of a

complete and dynamic panel of pharmacokinetic parameters for multicomponent dosage regimens to achieve desired therapeutic efficacies is essential to minimize toxicity, reduce overdosing and drug complications, keep healthcare costs at a minimum, and, ultimately, increase patient compliance and quality of life."

Intuitively, the poly-PK integrated with pharmacodynamics seems to be an appropriate approach to study the PK/TK of complex herbal products. It is, however, obvious that the presented scheme is just the first attempt to formulate a feasible research agenda to elucidate the PK/TK of complex herbal products. It also requires up-to-date, i.e., expensive and labor-intensive analytical and computational tools for metabolomic elucidation of the resulting complex biological fluids that encompass (1) the absorbed components of the herbal product; (2) their metabolites; and (3) endogenous metabolites (e.g., glucose, cytokines, prostaglandins, etc.), which may be affected by the effects of herbal products. Analogous to conventional medicines, these studies should be carried out at different herb dosages and administration regimens, in groups of sufficient numbers of patients to be representative of the possibly encountered variabilities due to for example, genetics (CYP profiles), age, hepatic and renal function status, clinical condition, etc. Still, at least theoretically, there is a risk of missing important information from possibly low-level but very active or toxic components of the herbal mixture.

## Conclusions and Perspectives

It should be obvious that the elucidation of the TK of a single component of an herbal medicinal product can follow the established paths when the compound is studied as a single isolated chemical. The elucidation of its fate as a component of an herbal medicine needs a consideration of various matrix-related effects, e.g., potential changes in bioavailability, metabolism, etc., which should be studied when a suspicion arises that other components would affect its TK significantly.

On the other hand, a comprehensive evaluation of the TK of the whole herbal medicine via the above-mentioned traditional single-substance pathway seems not to be feasible or even worthy of efforts for all components. Instead, the significance of TK elucidation of any single component should be reflected on the basis of its activity in the herbal medicinal product, whether in the area of efficacy or of safety. It is possible to screen the product itself and its constituents at group or single substance levels by various in vitro and ex vivo techniques to give a tentative view of potentially active components. However, the next consideration is whether the active concentration is actually reached in in vivo conditions. This question can be solved only by in vivo (human) studies in which the actual systemic pharmacokinetics of the active components is elucidated. This in vivo step requires a comprehensive approach, e.g., poly-pharmacokinetic integration with pharmacodynamics. The above considerations are formally outlined in Fig. 4.2.

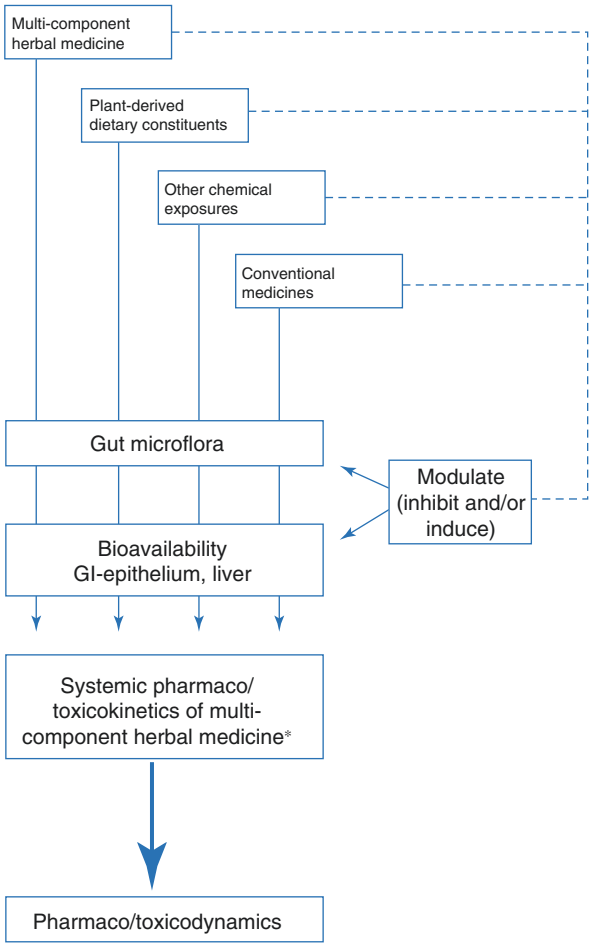


**Fig. 4.2** A simplified scheme of the factors to be taken into consideration when elucidating the pharmaco-toxicokinetics of a multi-component herbal medicine. This represents a complex example of *polypharmacokinetics that can only be resolved in a satisfactory manner when the active and/or toxic components have been identified

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