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Editorial

Citrus Species and Metabolic Syndrome what we need to know?

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Metabolic syndrome (MS) is a clustering of at least three of the five following medical conditions including obesity, high blood pressure, hyperglycaemia, high serum triglycerides and low high-density lipoprotein levels. MS has reached epidemic proportion in industrialized countries, exceeding a prevalence above 40% in > 40 years old subjects [1]. Several research articles evidenced the role of oxidative stress in the development of MS, contributing to disease progression [2]. This condition is caused not only by the increase of pro-oxidant species, but also by the drop on of endogenous antioxidant defence system, which inactivate pro-oxidant species [3].

Citrus fruits, which are one of the most important commercial crops grown in all continents of the world, have received attention not only for their nutritional properties but also for its healthy properties including antioxidant, antimicrobial, anticancer, anti-inflammatory, and hypoglycaemic activities. *Citrus* species are grown all over the world in more than 140 countries, with more than 8.7 million hectares and about 131 million tons of fruits produced in 2012. *Citrus* species are rich sources of ascorbic acid and other bioactive compounds particularly flavonoids, carotenoids, and limonoids [4,5].

In the last decades, several *in vitro* and *in vivo* studies demonstrated the activity of *Citrus* species in the treatment of type 2 diabetes and obesity. *Citrus medica* L. cv. Diamante peel showed a promising inhibition of the carbohydrate-hydrolysing enzyme α-amylase [6]. The phytochemical composition of peel extract revealed the presence of terpenoids, compounds for which the reported lipophilicity may facilitate access to the active enzymatic site [7]. Successively, Menichini., *et al.* [8] demonstrated that *C. medica* leaves ethanol extracts were able to inhibit both α-amylase and α-glucosidase. Moreover, all investigated Diamante *Citrus* extracts showed antioxidant potential by different mechanism of action as demonstrated by using diverse analytical approaches.

Diamante citron peel extract had a direct stimulatory effect on the exocytotic release of insulin in a concentration-dependent manner in MIN6 β-cells. This hydro-alcoholic extract administered in vivo was able to reduce plasma glucose level, plasma cholesterol and triglycerides [9].

A moderate α-amylase inhibitory activity was evidenced also with *C. macroptera* [10]. Moreover, administration of fruits extract *in vivo* reduced fasting blood glucose level not only in physiological condition but also during glucose tolerance test. The phenolic-rich extract of *C. maxima* (pummelo) peel inhibited both key enzymes linked to type-2 diabetes and also angiotensin converting enzyme which is linked to hypertension another frequently MS associated condition [11].

More recently, Zeng., *et al.* [12] demonstrated that *C. reticulata* pericarp extract was able to inhibit pancreatic lipase, which is considered a promising approach to the treatment of MS and obesity. Chenpi is a product derived from the dry peel of the fruit of *C. reticulata* Blanco after aging process. Chenpi extracts reduces intracellular lipid accumulation in adipocytes. The reduction in lipid accumulation is correlated with AMP-activated protein kinase (AMPK) activation and down-regulation of adipogenic transcription factors as well as lipogenic genes. This activity is probably linked to its 5-demethylated polymethoxy flavones content [13]. A significant lipase and α-amylase inhibitory activity was observed also with *C. limon* fruit ethyl acetate extract [14]. *C. unshiu* (mandarin) fruit extracts improved the metabolic function of liver and restored the antioxidant enzymes in streptozotocin induced diabetic rats [15]. Moreover, its administration in diet (1% or 3%) for 10 week in type 2 diabetic Goto-Kakizaki rats improved glucose tolerance [16]. Mandarin peel extract (2 g/100 g diet) supplementation in male C57BL/KsJ-db/db mice is partially mediated through the induction of insulin/glucagon secretion and inhibition of hepatic gluconeogenic phosphoenolpyruvate carboxykinase mRNA expression [17]. The promising activity in MS was evidenced also with *C. grandis* (pomelo) peel extracts that prevent high-fat diet-induced metabolic disorders in C57BL/6 mice through the activation of the PPARα and GLUT4 signaling [18]. A reduction of body weight gain, serum total cholesterol, and triglycerides (TG) serum concentrations was obtained with *C. sunki* extract administration in high-fat-diet–fed mice and prevented liver steatosis. Moreover, flavedo reduced advanced glycation and products and H_2O_2-induced oxidative stress in human adipocytes [19].

