molecular pharmaceutics

editorial

Commentary: Bioavailability of Flavonoids and Polyphenols: Call to Arms

Dietary polyphenols (Figure 1) are a main source of antioxidants for humans.[1] These polyphenols have a variety of biological activities, ranging from antiaging and anticancer to lowering of blood cholesterol levels and improving bone strength.[1–6] Millions of women also take a subclass of polyphenols called phytoestrogens to relieve symptoms associated with menopause.[7,8]

Dietary polyphenols are derived from plants and are consumed in the forms of fruits, vegetables, spices, and herbs. Dietary intake of polyphenols widely fluctuates between cultures, ethnic groups, and even within a narrow geological location. Large percentages of dietary polyphenols are consumed in the form of flavonoids, although cultural and dietary habit will dictate which forms of polyphenols are taken up. For example, in northeastern Asian countries such as China and Japan, isoflavones are the main source of polyphenols along with other flavonoids derived from teas, vegetables, and fruits.[9,10] In southeastern Asian countries such as India, a significant percentage of the population consumes large quantities of curcumin as result of ingesting the turmeric spices.[11] In European countries, a large population of people consume lignans as a result of ingesting cereal bran or whole grain breads or flax seed oils.[9,10] Finally, in the worldwide population, many people consume teas, which also contain large amounts of polyphenols and have a variety of effects including anticancer.[3]

A majority of the population takes sufficient amounts of dietary polyphenols and enjoys their beneficial effects. However, a large percentage of adults living in Western and developed countries and a smaller but growing adult population living in developing countries such as India and China are not taking sufficient quantities of dietary polyphenols.[12] This selected population appears to have a distaste for fruits and vegetables that are rich in flavonoids and other polyphenols. The reason for this lack of interest in healthy food probably varies greatly, but some researchers have attributed this to a fast-paced lifestyle and fast food restaurants that do not serve tasteful fruits and vegetables.

Many people hope that they can one day take pills that will provide the same beneficial effects of dietary polyphenols without eating, or eating minimal amounts of, fruits and vegetables. A large population of people (e.g., prostate cancer patients[13]) also believes that they should take additional pills with flavonoids and other polyphenols even though they are ingesting the recommended quantities of fruits and vegetables in the hope of achieving more beneficial effects, as evidenced by the ever-increasing amounts of dietary supplements consumed in developed countries. These people are motivated by scientific research that is widely carried in the news media, which indicates that these flavonoids and polyphenols could

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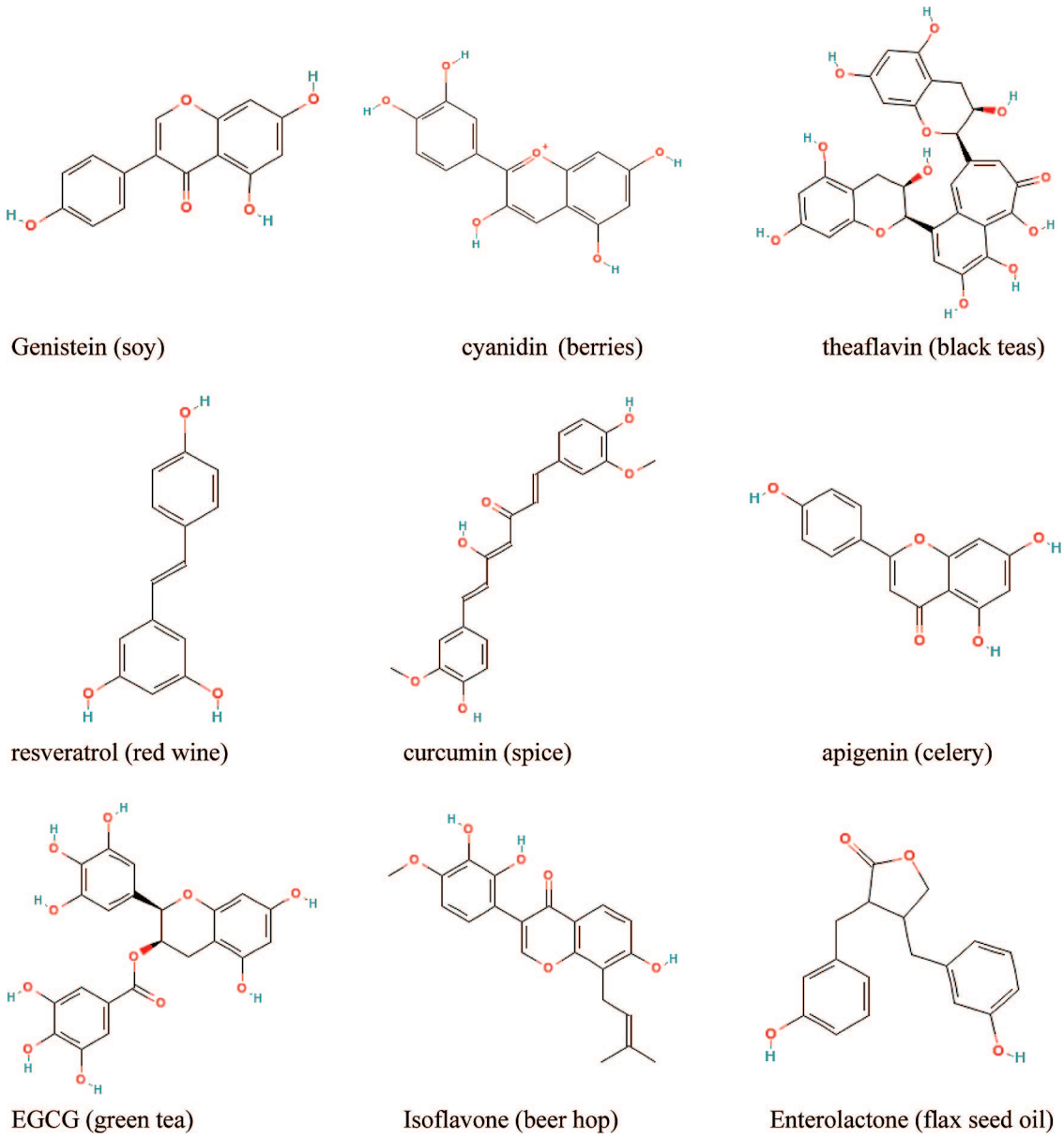

