Dietary Supplements and Health: The Essence of Bioavailability

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The Medical Wellness Association (MWA) Published White Paper, 8.28.2017

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1. Dietary Supplements

Dietary supplements are generally ingested in concentrated form to ensure that the body achieves adequate levels of specific nutrients. A healthy person on a healthy diet is evolutionarily well-equipped to ensure a proper nutrient balance from the daily intake of foods. Foods are commonly classified into biomolecules comprising carbohydrates, lipids, proteins, vitamins, and minerals. Under conditions of disease, malnutrition, or hyponutrition, the body requires other or additional nutrients to correct the metabolic and physiological imbalance and restore homeostasis.

Nutritional deficits that arise during illness, deviant eating patterns (malnutrition), or strenuous physical exercise (hyponutrition) may be corrected through the use of dietary supplements. For example, in some Asian countries such as China and Japan, cancer patients who have undergone chemotherapy receive Maitake mushroom supplements or rice bran hydrolyzed with Shiitake mushroom enzymes to boost the immune system after treatment. Individuals who are malnourished as a result of a medical condition (e.g., cancer, eating disorders, or mental conditions) or poor eating habits may benefit from certain supplements to correct deficits in essential biomolecules. Some forms of chemotherapy reduce appetite and lead to malnutrition, which may be partially corrected by ingestion of relatively small volumes of highly concentrated dietary supplements. People who suffer from aberrant stool composition may increase their intake of dietary fiber through supplements rather than eating bulk quantities of food, e.g., raw celery. Finally, athletes who subject their body to heavy physical exercise and consequent damage benefit from protein supplements to rebuild damaged muscle and from vitamin and mineral supplements to optimize restorative processes and compensate for the loss of minerals via excretory pathways (i.e., urine and sweat). Thus, dietary supplements serve as an alternative to ingesting large and sometimes intolerable quantities of food under special circumstances.

2. The Fate of Dietary Supplements after Oral Intake

For a dietary supplement to have the desired effect outside of the gastrointestinal tract, it must be taken up in the gut after oral intake and transported into the blood. The intestinal wall plays a critical role in this process and serves a first internal barrier between the outside and the systemic circulation. The intestinal wall is in that respect comparable to our skin, which also protects our inside from external dangers. Unlike the skin, however, it has a more sophisticated gatekeeper function, allowing easy passage of molecules that our body needs as building blocks (proteins and nucleic acids), as a source of energy (sugars), and for biochemical and physiological functioning (vitamins and minerals). On the other hand, the intestinal wall is very apt at preventing toxic substances from harming us through its multifold of detoxification functions. This aspect is key to bioavailability, as explained in the next sections. The detoxification functions are illustrated in the framework of xenobiotics, which are chemical substances that are not fabricated by our body but enter our system through oral ingestion. Some common examples include natural and synthetic drugs (e.g., antibiotics) and molecules in plant-derived foods (e.g., curcumin in curries).

The first hurdle that xenobiotics face is the mucosal layer that lines the intestines. Molecules may be retained in this layer and never make it to the enterocytes. Enterocytes are specialized intestinal cells that reside between the intestinal lumen and the blood vessels. The mucosal layer is shed at a high rate, as a result of which the trapped molecules are shed too and exit the body via feces. Accordingly, defecation is a very effective detoxification tool. When transmucosal passage does occur, the xenobiotic enters the enterocytes, where it is subjected to a complex detoxification machinery referred to as xenobiotic metabolism. The metabolic steps include changing the molecular structure of the xenobiotic (e.g., oxidation in phase I and conjugation in phase II) such that the xenobiotic is rendered more water-soluble and can be excreted via the urinary system after passage into the blood stream (renal clearance). Alternatively, phase III processing entails the transport of the modified xenobiotic back into the intestinal lumen, after which it is excreted in feces.

When a xenobiotic manages to escape enterocytic phase I-III metabolism, it is exported into the blood by the enterocyte. However, this step does not afford the xenobiotic a 'molecular sigh of relief.' All molecules that are passed forward by the enterocytes enter the so-called enterohepatic circulation, which in its entirety drains into the liver. The liver is our most effective and largest molecular sieve, ridding the blood of potentially toxic substances. The liver is replete with Kupffer cells, specialized liver-resident white blood cells, that can 'capture and eat' unwanted substances, particles, and even cells such as bacteria. Moreover, the specialized liver cells (hepatocytes) are equipped with a plethora of transporters that facilitate extraction of chemically distinct molecules from the blood and multidirectional efflux out of the cell after processing. Following uptake, hepatocytes execute phase I-III xenobiotic metabolism just as the enterocytes. Potentially harmful molecules are chemically transformed into more water-soluble counterparts and excreted back into the circulation for renal clearance or into the biliary system to end up in the intestines for fecal elimination.

