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Hypotensive effects of genistein: From chemistry to medicine

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ABSTRACT

Genistein (4′, 5, 7-trihydroxyisoflavone), a naturally occurring flavonoid characteristic of Leguminoseae plants, is a phyto-oestrogen exerting oestrogenic activity as both an agonist and an antagonist substance. A large body of evidence suggests that genistein possesses many physiological and pharmacological properties that make this molecule a potential agent for the prevention and treatment of a number of chronic diseases. Growing evidence suggests that genistein could act as a vasodilating, anti-thrombotic, and anti-atherosclerotic agent, exerting these effects through different mechanisms of action. This paper aims to review data from the literature assessing the beneficial effects of genistein on hypertension, one of the most important cardiovascular disease risk factors along with hyperglycemia and hyperlipidemia. In addition, we discuss the chemistry, main sources and bioavailability of genistein. Scientific findings support genistein's potential as a promising anti-hypertensive agent in different experimental models. However, clinical trials are very limited and more research will be required before genistein intake can be recommended as part of therapies targeting raised blood pressure.

Contents

1. Introduction

Hypertension is defined as systolic and/or diastolic blood pressure higher than 140/90 mmHg, respectively [1]. It is considered a

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major cardiovascular risk factor, along with obesity, diabetes, and high blood lipids, causing stroke, myocardial infarction, cardiac and renal failure, and blindness [2,3]. World Health Organization statistics for 2014 reported that about 40% of adults (age $\geq$ 25 years) suffer from raised blood pressure, with lowest prevalence in high-income countries (35%), where hypertension is controlled with drug treatment and non-pharmacological interventions [4]. Raised blood pressure was estimated to be responsible for 9.4 million deaths worldwide in 2010, with approximately 45% of these deaths being due to heart disease and 51% due to stroke [5,6]. The increase in hypertension registered over recent years, especially in regions such as Africa (prevalence of 46%) where hypertension is often left untreated, is caused by increasing population growth and aging [7,8]. Nevertheless, hypertension should not be seen as an inevitable consequence of aging, because in the majority of cases the causes of hypertension are unknown.

Epidemiological and randomized clinical trials have shown that a 10 mmHg decrease in systolic blood pressure decreases cardiometabolic mortality by 41–46%, reduces chances of stroke by 41%, and decreases coronary heart disease by 22% [9,10]. Therefore, prevention and control of hypertension is a crucial aspect to reduce the incidence of cardiovascular disease. Raised blood pressure can first be decreased through modifiable behavioral risk factors (e.g. tobacco use, harmful alcohol use, physical inactivity, and unhealthy diet) and then with pharmacological approaches (i.e. treatment with anti-hypertensive drugs) [11].

An unhealthy diet is characterized by a high intake of salt [12] and fats, especially trans fatty acids [13], and low consumption of fruits and vegetables. Two recent meta-analyses published in 2016 have assessed the role of fruit and vegetable consumption on hypertension risk. In 2016, Wu et al. verified the association between fruit and/or vegetable intake and the risk of developing hypertension, including seven articles comprising nine cohorts involving a total of 185 676 participants. These results showed that a high intake of fruit, vegetables, or a combination of the two, decreased the incidence of hypertension [14]. The other meta-analyses published in 2016 by Li et al. evaluated 25 studies with 334 468 patients. Here too, results showed that hypertension risk decreased with the consumption of fruit and vegetables. The authors ascribed the protective role of fruit and vegetables to their high content of minerals (such as potassium and magnesium), vitamins and provitamins (vitamin C, folic acid, and carotenoids), and polyphenols such as flavonoids, which decrease oxidative stress and improve blood pressure by the improvement of endothelial function, modulation of baroreflex sensitivity and induction of vasodilation. In addition, a diet rich in fruit and vegetables includes foods rich in dietary fiber and with low fat content [15]. A growing body of evidence suggests that certain nutrients (such as soy proteins) and minor food components exert positive effects against endothelial dysfunction, which in turn is a risk factor for hypertension [16–18].