Figure 1. Structures of representative dietary polyphenols.

prevent cancer, aging, and cardiovascular diseases.[3,12,14–16] However, these types of research are often carried out on animals, and their effects on humans remain uncertain.[17]

A critically important scientific question is then: are these flavonoids and polyphenols as effective as people believe? Many researchers have devoted significant efforts to the study of dietary polyphenols, and hundreds of grants have been funded by a variety of funding agencies to determine if the polyphenols are indeed active. A large body of evidence, mainly derived from preclinical studies in animals, has concluded that dietary polyphenols, when given in large quantities, can have desirable outcomes.[12,14,15] Although a few government-sponsored trials are ongoing, it is too complex or too costly to demonstrate the effectiveness in humans because these agents have limited if any intellectual property protection. In addition, poor bioavailability of polyphenols makes it even more difficult to conduct relevant but smaller clinical trials because large exposure differences are expected among the participants. Typical polyphenols have oral bioavailability (mostly in animals) of 10% or less, and a range of 2–20% is quite common. Assuming exposure in humans, which are more genetically diverse than experimental animals, shows similar differences, a very large

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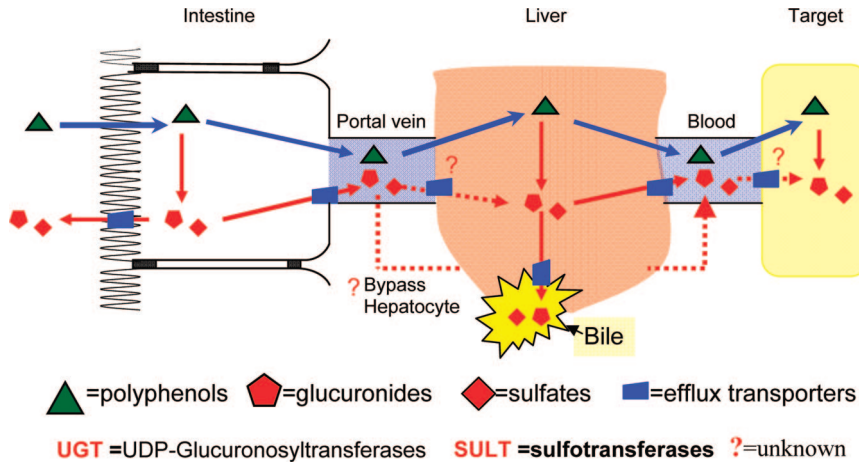

Figure 2. Organ bioavailability barriers to polyphenol bioavailability. An organ bioavailability that ultimately determines the bioavailability of polyphenols is depicted.

population is needed to demonstrate efficacy, which is often not affordable. Therefore, an urgent issue in the development of polyphenols as disease prevention agents is to find a way to increase their bioavailability so we can use a smaller population to conduct relevant trials.