Once a xenobiotic passes the liver, our body still has several safeguards in place to curtail toxicity to specific organs. One of the safeguards is the blood-brain barrier (BBB), which deters basically all large-molecule neurotherapeutics and a vast majority of small-molecular drugs from entering the brain. The BBB is not necessarily a physical barrier as the intestinal mucosa, but a barrier that is formed by the tight packing of endothelial cells. Endothelial cells are specialized cells that line all the blood vessels in the circulatory system. Most blood vessels have relatively large gaps between the endothelial cells, making the blood vessels permeable to large molecules and even nanoscopic particles such as low-density lipoprotein (LDL), the most common cholesterol carrier in blood. These gap junctions are a standard mechanism of exchange of solutes between blood and non-brain tissue, such as muscles. In the brain, however, the endothelial cells are more tightly packed and of slightly different phenotype. Consequently, trafficking is confined to only those molecules that the brain needs. In the case of orally administered melatonin (as a supplement), an otherwise endogenously produced hormone that regulates mainly sleep/wake timing referred to as circadian rhythm, the BBB is transgressed at sufficiently high concentration to affect sleep patterns. A neurochemical effect occurs despite the fact that about 90% of orally ingested melatonin is cleared by the liver and a small amount is excreted through urine.

The standard kinetics of most orally ingested compounds are depicted in Figure 1 in relation to targeting brain tumors inasmuch as this trajectory features all the pharmacokinetic hurdles. It is important to emphasize that orally ingested xenobiotics may still exert an effect at the target site after undergoing extensive metabolism in the gut and liver, such as in the aforementioned case of melatonin targeting its receptors in the brain. In other situations, the metabolism in the enterohepatic system is too extensive and precludes a sufficiently high concentration of the bioactive compound in the systemic circulation to instill the desired effects. A great example is that of curcumin, a phytochemical derived from the roots of the *Curcuma longa* plant that gives curry its yellow color. Curcumin is extensively retained in the intestinal mucosa, metabolized by enterocytes and hepatocytes, and excreted via urine in conjugated form, as a result of which plasma levels are very low even after ingestion of up to 12 g of curcumin (Heger et al., 2013). Curcumin has potent anti-cancer properties *in vitro* and *in vivo*, but its systemic concentration becomes too low in humans after xenobiotic metabolism for curcumin to act as an oncotherapeutic (Heger, 2017). On the other hand, systemic levels are high enough to pharmacologically interfere in certain non-cancer conditions, including inflammation in the colon and joints, depression, metabolic syndrome, and premenstrual syndrome (Heger, 2017).

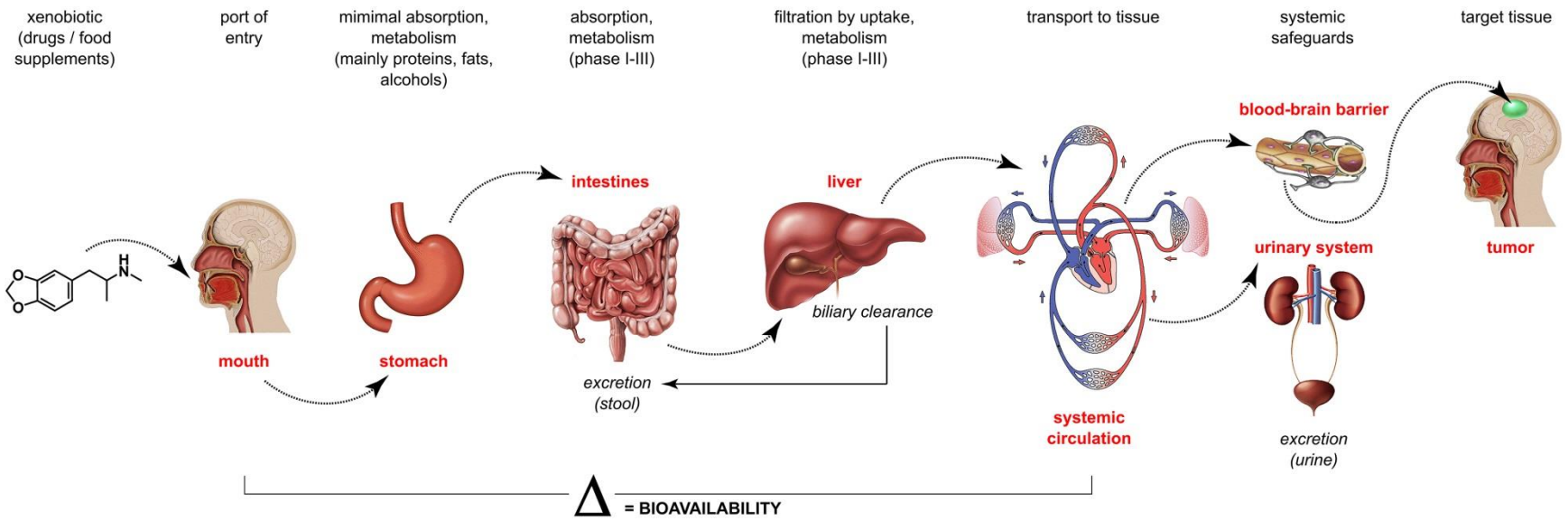

Figure 1.

