Bioavailability of phenolic compounds: a major challenge for drug development?

Biodisponibilidade de compostos fenólicos: um importante desafio para o desenvolvimento de fármacos?

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Resumo
As substâncias fenólicas constituem uma importante classe de metabólitos secundários, amplamente distribuídas no reino vegetal. Diversas atividades biológicas in vitro são atribuídas a essa classe de substâncias. Entretanto, algumas dessas substâncias não apresentam o mesmo perfil de atividade nos ensaios in vivo. Parte disso pode ser explicada pela baixa biodisponibilidade dessas substâncias. As principais razões encontradas para este fato podem ser a baixa solubilidade em meio aquoso, a fraca estabilidade gastrointestinal, a dificuldade em atravessar membranas e a rápida e extensa metabolização. Os metabólitos produzidos na biotransformação pela microbiota intestinal e por enzimas hepáticas poderiam explicar a baixa eficácia dessas substâncias. Em contrapartida, a biotransformação também pode originar metabólitos potencialmente mais ativos que as substâncias originais. Diante da relevância do tema, este artigo tem como objetivo abordar os impactos da metabolização das substâncias fenólicas sobre o efeito farmacológico. Adicionalmente, serão apresentadas estratégias que podem ser utilizadas para aumentar a bioeficácia dessas substâncias, e consequentemente, contribuir para o aproveitamento dessa classe química no desenvolvimento de fármacos de origem vegetal.

Palavras-chave: Substâncias fenólicas; atividades biológicas; metabolismo; biodisponibilidade; formulações; pró-drogas.

Abstract
Phenolic substances are an important class of secondary metabolites widely distributed in the plant kingdom. Several biological activities in vitro are assigned to this class of substances. However, some of these substances do not have the same profile of activity in in vivo assays. This fact could be partially explained by the low bioavailability of these substances. The main reasons for this low bioavailability may be low aqueous solubility, poor gastrointestinal stability and difficulty crossing membranes. The rapid and extensive metabolism by the intestinal flora and by some liver enzymes of phenolic substances after oral administration, may explain the poor bioavailability. In contrast, biotransformation can also lead to metabolites potentially more active than the original substances. Given the importance of the topic, this article aims to address the impacts of metabolism of phenolic substances on their pharmacological effects. Additionally, we show strategies to improve the bioefficacy of these substances, contributing to their use in the development of drugs of vegetal origin.

Keywords: Phenolic compounds; biological activities; metabolism; bioavailability; formulations; pro-drugs.
Introduction

Phenolic substances are an important class of secondary metabolites and are widely distributed in the plant kingdom (Crozier, Jaganath and Clifford, 2009; Cheynier et al., 2013). These substances are synthesized in different parts of the plant and participate in functions such as pigmentation, attraction of pollinators, defense against pathogens, protection against UV radiation and various signaling processes (Quideau et al., 2011). Although present in all groups of plants, phenolic substances present more diversity in higher plants, and are often found in the form of esters, amides and glycosides (Boudet, 2007; Cheynier et al., 2013). The phenolic compounds are biosynthesized by the shikimate pathway, producing phenylpropanoids and derivatives or by the acetate/malonate pathway, as can be seen in FIGURE 1 (Quideau et al., 2011). These pathways may yield a wide range of phenolic substances exhibiting a diversity of structures.

Epidemiological studies have linked a diet rich in phenolic substances to protection against degenerative diseases, cardiovascular, diabetes and cancer (Arts and Hollman, 2005; González et al., 2014). Additionally, in vitro studies have shown that phenolic compounds are of considerable importance due to their diverse biological activities. However, some of these substances presenting an in vitro activity do not show the same profile when tested in in vivo models. The concentrations of these substances that reach the target tissues are very low when compared to the concentrations used in in vitro assays. Part of this is due to the low bioavailability of these substances in the gastrointestinal tract (Férriz and Vinová, 2010).

Bioavailability could be defined as the rate and extent to which an administered drug or substance reaches the systemic circulation or tissue targets to exert a given activity. Parameters such as route of administration, absorption and metabolism of these substances, among others, will influence their effectiveness (D’Archivio et al., 2010; Velderrain-Rodríguez et al., 2014).