In order to increase the bioavailability of polyphenols, we must overcome multiple challenges associated with their development. Because these agents are targeted for disease prevention, oral administration is the only viable route, except for topical application on external organs such as skin. For polyphenols to become bioavailable, the following barriers must be overcome: solubility, permeability, metabolism, excretion, target tissue uptake, and disposition (Figure 2). If we deliver hydrophilic polyphenols, which are typically glycosides, they are usually too polar or sometimes are too large to rapidly penetrate the intestinal membrane.[18] Instead, these glycosides often need the action of intestinal or more likely the microfloral enzymes to release sugar so the polyphenols are available as the more absorbable aglycon forms.[18,19] Aglycon forms are highly permeable in Caco-2 and perfused rat intestinal models and are expected to be rapidly absorbed.[20–22] However, the bioavailability is not high because pure aglycon forms have very poor solubility, often less than 20 μg/mL in water. This low solubility can cause slow dissolution rates, which can slow down the absorption. Coupled with the fact that absorbed aglycons are rapidly conjugated to glucuronides via UGT and sulfates via SULT in intestine and liver,[23,24] solubility can become a critical factor as higher aglycon concentrations can overwhelm the metabolic enzymes and allow more drugs to reach the systemic circulation intact. Therefore, there is an urgent need to perform systematic studies to demonstrate how changes in polyphenol structures affect solubility and dissolution rates and how various pharmaceutical excipients may be used to improve their dissolution rate.

The bioavailability issue is important since we only know that the aglycons are active. Very few studies have attempted to determine if the metabolites are active. Historically, conjugates of polyphenols are considered to be inactive even though studies are not published to demonstrate that this is the case, primarily because it is difficult to purchase these metabolites from commercial sources. Although many phase II conjugates are shown to be pharmacologically inactive, some are more pharmacologically active than the parent compound, including morphine−glucuronide and ezetimibe−glucuronide.[25] Therefore, we believe that it is necessary to conduct more mechanistic studies to determine the activities or functions of these phase II conjugates.

How metabolites move across different biological membrane is critically important, assuming some metabolites are active or can be converted into active parent compounds at target organs. Transport of lipophilic conjugates out of the main metabolic organs such as liver and intestine has only been studied recently, and available evidence suggests that a variety of organic transporters may be involved in the

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transport of these conjugates in and out of cells. However, these studies have mainly been conducted in liver and intestine, and almost no studies have been conducted in other vital organs (e.g., heart) or target organs (e.g., mammary glands). The latter is partially because we are unable or incapable of determining the concentrations of metabolites as we lack standards to do so. We believe that more studies in this area of research would help us understand how active metabolites may work in vivo.

Lastly, the use of large amounts of concentrated flavonoids may post as public health concerns, as limited in vivo information is known about their adverse effects and their ability to interact with other drugs. This hotly debated subject includes the use of soy isoflavones in women.[26] Limited studies have shown that soy isoflavone genistein can stimulate the growth of MCF-7 cells in the absence of hormone,[27] but this remains a debatable point since genistein inhibits estradiol or estrone sulfate stimulated MCF-7 cell growth. Another important point is that flavones and isoflavones may interact with broad spectrum efflux inhibitors such as breast cancer resistance protein.[28]

In this special issue of *Molecular Pharmaceutics*, we have assembled a group of active and experienced researchers. They each provided their own research results or surveyed current research landscape in the form of review articles. Taken together, our collection serves to make a broad assessment of the current knowledge base and state-of-the-art techniques. Additional papers represent current or new methodologies that can be used to assess the bioavailability of flavonoids and polyphenols. As you will find, the lack of ability to improve bioavailability other than through the use of methylated prodrugs[29] suggests the need to further our research into this field since methylation often can change the activities of polyphenols. More bioavailable or highly bioavailable polyphenol formulations or derivatives are very desirable because they will be easier to develop and less costly to test. Therefore, we hope that this *Molecular Pharmaceutics* Special Issue will also serve the purpose of stimulating more discussion and research of the bioavailability problems among molecular and pharmaceutical scientists. With their help, the successful development of polyphenols as chemopreventive agents in the future will soon be within our reach.

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