Citrus juice is considered since ancient time a source of healthy compounds. *C. hystrix* and *C. maxima* (Red and White var.) fresh juice demonstrated a promising antioxidant and carbohydrate-hydrolysing enzymes inhibitory activity [20]. The hypoglycaemic potential was observed also with *Citrus* × *clementina* juice. This juice showed the presence of neohesperidin, hesperidin and narirutin as main compounds. In carbohydrate-hydrolysing enzymes inhibitory activity tests, samples showed higher potency against α-glucosidase. In particular, juice from the hill was the most active [21]. Administration of 237 mL of grapefruit (*Citrus* × paradisi) juice in obese patients for 12 weeks determined a weight loss of 1.6 kg [22]. Recently, Chen., *et al.* [23] demonstrated that administration of orange pomace, a fiber-rich by-product of orange juice production, reinserted in a variety of food products diminishes postprandial glycaemic responses to a high carbohydrate/fat breakfast and the second meal in overweight men.

The described bioactivity of *Citrus* species are frequently associated to their flavonoids content. Naringin, naringenin, nobelitin, narirutin, and hesperidin are the most abundant and important flavonoids thus far isolated from *Citrus* fruits [24].

These flavonoids significantly inhibited carbohydrate-hydrolysing enzymes [25]. Naringin is 196.83 times more active than the widely prescribed drug acarbose. Poncirin led to a 43-fold improvement in α-amylase inhibition over acarbose. Lineweaver-Burk plot evidenced a competitive inhibition mode towards both α-amylase and α-glucosidase [26]. Hesperidin demonstrated to inhibit α-amylase and α-glucosidase enzymes with IC_{50} values of 26.04 and 15.89 μM, respectively [27]. These data are of interest if compared with the positive control acarbose with IC_{50} values of 77.45 and 54.99 μM, respectively. The most promising flavonoid against α-glucosidase was didymin (IC_{50} value of 4.20 μM), followed by naringin and narirutin with IC_{50} values of 10.33 and 14.30 μM, respectively [27].

Citrus flavonoids acts at in hepatic level to increase glycolysis and reducing gluconeogenesis [25]. Moreover, hesperidin, naringin, and nobiletin are able to lowering hepatic gluconeogenesis and improving insulin sensitivity *in vivo* [28]. Recent investigations evidenced that the hypoglycaemic effect of naringin is mediated by the uptake of glucose in the skeletal muscle via up-regulation of AMPK [29] whereas naringenin exerted anti-hyperglycaemic and anti-oxidant properties in streptozotocin–nicotinamide-induced experimental diabetic rats [30]. Moreover, a clinical study showed that naringenin could prevent the functional changes in vascular reactivity in models of diabetes [31]. The effect of *Citrus* flavonoids in MS is related also on their action on adipose tissue. In fact, naringenin supplementation lowered adiposity and TG contents in in rats trough an increase expression of liver PPARα, carnitine and palmitoyltransferase 1 (CPT-1) [32]. All these proteins are involved into adipocyte differentiation that represent a key regulatory step in fat deposition in adipose tissues [33].

These studies represent a selection of investigation that cover the topic *Citrus* and MS. It is interesting to note that not only the edible portion of the fruits but also *Citrus* by-products are rich in bioactive compounds able to be use in the treatment of insulin resistance, dyslipidaemia, and obesity. The effect is linked to flavonoids that acts through multiple mechanisms.

Future human studies focused on efficacy, bioavailability, and safety of *Citrus* nutraceuticals products are required in order to promote their use I clinical arena.

Conflict of Interest

The Authors declare no conflict of interest.

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