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Benefits of Xanthohumol in Hyperlipidaemia, Obesity and Type 2 Diabetes Mellitus: A Review

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Abstract

Diabetes, obesity, hyperlipidaemia, as well as cardiovascular diseases in general, have become an increasing social and economic problem in developed countries. Hops contain Xanthohumol (XN), a chalcone within a group of prenylated phenols. Used alone, it has recently shown promising results in the management of these individual conditions and we have therefore undertaken a review and assessed the evidence for XN as a food supplement in this setting.

Materials and Methods: A PubMed and Cochrane search was performed for the terms: xanthohumol; hyperlipidaemia; obesity; type 2 diabetes mellitus. All relevant articles published over the last 15 years were considered for this review.

Results: A total of 39 papers were considered and 18 papers met the criteria for review and these included both *in vitro* and *in vivo* (including animal) studies. The studies suggest that XN improves high density lipoprotein (HDL) levels and optimise cholesterol transport, thus having a protective effect against atherosclerosis. Furthermore, XN might exert an anti-obesity effect by decreasing adipogenesis and inducing lipolysis. Finally, XN might also prevent insulin resistance and modulate glucose metabolic pathways.

Conclusion: *In vitro* and *in vivo* studies (predominantly animal studies) showed promising results for XN in the prevention and treatment of hyperlipidaemia, obesity and T2DM. However, further studies in humans are required to draw more robust conclusions.

Keywords

Xanthohumol, Hyperlipidaemia, Obesity, Type 2 diabetes mellitus

Abbreviations

AMPK: AMP-Activated Protein Kinase; DXN: α, β-dihydro-XN; FXR : Farnesoid X Receptor; HDL: High Density Lipoprotein; HFD: High Fat Diet ; LDL: Low Density Lipoprotein; PK: Pharmacokinetics; PCSK9: Proprotein Convertase Subtilisin/Kexin Type 9; TXN: Tetrahydro-XN; SREBP-1c: Sterol Regulatory Element-Binding Transcription Factor 1; VEGFR-2: Vascular Endothelial Growth-Factor Receptor; XN: Xanthohumol

Introduction

The increase in lifestyle-related diseases such as diabetes, obesity, hyperlipidaemia and cardiovascular diseases have become an increasing social and

economic problem in developed countries. Obesity is a well-recognized risk factor for the occurrence of dyslipidaemia, hypertension, and type 2 diabetes mellitus (T2DM) [1], thus, prevention or improvement of obesity is key in preventing these other diseases. Diet and food supplements are of increasing interest in view of their potential in obesity management. Xanthohumol (XN) is a prenylated flavonoid found in hops, a well-known medicinal plant. Traditional medicinal indications included the treatment of anxiety and insomnia, as well as treatment for mild pain and dyspepsia [2]. Hops are commonly used in the manufacturing of beer and plants such as *Humulus lupulus* L, are grown for their brewing properties. In the brewing process it is the biologically active substances concentrated inside the hops which are important and these include the hop resins, bitter acids, essential oils and prenylated flavonoids. XN has also been demonstrated to enhance lipid and glucose metabolism in KK-A(y) mice [3]. XN additionally inhibits metabolic activation of food-borne carcinogens [4], as well as inducing enzymes related to detoxification of xenobiotics [5]. XN also inhibits prostaglandin and nitrous oxide pathways associated with carcinogenesis [6-8] and demonstrates anti-tumor activity in hypoxic tumour cells [9]. XN affects the metabolic pathway involving diacylglycerol acyltransferase (DGAT) and microsomal triglyceride transfer protein (MTP) thus enabling a reduction of triglyceride and apolipoprotein B [10, 11]. Doses of 30-300 mg/kg of xanthohumol (70-90% purity) have been given in animal studies achieving plasma concentration of 5-20 uM (3, 5, 21, 22, 24). Beer is the predominant dietary source of XN in humans, however the concentration of XN within beer depends on the type (range 0.052-0.628 mg/l) [12], meaning that beer cannot provide similar doses to hop extracts or pure xanthohumol.

Furthermore, there has been recent attention to the benefits of hop extracts in women due to their estrogenic as well as chemopreventive properties. Hop extracts have thus been utilised as dietary supplements and even proposed as an alternative to hormone replacement therapy for the management of menopausal flushing [13]. XN is reported to exert anti-proliferative activity against breast, colon and ovarian cancer cell lines by inducing chemopreventive enzymes which regulate the antioxidant response element [14, 15]. In a recent study of menopausal women, once daily consumption of a standardized preparation of hops was shown to be safe. Xanthohumol and the other prenylated phenols have long half-lives but no acute toxicity [16].

Herein, we review the potential beneficial role of XN in hyperlipidaemia, obesity and T2DM.