The relation between the actual pharmacological effect of phenolic compounds and their metabolites is considered a controversial and paradoxical question (D’Archivio et al., 2010; Perez-Vizcaino, Duarte and Santos-Buelga, 2012; Heleno et al., 2015). To raise these molecules to the status of drugs is a great challenge. There are many obstacles, among them the paucity of studies for determining the therapeutic index values of these substances (Peluso and Palmery, 2015). Application of technology to formulation development can confer great advantages such as increased solubility, minimization of degradation processes, reduction of toxicity or unpleasant taste, and control of the absorption and effectiveness of the active substance (Bonifácio et al., 2010).

FIGURE 1 – Scheme of the biosynthesis of phenolic substances (adapted from Cheynier et al., 2013). Abbreviations of enzymes: anthocyanidin synthase (ANS), chalcone isomerase (CHI), chalcone synthase (CHS), cinnamate-4-hydroxylase (C4H), dihydroflavonol reductase (DFR), flavanone 3-hydroxylase (F3H), flavonol synthase (FLS), flavone synthase (FS), isoflavone synthase (IFS) and phenylalanine ammonia-lyase (PAL), 4-coumaroyl-CoA ligase (4CL).
Materials and Methods

The search in SCOPUS database (www.scopus.com, 16.03.2015) was carried out using the keywords “phenolics” or “polyphenols” and “plant” and was further refined with the keyword “bioavailability”. An additional search was carried out in the site ClinicalTrials.gov (access on March 15, 2015) with the keywords phenolics” and “polyphenols”.

Results and Discussion

The search in SCOPUS using the terms “phenolics” or “polyphenols” and “plant” resulted in 34,634 articles. The search was further refined with the keyword “bioavailability”, affording 3401 publications; the earliest publication dating back to 1983. Among them, there were 645 review articles about bioavailability and phenolics; the first ones published in 1997 and 1998 (Hollman and Katan, 1997; Bravo, 1998). In the last 30 years, publications involving bioavailability had a linear increase, as can be seen in FIGURE 2. However, the number of publications related to bioavailability and phenolic substances is still small compared to the number of publications about phenolic substances. The subject aroused great interest primarily to researchers in the field of nutrition and food. The main areas of interest should reflect the most studied classes and subclasses of phenolics - anthocyanidins, stilbenes, catechins and phenolic acids -, substances commonly found in foods.

FIGURE 2 – Number of studies in the Scopus database found for the keywords “polyphenols and bioavailability”

Source: www.scopus.com, on March 03, 2015.

The search for “phenolics” and “polyphenols” in the site ClinicalTrials.gov resulted in 49 and 213 reports, respectively, which are related to the evaluation of the pharmacokinetic profile of phenolic as supplements, associations with drugs and formulations. Although phenolic substances arouse great interest, the number of studies involving clinical trials is low. This can be explained by the relatively low bioavailability and high doses required to produce in vivo the antitumor effect, which could result in increased toxicity and adverse effects. Additionally, there are other difficulties for the realization of clinical trials such as the required number of patients and the high costs (Khushnud and Mousa, 2013). Another important point is the moderate interest of pharmaceutical companies in phenolic substances, despite the plethora of their activities and interesting results. Many of these substances are not object of industrial investment because of their oral bioavailability below 30% (Gao et al., 2012). The following topics will address the metabolism of phenolic substances and its impact on their pharmacological effects, as well as some strategies to improve the bioefficacy of these substances.

Bioavailability of phenolic substances: absorption and metabolism

The metabolism reactions for providing bioavailability to phenolic compounds, present in foods and formulations, begin in the oral cavity. Mastication has an important role in food transformation, since the mechanical action disrupts the food structure and permits the release of compounds. The metabolism of glycosylated phenolic compounds can begin as soon as they come in contact with glycosidase enzymes of bacteria in the oral cavity (Velderrain-Rodríguez et al., 2014). Experiments with extracts of fruit rich in human saliva and phenolic substances revealed that the anthocyanins were partially metabolized by enzymes in oral microflora (Kamnopatana et al., 2012). The food passage through the stomach is essential to promote the degradation of the matrix. Some substances may undergo hydrolysis during this passage; however, many polyphenols reach the intestine in their intact forms. It is suggested that the most important process for the modification and stability of these substances is related to the reactions promoted by the intestinal microbiota (Correa-Betanzo et al., 2014). Many of phenolic substances require structural changes for their absorption in the gastrointestinal tract. Some ex vivo studies in rats showed that absorption of phenolic acids can occur at the gastric level or in portions of the intestine, such
as jejunum, ileum and colon (Lafay et al., 2006; Zhao and Moghadasian, 2010). The permeability and transport of polyphenolics from the gut lumen into the cytosol of enterocytes depend on their chemical characteristics, such as lipophilicity, the presence of groups capable of hydrogen bonding, molecular weight and stereochemistry (Tzounis et al. 2008; Tian et al., 2009; Rein et al., 2012; Kobayashi et al., 2013). It is believed that the phenolic compounds are absorbed by a passive diffusion mechanism or by carriers present in the intestine, such as P-glycoprotein and cotransporters for SGLT1. These transporters are expressed on the cell membrane, and transport the drugs into the cell interior (Lewandowska et al., 2013; Zhang et al., 2013). The phenolic aglycones, for example, are capable of crossing the membranes of the epithelial cell by passive diffusion (Velderrain-Rodríguez et al., 2014).

