FRUIT JUICE
SCIENCE CENTRE

Hesperidin – does this bioactive compound drive the health effects of citrus fruits?

This dossier will build on the knowledge that plant polyphenols are beneficial for health by focussing on a promising polyphenol found in citrus fruits and juices, called hesperidin.

Benefits of plant-based diets

Interest is growing in the health-protective effects of plant-based diets. Indeed, the World Health Organisation recommends boosting consumption of fruit, vegetables and fibre-rich foods to help lower the risk of non-communicable diseases, such as cardiovascular disease (CVD), type 2 diabetes and some cancers[1].

Meta-analyses[2,3,4] and prospective cohort studies[5] consistently demonstrate that fruit and vegetable consumption is associated with a reduced risk of heart disease and stroke. A common explanation for these associations is the wide range of essential vitamins and minerals found in fruits and vegetables. Less well known by healthcare professionals, but of growing interest to scientists, are the bioactive plant compounds, including polyphenols, carotenoids (vitamin A precursors) and phytoestrogens.

WHAT ARE POLYPHENOLS?

Polyphenols are a diverse group of bioactive plant compounds, including flavonoids, stilbenes, phenolic acids and lignans. Of these, flavonoids are further classified into the subgroups flavan-3-ols, flavonols, flavones, isoflavones, flavanones and anthocyanins. Figure 1 shows the food sources of different polyphenols.

In planta, polyphenols are typically a vital part of the natural defence system of the plant, e.g. acting against harmful micro-organisms and enabling the plant to 'heal' wounded parts. Humans derive these bioactives only from plant-based foods. Besides their direct absorption, many polyphenols are metabolised in the gut prior to absorption, making their total availability and activity prone to variation as a consequence of individual differences in intestinal bacteria species (microbiota).

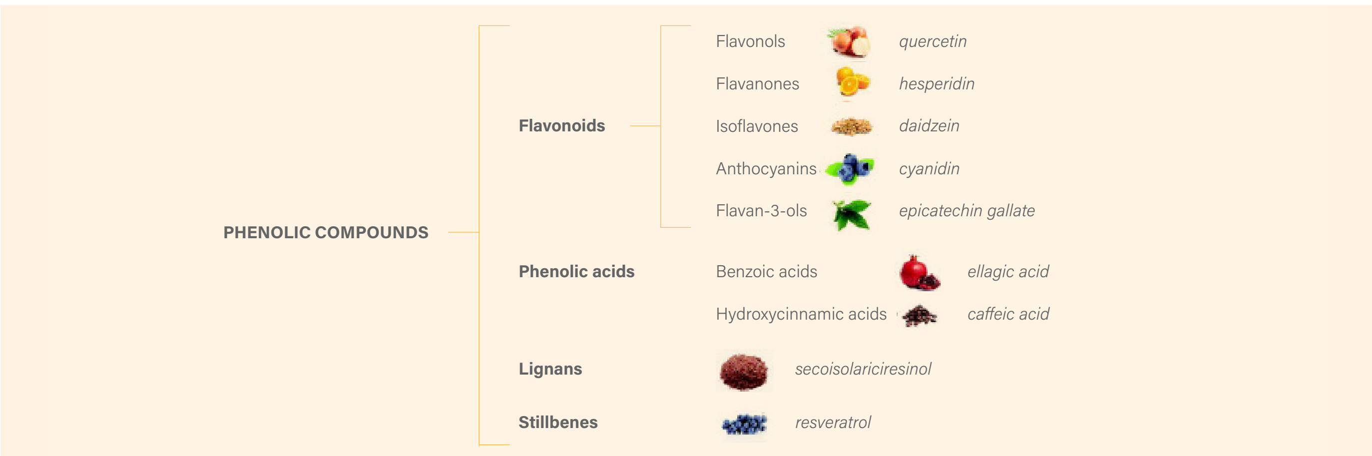

Figure 1: Structure and food sources of polyphenols in fruits and vegetables[6]

Polyphenols and human health

Observational and intervention studies report that polyphenols confer health benefits, particularly for chronic diseases and their intermediate risk factors[2,7,8]. There is also convincing evidence from several meta-analyses that dietary flavonoids are associated with lower all-cause mortality[9] and CVD mortality[10], risk of stroke[11], heart disease[12], CVD4 and type 2 diabetes[13], as well as more favourable vascular and cognitive function[14].

Various mechanisms of action have been proposed to explain these findings. Historically, the benefits of polyphenols were attributed almost exclusively to their antioxidant activity. More recent opinion favours modulation of human proteins, such as metabolic enzymes and transporter proteins, which are relevant to immunomodulatory and vasodilatory effects[15].