Of the polyphenols, isoflavones are one of the main groups of flavonoids. They occur almost exclusively in leguminous plants, especially soyabean (Glycine max (L.) Merr., and *Trifolium* species. The main isoflavone compounds are genistein and daidzein, known as phyto-oestrogens due to their resemblance to oestradiol and their oestrogenic activity, as both an agonist and antagonist substances.

A large body of evidence suggests that genistein possesses many physiological and pharmacological properties, ranging from antioxidant, antimutagenic and anticancer activities to cardioprotective and immunomodulatory capacities that make this compound a potential agent for the prevention and treatment of a number of chronic diseases, including cardiovascular diseases and cancer [19–24]. Numerous investigations, published over the last decade, have studied the mechanisms of action by which genistein exerts its beneficial effects on human health, showing that genistein acts as an immunosupressor agent and inhibits topoisomerase-II, an enzyme required for the recognition of double stranded breaks in DNA [25,26]. This latter property is associated with the potential anticancer activity ascribed to genistein. In fact, a growing body of evidence suggests that genistein and daidzein intake is associated with a decreased incidence of prostate cancer in humans through the reduction of androgen testosterone levels and inhibition of tumor development [27]. Moreover, recent studies support the role of genistein in the suppression of breast cancer via the competition of phyto-oestrogen with natural oestrogens, lowering their bioavailability and thereby inhibiting cancer cell growth [28]. The anti-cancer activity of genistein concerns mainly but not only hormone-dependent cancers.

In addition, genistein was found to reduce platelet aggregation and to act on eNOS transcription inducing the synthesis of NO at physiological concentrations, exerting vasodilation, anti-inflammatory, anti-atherogenic and anti-thrombotic activities [29–31].

Thus, considering the potential health benefits of genistein exerted through different mechanisms of action on the cardiovascular system, the aim of this review is to collect literature data regarding the potential hypotensive effects of genistein. In addition, this paper aims to review the chemistry, sources and bioavailability of genistein to provide a broad spectrum on this bioactive natural product.

2. Chemistry

Genistein (4′, 5, 7-trihydroxyisoflavone) (Fig. 1) has the same phenolic ring base and distance between the 4'- and 7'- hydroxyl groups as 17β-estradiol, a potent estrogen [32,33]. These characteristics confer it the ability to bind to sex hormone binding proteins and estrogen receptors [32]. As this would suggest, it possesses strong estrogenic activity, and thus is considered to be a phytoestrogen [34,35]. Pure genistein ($C_{15}H_{10}O_5$) is a white powder insoluble in water and soluble in dimethyl sulfoxide with a molecular weight of 270.239 Da, a melting point at 301.5 °C, a log P (octanol-water) of 2.840 and an atmospheric OH rate constant of 2.31 E^{-10} cm^3/molecule-sec at 25 °C (ChemIDplus advanced and http://chem.sis.nlm.nih.gov/chemidplus/name/startswith/genistein). Genistein also has structural similarities with tamoxifen, a compound used as chemopreventive in women with increased risk of breast cancer, and with equol, a dietary isoflavonoid metabolite formed by gastrointestinal flora [32]. Besides the estrogenic activities of genistein, it can also contribute antiestrogenic activities by competitively binding to the same receptors as estradiol [32].

In plants, isoflavones such as genistein can promote symbiosis with rhizobacteria in order to defend the plant against pests and pathogens [36].

3. Sources

Genistein is a precursor of antimicrobial phytoalexins (synthesized following pathogen infection) and phytoanticipins

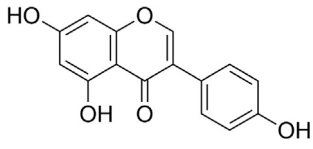

Fig. 1. Chemical structure of genistein (CAS 446-72-0).