Naturally occurring polyphenolics are found as esters, glycosides, polymers, and often cannot cross membranes by passive diffusion. Although the liver is recognized as the main organ for biotransformation reactions, most glycosylated phenolic substances are metabolized in the small intestine by the action of intestinal cell membrane hydrolases (e.g. lactase phlorizin hydrolase) and enzymes of the intestinal microbiota. These first passage reactions occur in the intestine, allowing the prior metabolism of substances, which, in turn, promote absorption. The colonization of the gastrointestinal tract is considered an important step as it modulates the beneficial effects of (Selma, Espín and Tomás-Barberán, 2009). These substances are absorbed from the colon and distributed via the bloodstream by plasma proteins or transported to the liver by the portal vein. Concentrations of substances in the bloodstream depend mainly on the absorption and structural changes during the metabolism. Plasma proteins such as albumin carry phenolic substances and their metabolites (Bolli et al., 2010). In the liver, the phenolic substances can still undergo further biotransformation reactions, which aim to make them more polar molecules, facilitating their elimination. The biotransformation process in the liver is divided into two well defined phases. Phase I comprises hydrolysis reactions, oxidation and reduction, catalyzed by CYP450 enzymes (Wu et al., 2011a; Lewandowska et al., 2013). The conjugation reactions of phase II increase the hydrophilicity of the molecules before their elimination (Velderrain-Rodríguez et al., 2014).

The low oral bioavailability of some phenolic substances could be explained by the rapid glucuronidation (Wu et al., 2011a; Wu et al., 2011b). Uridine diphosphate glycosyltransferase enzymes (UGT) are responsible for catalyzing the transfer of a sugar unit to acceptor molecules. One of the structural requirements for an acceptor molecule is the presence of a hydroxyl (OH) group, capable of acting as a nucleophile. It is suggested that the active site of the UDP-glucosyltransferase is located on the lumen of the endoplasmic reticulum, and that the resulting glucuronides are transported from the intracellular to extracellular compartments via efflux transporters. Although the mechanism is not fully elucidated, it is believed that an S_{2} reaction takes part in the process (FIGURE 3) (Wu et al., 2011a; Wu et al., 2011b; Chen et al., 2014).

Phenolic substances may also suffer the action of sulfotransferase enzymes that make the molecules more hydrophilic, facilitating their elimination (Chen et al., 2014). In addition to the glucuronides and sulfated metabolites, high concentrations of O-methylated metabolites can be observed. An in vitro study showed that the catechol-O-methyltransferase (COMT) is responsible for the production of 3’-O-methylated derivative from catechins and procyandins (Weinert et al., 2012).

In general, the large and extensively conjugated metabolites are eliminated in the bile, whereas small conjugated metabolites, such as monosulfate

**FIGURE 3** – Glucuronidation of flavonoid naringenin by UGT.
derivatives are preferably excreted in the urine (Manach et al., 2004). The glucuronide conjugates and other metabolites may also be impacted by β-glucuronidase enzymes affording free aglycones. These can be reabsorbed from intestinal lumen due to enterohepatic recirculation resulting in an increase in its half-life time (Marier et al., 2002; Wu et al., 2011b). A summary of the important events in the bioavailability of phenolic substances is shown in FIGURE 4.