Materials and Methods

A bibliographical search was performed in PubMed and Cochrane for the Mesh terms xanthohumol and; hyperlipidaemia; obesity; type 2 diabetes mellitus. Reference lists from the selected studies were manually searched to identify additional relevant reports. Only papers published in the past 15 years were assessed. Non-English language papers were excluded. A total of 28 papers were reviewed and 18 met the criteria for final consideration.

Xanthohumol and hyperlipidaemia

Atherosclerosis is associated with cardiovascular disease. Lowering low-density lipoprotein (LDL) cholesterol has been shown to reduce cardiovascular disease morbidity and mortality by 20%-40%, although a residual risk still remains [17].

There is evidence from *in vitro* and *in vivo* animal studies that XN might exert beneficial effects in hyperlipidaemia.

In vitro studies: *In vitro* studies have shown that XN decreases apolipoprotein B (apoB) secretion, inhibits triglyceride (TG) synthesis and prevents LDL oxidation [18]. XN at doses of 20-25 umol/l inhibits diacylglycerol acyltransferase (DGAT) activity or expression as well as microsomal triglyceride transfer protein thus reducing TG levels in HepG2 cells [11]. In a study of adipocytes, incubation with XN 25-100 uM resulted in a reduction of lipids and decreased adipocyte marker [19]. The molecular mechanisms through which XN exerts its anti-lipogenic effect are still not completely understood.

In vivo studies: Nozawa et al., demonstrated that XN activated the farnesoid X receptor (FXR), with modulation of genes involved in lipid and glucose metabolism resulting in the lowering of plasma glucose as well as plasma triglycerides and hepatic triglyceride [3]. XN has also been shown to reduce aortic atherosclerotic plaque formation by reducing lipogenesis and increasing faecal cholesterol excretion in apolipoprotein (apoE)-deficient mice [20]. Moreover, in a transgenic mouse model XN increased HDL cholesterol via cholesteryl ester transfer protein (CETP) inhibition [21]. Hirata et al., recently investigated the effects of XN on reverse cholesterol transport and HDL cholesterol levels using a hamster model. They showed that XN improves the cholesterol efflux capacity of HDL and increased reverse cholesterol transport from macrophages to faeces. Hamsters, like humans, express CETP, and appear to have a similar RCT system and so this mechanism could potentially translate to benefit in humans [22].

Another group demonstrated that the addition of XN to a western-type diet also inhibits atherosclerotic plaque formation in ApoE-/- mice by improving plasma cholesterol and monocyte chemoattractant protein 1 (MCP-1) concentrations [20].

Summary*: There is evidence that XN might exert beneficial effect in hyperlipidaemia. Daily intake of xanthohumol enhances HDL metabolic pathways as well as reducing lipogenesis, leading to protection against atherosclerosis. However, further studies in humans are required to draw more robust conclusions.*

Xanthohumol and obesity

The increase in cases of obesity has become a serious social problem in developed countries especially as obesity is increasingly causally related to the development of many diseases, for example, type II diabetes, hypertension, cardiovascular disease, as well as cancer [23, 24]. Obesity most frequently occurs when energy intake from food exceeds energy expenditure [25, 26]. There are two functionally and

morphologically distinct types of adipose tissue: white adipose tissue (WAT) and brown adipose tissue (BAT) the latter being associated with control of a better metabolic profile and the body's ability for thermogenesis. In certain circumstances WAT has the ability to gain BAT features thus leading to improved metabolism as well as thermogenesis [27, 28].

In vitro studies: In a study of adipocytes and primary human subcutaneous preadipocytes, addition of XN 6.25-25 uM demonstrated anti-obesity potential by stimulating conversion of WAT to BAT via MAPK signalling pathways as well as decreasing adipogenesis and promoting lipolysis [29]. Such findings were also confirmed in adipocytes by Yang et al., at 25-100 uM [19]. However, Mendes et al., reported that XN up to 50 uM may reduce adipocyte number, but that this resulted in adipocyte hypertrophy without an improvement in metabolic profile [30].

In vivo studies: XN has been shown in many animal models to have anti-obesity properties [3, 31-34]. Miranda et al., demonstrated in a mouse model with a high fat diet, that XN 30-60 mg/kg was able to lower plasma LDL by 80%, interleukin-6 by 78%, as well as other pro-lipid enzymes also reduced by more than 40% compared to control [34]. The same group found that XN and its hydrogenated derivatives α, β-dihydro-xanthohumol (DXN) and tetrahydro-xanthohumol (TXN) improved glucose tolerance as well as cognitive function in mice fed with high fat diet. The study suggested beneficial effects of DXN and TXN in obese mice, fed high fat diet, with metformin associated neuro-metabolic impairments, without risk of liver injury and adverse estrogenic effects [35].