Several cardio-protective pathways are likely, with the most plausible relating to improved endothelial function, blood pressure control and anti-inflammatory properties[16,17,18]. For example, it has been suggested that consuming polyphenol-rich fruits can lessen the inflammatory processes associated with high fat, Western-style diets6,[19]. Other studies additionally report that fruit polyphenols inhibit platelet aggregation, improve blood lipid profile and increase insulin sensitivity[20,21]. Synergistic effects are thought to be mediated by polyphenol metabolites produced by the gut microbiota and the influence of other fruit compounds, such as nitrates and fibres.

Focus on hesperidin

An increasing body of research has focussed on one of the polyphenols in the subclass of flavanones. Hesperidin occurs in food as a glycoside comprising hesperetin and the disaccharide rutinose. Hesperidin is found almost exclusively in the peel, fruit and juices of citrus fruits, particularly oranges.

Orange juice is a recognised source of vitamin C, folate and potassium but is less well known for being rich in flavanones such as hesperidin, naringin and narirutin. Indeed, a recent study suggested that there can be more hesperidin (520 mg/L) than vitamin C (450 mg/L) in orange juice, delivering around 78 mg per 150 mL glass. Table 1 presents the content of naturally occurring hesperidin and principle nutrients in 100% orange juice. In the gut, hesperidin is metabolised through the action of gut bacteria converting it into metabolites, such as the biologically active form hesperetin, which is more readily absorbed[22].

	100 mL	150 mL	200 mL
Energy (kcal)	41	62	82
Total sugars (g)	9	14	18
Vitamin C (mg)	45	67.5	90
Potassium (mg)	176	264	352
Folate (mcg)	21.5	32.3	43
Total carotenoids (mg)	0.7	1.1	1.4
Hesperidin (mg)	52	78	104
Pectins (mg)	33.4	50.1	66.8

Table 1: Components of 100% orange juice

Hesperidin and health

Studies have explored whether hesperidin, alone or within the natural matrix of 100% citrus juice, contributes to reduction of CVD risk and the maintenance of normal cognitive function. Attention has also focussed on how hesperidin and hesperetin influence glucose absorption and glycaemic control.

Cardiovascular markers

Statistically significant changes to intermediate risk factors for CVD following regular citrus juice consumption have been observed in several population groups, including healthy adults[23], those with raised lipids[24], and those who are obese or have a high waist circumference[25,26]. For example, in a randomised controlled crossover trial[27], 24 overweight men drank 2 x 250 mL servings of orange juice, or an energy-matched drink enriched with hesperidin, versus an energy-matched placebo drink without hesperidin daily for 4 weeks. The results showed that, compared with the placebo, both hesperidin-containing beverages reduced diastolic* blood pressure and improved the elasticity of blood vessels. The authors concluded that *"orange juice decreases diastolic blood pressure when regularly consumed"* and *"hesperidin could be causally linked to the beneficial effect of orange juice".*

* Diastolic refers to the smaller blood pressure number

These findings are backed by other human intervention studies reporting lower blood pressure[25], improved vascular function28,29 and antioxidant activity[25,30], lower blood lipid levels[24] and lower inflammation[29,31] following orange juice consumption. In addition, a meta-analysis[32] concluded that fruit juices and whole fruits confer similar effects on blood pressure, with regular consumption of 100% fruit juice linked to a modest, yet consistent, reduction of 2.07 mmHg in diastolic blood pressure. These protective changes may explain why a recent observational study reported statistically significant associations between drinking up to one glass per day of 100% fruit juice and reduced risk of coronary heart disease and stroke[33].

Proposed modes of action for hesperidin

- Blood pressure: reducing arterial stiffness, improving elasticity of vessels, stimulating the endothelial production of nitric oxide.
- Inflammation: inhibiting proinflammatory enzymes34 and cytokines35, inhibiting inflammatory signalling in glial cells36.
- Lipids: modulating enzymes and proteins involved in the assembly of Apo-B lipoproteins37.
- Antioxidant: reducing lipid peroxidation38, modulating genes implicated in chemotaxis, adhesion, infiltration and lipid transport39. Lowering uric acid, a risk factor for gout, by inhibiting xanthine oxidase.

Hesperidin, glucose absorption and glycaemic control

Despite having a similar total sugars content to sugar-sweetened beverages (around 10%), the glycaemic index (GI) of 100% citrus juice is considerably lower. For example, the GI for a carbonated sugary drink is 63-68 while the GI for 100% orange juice is 50[40], which is closer to the GI of whole oranges (43). The unexpected GI may be due to the actions of hesperidin in the gut.