Impact of the metabolism of phenolic compounds on the biological activity

The number of publications on bioactive substances of plant origin is growing, with special emphasis on phenolic substances. Given the importance of phenolic bioavailability studies, many researchers have dedicated their attention to kinetic studies of phenolic compounds as well as the pharmacological potential of the respective metabolites (Crozier, Rio and Clifford, 2010; Williamson and Clifford, 2010; Wu et al., 2011a; Wu et al., 2011b; Rubió et al., 2014). The relationship between bioavailability and biological activity is considered controversial. Some authors believe that the study of the biological effects of polyphenolics in cell lines should use metabolites (conjugates) produced in in vivo assays at concentrations achieved in biological fluids and tissues (nanomolar) to provide an accurate estimation of the effects (Tomás-Barberán and Andrés-Lacueva, 2012; Santos et al., 2014).

Positive impact of the metabolism

The intestinal and hepatic biotransformation may lead to more or less active metabolites depending on the substrate and the products formed. The hydrolysis reactions of glycosides sometimes lead to potentially more active metabolites (Lambert, Sang and Yang, 2007; Williamson and Clifford, 2010; Lu et al., 2013). Lignans, for example, need to be bio-transformed by gut microflora to be biologically active. Some authors use the term mammalian lignans to specify the lignan metabolites with estrogenic activity. Studies performed in an artificial stomach model reveal that lignans are stable at gastric pH but are metabolized by anaerobic bacteria such as Bacteroides previalis present in the distal part of the bowel. The lignan secoisolariciresinol diglucoside is hydrolyzed and converted by intestinal bacteria into the aglycone secoisolariciresinol (SECO). The dehydroxylation reactions lead to enterodiol, which, in turn, is oxidized giving rise to enterolactone (Clavel et al., 2006; Landete, 2012). Of the two classes of metabolites formed, the enterolignans are mostly produced and absorbed in the colon (FIGURE 5). A pharmacokinetic study of diglucoside isolated from linseed was performed in healthy postmenopausal women with single doses of 86 and 172 mg. The experiments showed that independently of the administered dose, the aglycone SECO was detected in plasma 5-7 hours later, but enterolactone and enterodiol were detected in urine only after 2-5 days. The presence of the aglycone in the plasma and of the two other metabolites in urine corroborates the...
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Another positive interface of the metabolism for activating substances can be exemplified by the study of anxiolytic activity of flavonoids kaempferol and quercetin orally (p.o.) and intraperitoneally (i.p.) administered. Kaempferol (1) and quercetin (2) showed anxiolytic activity when orally administered. However, the same flavonoids proved to be inactive by i.p. route. This result led the authors to suggest that the anxiolytic activity of flavonoids is related with their 3,4-dihydroxyphenylacetic acid (3) and p-hydroxyphenylacetic acid (4) metabolites produced by the intestinal microbiota during the metabolism. Given the different effect observed in the two administration routes, the activity of 3,4-dihydroxyphenylacetic acid and p-hydroxyphenylacetic acid was investigated by i.p. administration. These two substances showed anxiolytic activity. Additionally, the anxiolytic activity of both flavonoids was not observed when orally administered in rats that had undergone prior sterilization of the intestinal microflora. These studies support the hypothesis that the biotransformation of flavonoids by bacterial intestinal flora is the key step for anxiolytic activity (Vissiennon et al., 2012).

Soy isoflavones also become active after biotransformation; the metabolism is favorable to the pharmacological activity. These glycosidic isoflavones have proven effective for treating certain symptoms of menopause, constituting an alternative to hormone replacement. However, they need to be metabolized by the intestinal microbiota, which releases the free aglycone, consequently, producing the therapeutic effect (Marques and Souza, 2012; Hajirahimkhan, Dietz and Bolton, 2013).

Negative impact of the metabolism

In some cases, the phenolic compounds may exhibit high absorption, but, in spite of this, low bioavailability due to extensive metabolism reactions. To exemplify this recurrent difficulty, one can mention the case of resveratrol, a phenolic substance found in wine. Many biological activities are related to this substance, especially antitumoral, neuroprotective and anti-diabetic properties (Santos, Veiga and Ribeiro, 2011).