The anti-obesity properties of XN up to 10 mg/ml was shown in another animal study to be due to its positive effect on lipid metabolism as well as inhibition of intestinal fat absorption [36]. Studies demonstrating the anti-hyperlipidaemia effects of 1% XN-rich extract also showed suppression of increased weight compared to controls including decreased liver weight, as well as plasma triglycerides via effect on hepatic fat metabolism as well as inhibition of intestinal fat absorption [32].

Summary: *There is pre-clinical evidence that XN exerts its anti-obesity effect by decreasing adipogenesis and inducing lipolysis as well as inhibiting intestinal fat absorption however human studies are needed.*

Xanthohumol and type 2 diabetes mellitus

The prevalence of T2DM, which is often associated to obesity, has hugely increased over the last decades. T2DM has a multi-factorial etiopathogenesis, which affects more than 300 million people worldwide. Hyperglycemia secondary to a deficiency in insulin production and/or its resistance characterizes diabetes and contributes to endothelial dysfunction, leading to both macro and micro-vascular complications [37, 38]. Abnormal neovascularization is a feature in chronic T2DM.

In vivo studies: Costa et al., reported that XN consumption 10 mg/l reduced angiogenesis, vascular endothelial growth-factor receptor (VEGFR)-2 expression and activity, and also reduced levels of VEGF-B and its receptors (i.e. VEGFR1 and neuropilin-1), VEGF-A as well as endothelial markers in T2DM mice [39]. Altogether, these findings suggest that XN may have a preventative effect on neovascularisation and the associated pathways seen as complications in T2DM. Another study by Costa et al., found that XN protects mice against the development of T2DM metabolic-related complications. XN at 10 mg/l was reported to reduce body weight gain, prevent insulin resistance and benefit the metabolism of lipid and glucose mediated by a metabolic switch from fatty acid synthesis to oxidation and by promoting muscle glucose uptake [40]. Furthermore, Nozawa et al., showed XN (1% purified) fed KK-A(y) mice exhibited lowered levels of plasma glucose. The hepatic gene expression of XN-fed mice showed lowered levels of SREBP-1c including its targets involved in fatty acid synthesis and lowered levels of gluconeogenesis genes [3].

Summary: *Studies have shown promising results for XN as therapy or for prevention of T2DM via the decrease of body weight gain, the prevention of insulin resistance and the modulation of glucose metabolic pathways. However, further studies in humans are required to draw more robust conclusions.*

Evidence in humans

Legette et al., conducted a study in healthy men and women to determine the pharmacokinetic (PK) parameters for XN in order to both establish dose-concentration relationships and to define dose-effect association in humans with a confirmed diagnosis of metabolic syndrome. Doses of oral Xanthohumol 20 mg, 60 mg, or 180 mg were given to men and the PK studies showed a distinct biphasic absorption pattern for XN with isoxanthohumol conjugates being the major circulating metabolites [41]. Another PK study in menopausal women confirmed that short-term consumption of a chemically and biologically standardized preparation of spent hops supplying 21.3 mg to 85.2 mg XN/d is safe for women and that once daily dosing might be appropriate [16]. XN metabolism appears to be similar in both animals and humans, which therefore enables confidence in translating animal study discoveries to future human clinical studies. Based on these and previous findings, clinicians could predict effective XN doses for use in clinical studies with the potential to improve lipid and glucose metabolism in humans affected from metabolic syndromes [16, 41, 42].

Conclusion

The prevalence of obesity and T2DM has hugely increased over the last decades and is a significant social and medical issue. The associated metabolic and disease sequelae are a burden to the individual as well as society despite improved medical treatment options. Accordingly, lifestyle modification and improved pharmacological preventive and therapeutic approaches are needed.

Various dietary ingredients are gaining attention due to their possible effect on obesity management. XN has been shown to exert antioxidative, chemopreventive, and anti-inflammatory effects. *In vitro* and *in vivo* studies (i.e. animal

studies) show promising results for XN in the prevention and treatment of hyperlipidemia, obesity and T2DM. Daily intake of XN might protect against atherosclerosis by improving HDL function. Furthermore, XN might exert anti-obesity effect by inducing efficient fat metabolism, decreasing adipogenesis and inducing lipolysis. Finally, XN may reduce body weight gain, prevent insulin resistance and modulate glucose metabolic pathways. XN food supplements are of great interest as a 'nutritional therapy' however, despite a large body of *in vitro* and more recently *in vivo* animal studies, there is no long term safety data in humans. Thus further clinical trials in humans are required to draw more robust conclusions.

Conflict of Interest

MC is medical advisor to a food supplement company, ProfBiotics™, TW is also nutrition advisor to ProfBiotics™.

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