The Flavonoids Hesperidin and Diosmin: Adjuvant Therapy for Obesity

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Abstract

The flavonoids are polyphenolic plant products, characterized by a 15-carbon skeleton which includes two benzene rings. Two active flavonoids, diosmin and hesperidin, are used as venotonic and vasculoprotective agents in clinical practice. They are indicated for the management of varicose veins, chronic venous insufficiency and haemorrhoids. They help improve circulatory tone, reduce inflammation, strengthen venous walls, and alleviate symptoms such as discomfort, pain and swelling. In this communication, we explore their potential use in obesity, especially obesity related oedema (obestasis).

Keywords: Daflon, lymphatic, obesity, oedema, overweight, venous disorders

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Introduction

The flavonoids are polyphenolic plant products, characterized by a 15-carbon skeleton which includes two benzene rings. Anthocyanidins, flavanols, flavanones, flavan- 3-ols, flavononols, flavones, isoflavones and chalconoids are some examples of flavonoids. Two active flavonoids, diosmin and hesperidin, are used as venotonic and vasculoprotective agents. They are indicated for the management of varicose veins, chronic venous insufficiency and haemorrhoids.[1] They help improve circulatory tone, reduce inflammation, strengthen venous walls, and alleviate symptoms such as discomfort, pain and swelling. In this communication, we explore their potential use in obesity.

Hesperidin

Mechanism of Action

Recent research has uncovered the potential role of these drugs in the management of obesity and its complications. Hesperidin has been shown to improve obesity in mice by modulating the gut microbiome. The intestinal microbiota influences the bioavailability of hesperidin, and may be responsible for the significant interindividual variability observed with this drug. In fact, it has also been studied in conjunction with faecal transplantation in mice.[2,3]

Hesperidin has also been reported to exert an anti-diabetic as well as hepatoprotective effect in high fat diet induced obese mice. One mechanism of action is that hesperidin improves serum and tissue levels of leptin, interleukin-6 and tumour necrosis factor-α (TNF- α).[4] Hesperidin binds to leptin receptor with greater affinity that orlistat. It favourably impacts the geometrical conformation of the leptin receptor, making it more sensitive to its ligand, leptin, thus stimulating lipolysis.[5]

Clinical Pharmacology

A randomized double-blind placebo-controlled study in overweight and obese adults showed that a combination of 500mg glucosyl hesperidin (G-hesperidin) and 50/75mg caffeine reduced fat accumulation, without reducing serum triglycerides.[6] A similar study on green tea and G-hesperidin, in a dose of 178 mg H-hesperidin and 146 mg epigallocatechin – 3-0-gallate (EGCG) demonstrated a reduction in weight, visceral fat, and triglycerides, better results were noted in participants aged <50 years.[7]

A systemic review and meta-analysis of randomized controlled trials shows that hesperidin reduces fasting glucose, lipids, systolic blood pressure and TNF-α, without impacting insulin, insulin resistance, HDL-cholesterol, diastolic blood pressure and he-CRP. Interventions lasting > 12 weeks, with doses exceeding 500 mg/day, which were more effective.[8] Thus, hesperidin offers robust potential for the management of lifestyle disorders. Another metanalysis focusing on anthropometric measures in randomized controlled clinical trials, however, found no effect of hesperidin on body weight, body mass index, body fat percentage and waist circumference.[9]

Diosmin

Mechanism of Action

Diosmin has been found to ameliorate inflammation, insulin resistance and hepatic fibrosis in murine models. Regulation of the AMPK pathway has been proposed as a mechanism of action.[10] Along with its anti-oxidant, anti-

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apoptotic effect, it indirectly mediates NF-KB signalling pathway to regulate inflammation and body weight. Diosmin has also been found to be a selective peroxisome proliferator-activated receptor ¥ (PPAR ¥) modulator. When delivered locally in fat tissue, it improves insulin sensitivity and attenuates obesity by enhancing browning of white fat, and increasing energy expenditure.[11] The molecule has also been shown to exert an anti-obesity effect by activating adipose estrogen receptors in male mice.[12]

A network analysis has identified multiple targets of diosmin for the management of obesity- related kidney injury. These have been validated by molecular docking and invitro validation. Similarly, mechanisms have also been proposed for the anti-diabetic effect of diosmin.[13]

Clinical Pharmacology

A combination of hesperidin and diosmin was used in a randomized controlled trial on 129 adults with type 2 diabetes and neuropathy, to improve Michigan (MNSI) scores, fasting glucose, LDL cholesterol and triglycerides.[14] Good results were observed. Diosmin has also been studied in combination with saroglitazar.

Potential Place in Therapy

The contemporary definition of clinical obesity includes venolymphatic disorders such as lower limb oedema, lower limb lymphoedema, and recurrent deep vein thrombosis or pulmonary embolism.[15] The term obestasis has been given to the multifactorial oedema that often accompanies obesity.[16] It is in persons with obesity and obestasis, or venous insufficiency, that a diosmin- hesperidin combination may prove to be most useful. Further trials are needed to elucidate the exact role of these flavonoids in obesity care.

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