In order to evaluate the distribution of trans-resveratrol (5) in the body after oral administration, the substance was 14C labeled and administered to a group of volunteers (dose: 25 mg). The concentration of the substance in the plasma reached 2 uM after 1 hour. Very low concentrations of resveratrol intact and high concentrations of plasma metabolites were observed showing that this substance is extensively metabolized (Walle et al., 2004). Vitrac and collaborators (2003) observed a similar behavior in Balb/c mice administered with resveratrol. The plasma concentrations of resveratrol found in both studies were very low when compared to the concentrations used in in vitro pharmacological tests (Tomé-Carneiro et al., 2013). The sulfated metabolites of trans-resveratrol (6) showed little cytotoxic potential in breast cancer cell lines, compared to resveratrol (Miksits et al., 2009). The glucuronides also showed little cytotoxic activity in colon and lung cancer cells (Lu et al., 2013). The replacement of OH functions of resveratrol by glucuronide or sulfate groups could

FIGURE 5 – The biotransformation of lignans by gut microflora resulting in a bioactive metabolite (enterolactone), according to Clavel et al., 2006.
reduce the permeability of these substances in the cells (Miksits et al., 2009).

Another interesting example are the catechins present in green tea (Camellia sinensis). These phenolic compounds have an important range of pharmacological activities, such as the in vitro anti-tumor activity (Yu et al., 2014). However, they have low bioavailability because their wide biotransformation into glucuronides, and methylated and sulfated derivatives. Catechins can also be metabolized by the intestinal microbiota resulting in 5-(3’,4’,5’-tri-hydroxyphenyl) γ-valerolactone (7) and isomers thereof (Van der Hooft et al., 2012). The metabolites (7) and methoxylated derivatives were not active in in vivo inflammation models (Lambert et al., 2005).

Curcumin (8) is the main active component of Curcuma longa rhizomes, notable for having anti-inflammatory, antioxidant and antitumor activities. However, its potential as a candidate drug is hampered by the low bioavailability. As shown in previous examples, curcumin is also extensively biotransformed leading to inactive metabolites (Anand et al., 2007). The metabolite tetrahydrocurcumin (9) showed weak activity in the inhibition of tumor growth when compared to curcumin. In this case, since the activity depends on the antioxidant potential; without conjugated double bonds to extend the resonance throughout the molecule, tetrahydrocurcumin is not able to stabilize free radicals in the same manner as curcumin (Sandur et al., 2007).

In a clinical phase II trial, patients with pancreatic cancer were treated daily with doses of 8 g curcumin orally. Only glucuronides and sulfated metabolites were detected (Dhillon et al., 2008). These results are consistent with other studies that have observed only the conjugated metabolites in plasma (Vareed et al., 2008). The free curcumin in plasma was detected only at higher doses, which does not reflect the actual concentration on the target, which makes difficult to determine a safe and effective dose (Lao et al., 2006; Gota et al., 2010). Some authors propose the use of phenolic substances only as food supplements because of the difficulty of establishing the efficacy and the therapeutic index (Peluso and Palmery, 2015).

**Strategies to increase the bioefficacy of phenolic substances**

Given the difficulties in the bioavailability of this class of substances, some studies suggest the development of structural changes in molecules or formulations as a way to improve their pharmacokinetic profile or their bioefficacy. Bioefficacy could be defined as the amount of compound absorbed and converted into its active form.

Some substances with therapeutic potential have been the object of formulation studies, such as stilbenes, flavonoids and tannins (Anand et al., 2007; Kidd, 2009; Santos, Veiga and Ribeiro, 2011; Singh and Pai, 2014). Some strategies for improving the bioavailability and efficacy of these substances will be presented in the next topics.

**Formulations**

The utilization of formulations is a good strategy for modulating the bioavailability of certain components. The various barriers that phenolic substances have to face to reach the target present major challenges in the development of herbal products. Among the delivery systems applied to plant extracts and substances are liposomes, phytosomes, cyclodextrine inclusion and nanoparticles (Kidd, 2009; Rein et al., 2012;). Some of these options will be shown.