Kinetics of orally ingested xenobiotics in relation to brain tumor targeting. Multiple hurdles are encountered by xenobiotics before reaching their target destination, the most important being organs responsible for xenobiotic metabolism (intestines and liver) and elimination (liver and kidneys). In special cases, certain organs impose additional hurdles, such as the blood brain barrier in the vasculature of the brain. The brain tumor is represented by the green tissue bulk. Bioavailability refers to the difference (indicated with a 'Δ') in the amount of molecules in native state in the systemic circulation versus the amount of these molecules that was ingested.

3. Pharmacokinetics and pharmacodynamics

The dose-effect relationship as alluded to in the case of curcumin perfectly exemplifies the interconnectedness between pharmacokinetics and pharmacodynamics in achieving a biological effect. Pharmacokinetics refers to what our body does to a xenobiotic (i.e., metabolism and excretion), while pharmacodynamics refers to what the xenobiotic does to our body (e.g., tumor cell death and amelioration of inflammation). Although curcumin kills cancer cells *in vitro* and shrinks tumors in animal models, the therapeutic effect on human tumors is minimal because of the dismal pharmacokinetics in our species. In contrast, curcumin exhibits pharmacodynamic efficacy in several non-cancer indications in humans. Accordingly, pharmacokinetics dictate a compound's pharmacodynamic efficacy, where the pharmacodynamic efficacy is highly dependent on the specific condition for which the xenobiotic was administered.

4. The Essence of Bioavailability Related to Xenobiotic Efficacy

Bioavailability is essentially defined as the difference between the amount of molecules present in the systemic circulation relative to the amount of molecules ingested. Bioavailability is therefore the end result of pharmacokinetics. Theoretically, bioavailability can be expressed as a fraction or percentage. So, if 100 molecules are ingested and one molecule reaches the systemic circulation, then we can speak of a 1% bioavailability. Some might say that the bioavailability is 'poor' at a 1% rate. However, we want to stress the importance of pharmacological context. Indeed, for some conditions, a bioavailability of 1% is insufficient to instill a pharmacological effect (e.g., curcumin and cancer). For other conditions, it may be enough (e.g., curcumin and inflammation). Thus, the use of the phrase 'poor bioavailability' may therefore inadvertently misconstrue the reputation of a dietary supplement, despite the fact that, mathematically, a dietary supplement is associated with a 1% bioavailability.

The bioavailability of a xenobiotic is influenced by more factors than metabolism in the gut and liver (Figure 1), including biological and (patho)physiological factors such as age, gender, circadian rhythm, dietary state (fed versus fasted), gastric emptying rate, health of the gastrointestinal tract, and liver and kidney function. These factors do not only differ between individuals, but also in the same person over time. Additionally, pharmacological and biochemical variables also govern bioavailability, such as the physical properties of the xenobiotic (e.g., water-soluble versus fat-soluble), drug-drug and drug-food interactions, expression levels of metabolic enzymes and their postprandial induction, and the formulation used to deliver the xenobiotic. The cumulative end result of these factors may be responsible for a xenobiotic to lack dose linearity, meaning that some individuals may exhibit a 2% bioavailability at 100 mg dose, while others will show a 0% bioavailability at a 10-fold higher dose. Xenobiotics are particularly prone to an absence of dose linearity and hence variation in pharmacodynamics efficacy. The rule in dietary supplements therefore is: what works for one person does not necessarily work for another person.

5. Practical Considerations Related to Bioavailability

Aside from explaining the importance of bioavailability, the essence of this article is that bioavailability of a xenobiotic should be used in the context of the condition for which it is administered. If we continue with curcumin as example, then the amount of molecules that enters the systemic circulation following oral ingestion of curcumin is not sufficient to kill millions of tumor cells. The rate of cell death induction does not exceed the rate at which the tumor cells proliferate, so the net effect is continued cell proliferation, albeit at a reduced rate. From the perspective of bioavailability and pharmacodynamics, it is not difficult to grasp that it is theoretically difficult to kill a tumor at 1-2 micromolar concentration (measured in human plasma) when the 50% lethal dose *in vitro* is 10-30 micromolar (Heger et al., 2013), i.e., 5-30 times higher than what is achieved after oral curcumin intake. So, in terms of cancer treatment, curcumin has poor bioavailability and should be advertised as such. On the other hand, the poor bioavailability should not be extended to other medical indications insofar as curcumin has been shown to work in independently conducted placebo-controlled, double blind randomized clinical trials for non-cancer disorders (Heger, 2017). For those conditions, curcumin bioavailability is still mathematically poor, but clinically and practically sufficient.

Finally, the most optimal manner in which we can gauge the pharmacodynamics potential of a xenobiotic, whether a dietary supplement or a drug, is by measuring bioavailability on a personalized basis. For plant extract-based dietary supplements, which can contain hundreds of different phytochemicals that collectively relay a biological effect, this will be a nearly impossible feat. In those cases, we will have to rely on placebo-controlled, double-blind randomized clinical trials and a statistical probability that the supplement is effective in individual cases. The dietary supplement market as well as the end-users will benefit greatly from the implementation of scientific methods to determine pharmacokinetics, bioavailability, and pharmacodynamics efficacy as is currently being done for drugs.

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