A recent acute intervention trial using different strengths of 100% orange juice concluded that hesperidin modulates the postprandial glycaemic response by slowing down glucose transport across the intestine via modulation of GLUT2 and GLUT5 transporters[41]. This results in a significantly lower rate of glucose uptake and may explain why meta-analyses of randomised controlled trials have found that regular fruit juice consumption has a neutral effect on markers of glycaemic control[42,43]. Individual studies have reported favourable effects on insulin sensitivity when orange juice is consumed as part of a calorie-controlled diet[26], and a less variable daylong glycaemic response when orange juice is consumed instead of a sugar-sweetened beverage[44]. Interestingly, despite media concerns, 100% fruit juice is not associated with risk of developing type 2 diabetes[45].

Less benefit from hesperidin pills

In contrast, results from trials using hesperidin supplements have been inconsistent. A recent meta-analysis[46] of ten randomised controlled trials concluded that hesperidin given alone had only insignificant effects on serum cholesterol, LDL-cholesterol, HDL cholesterol or triglycerides, and no impact on blood pressure. Reviews which have included animal, human and mechanistic studies have given a more favourable opinion, suggesting that hesperidin supplements may improve lipid metabolism or lower blood lipids[47,48]. These findings suggest that hesperidin may be more effective when provided in a natural food matrix, such as citrus fruits, perhaps due to interactions with other substances, such as vitamin C, potassium, pectin and narirutin. More research is needed to clarify this.
Cognitive function: a new horizon for hesperidin?
Clinical studies and reviews suggest that polyphenol ingestion has the potential to support cognitive function both acutely and chronically. A small number of trials found that hesperidin had a beneficial association with neurological conditions[49]. In one randomised controlled trial[50], drinking a flavanone-rich juice for eight weeks resulted in significantly improved global cognitive function compared with a control beverage. A second study concluded that consumption of flavanone-rich citrus juice may acutely enhance blood flow to the brain in healthy young adults[51]. Furthermore, a study in healthy male adults[52] found that a flavonoid-rich orange juice containing 220 mg hesperidin led to a significant improvement in executive function and attention compared with a placebo drink.

It has been proposed that the impact of citrus flavanones on brain health may be explained by their ability to cross the blood-brain barrier and protect neurones against the damage associated with neurodegenerative conditions[53,54]. A plausible mechanism is that flavonoids enhance cerebral blood flow due to improved endothelial function and increased bioavailability of nitric oxide, mirroring the effects seen in the vascular system outside the brain.

Consuming more dietary hesperidin

Citrus fruits are the best source of hesperidin, and both whole fruits and juices are excellent choices. There is sometimes confusion about whether the processing of oranges into juice has an impact on nutritional composition and bioavailability. However, studies show that pasteurisation and chilling of 100% orange juice does not destroy the nutrients or bioactive plant compounds. Consequently, the content of these in 100% orange juice is similar to that found in whole oranges, except for fibre which is reduced due to the separation of cell wall materials during dejuicing. In addition, although hesperidin is found throughout the fruit, its highest concentrations are within the whitish spongy substance, the so-called albedo, or pith, of the fruit. Therefore, total hesperidin concentrations are commonly higher in whole fruit than in orange juice.

Nevertheless, a previous study revealed that, although whole oranges contained 2.4 times more hesperidin than 100% orange juice, similar amounts were absorbed into the human blood stream. Consequently, absorption of hesperidin from orange juice appeared to be more effective than from the fruit, possibly due to limitations in the solubility of hesperidin in the digestive fluids, which meant that higher amounts, as found in whole oranges, were unavailable for metabolism and absorption[55]. Interestingly, when comparing freshly squeezed orange juice with commercially squeezed types, the latter contained three times more hesperidin and resulted in higher blood levels of the metabolite hesperetin[56].

In many countries, a 150-250 mL glass of 100% orange juice counts as a portion of fruit within recommendations to eat at least five portions of fruit and vegetables daily. Unfortunately, fruit and vegetable consumption across Europe remains too low, while average fruit juice consumption is only around 40 mL daily – a factor which contributes to low hesperidin intakes, estimated to be 25 mg/day in the UK and 7.1 mg per day in Denmark[57]. Hence, there is scope for increased consumption of 100% citrus juice as a way to complement fruit consumption as well as to boost hesperidin intakes.

Conclusion

- Polyphenols from fruits and vegetables are believed to confer health benefits.
- Hesperidin is a polyphenol found almost exclusively in citrus fruits and their juices. The hesperidin in 100% orange juice is particularly bioavailable.
- A 150 mL glass of orange juice contains 78 mg of hesperidin and 67.5 mg of vitamin C.
- Clinical trials find that both hesperidin and 100% orange juice are associated with improved markers of cardiovascular health, especially vascular function.
- It is likely that the action of hesperidin is synergistic with other compounds in citrus fruit juice, e.g. potassium, vitamin C and narirutin.
- Due to low levels of fruit juice consumption, there is scope for a daily glass of 100% orange juice to contribute both to hesperidin and optimal fruit intakes.

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