Nanoparticles or nanocarriers are submicron colloidal systems with particle size of about 1-100 nm. From a technological point of view, the nanoparticles are easily produced on an industrial scale. There has been a growing number of studies depicting successfully and efficiently the incorporation of phenolic substances into nanocarriers (Soppimuth et al., 2001; Bonifácio et al., 2014; Li, Z. et al., 2015). The use of nano-based formulations has become promising due to the advantages of physical and chemical stability, increased solubility and bioavailability, protection against toxicity and concentration in the target tissue. In some studies, coating nanoparticles were used as a protection against oxidation, some other degradation reactions and glucuronidation in the gastrointestinal tract. This strategy was employed in stability studies with encapsulated catechin nanoparticles (Curcio et al., 2012; Li, Z. et al., 2015). Nanoparticles were used for the coating of resveratrol applied to HIV control (Singh and Pai, 2014). A recent study developed a nanoemulsion formulation base, using as excipient a substance inhibitory to glucuronidation, to avoid extensive metabolism of resveratrol. *In vivo* pharmacokinetic studies with the formulation containing labrasol, a glucuronidation inhibitor, showed a dose-dependent inhibition by increasing the concentration of resveratrol in its free form in the circulation. This type of strategy is interesting for phenolic substances that are substrates for UGT enzymes (Zhou et al., 2015).
Some natural products when co-administered with phenolic compounds were able to increase the bioavailability. The term bioavailability enhancer is used to designate a compound co-administered with drugs to increase the bioaccessibility and efficacy. The use of bio-enhancer is an old tradition in Ayurvedic medicine. Among drug facilitators described in the literature, there are inhibitors of efflux pumps like P-glycoprotein (Sousa and Bernkop-Schnürch, 2014). Capsaicin and piperine, for example, are known to interact with the CYP450 enzyme system and other metabolism enzymes. In vivo experiments for determining the kinetics of curcumin associated with piperine pointed to a higher availability of the phenolic substance in plasma (Suresh and Srinivasan, 2010).

The preparation of silibinin (10) in phytosomes (silibios®) was the first commercial application of this technology, which has been used to promote the aqueous solubility and intestinal absorption of this phenolic substance. This flavolignan is the major constituent of *Silybum marianum*, whose extract was already used by the ancient Greeks to treat some disease symptoms. The silibinin complexed to a phytosome presents a wide range of pharmacological activities (antioxidant, anti-inflammatory, antitumor and hepatoprotective). Among the various clinical indications for this formulation, the use in liver diseases is probably the most important (Semalty et al., 2012).

A different strategy was used in the development of the phytomedicine Aglycon-soy® by Apsen and Steviafarmaceuticals. The glycosyl isoflavones present in soy extract (*Glycine max L.*) need to be biotransformed to become active. However, their bioavailability is highly variable, due to changes in the microbiota and intestinal dysbiosis. The prior hydrolysis of these substances in the extract using a β-glucosidase enzyme was the solution proposed (Marques and Souza, 2012).

### Pro-drugs

The pro-drug strategy is used in some studies to increase the oral bioavailability of some substances that have limitations in some stage of the bioavailability process, in order to increase the concentration of the substance in the target tissue without causing any toxicity (Bansal et al., 2013; Biasutto and Zoratti, 2014). Pro-drugs are precursors showing favorable kinetics in the biological system, permitting regeneration of the original substances. Hydrolysis reactions may be involved in this process (Biasutto and Zoratti, 2014). Through chemical reactions it is possible to protect groups susceptible to undergoing reactions during metabolism which would result in loss of activity obtaining substances which will act as pro-drugs. In the case of phenolic substances, the hydroxyl groups are more susceptible to phase II and oxidation reactions; however, sometimes the presence of these groups is an important structural requirement for pharmacological activity. For this reason, strategies for protection of hydroxyl groups have deserved the attention of researchers (Biasutto and Zoratti, 2014). (-) Epicatechin 3-gallate (11) has low bioavailability due to extensive metabolism and instability in medium and alkaline pH conditions. Structural changes can improve the physicochemical
properties and avoid a rapid metabolization. Studies led to peracetylation of catechins to enhance the hydrophobicity and make hydroxyl groups unavailable for biotransformation (Lambert et al., 2006). A more sophisticated strategy proposes the transformation of the phenolic substances into a pro-drug, which is associated with a nanoformulation. In a recent study, curcumin was transformed into a pro-drug by conjugation with hyaluronic acid through a carbodiimide reaction. This combination makes curcumin more soluble and protects the OH groups, which is the major structural requirement for antioxidant activity (Li, J. et al., 2015).

Conclusion

Bioavailability studies of phenolics are an important step for the drug development with these bioactive compounds. The lack of therapeutic efficacy in clinical trials, sometimes attributed to extensive intestinal or hepatic metabolism, constitutes a controversial topic that invites a deeper investigation. When the problems involved in the various stages of the bioavailability process are better understood, strategies can be developed to overcome these barriers and increase the concentration of the substance in the target organ. Thus, phenolic-based formulations can be developed, and new medicines from vegetal origin can be proposed.

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