·综述·

异黄酮的医用价值

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[摘要] 异黄酮是广泛存在于豆类植物中的植物雌激素,能够调整人体的内分泌功能,防治妇女更年期综合征,降低血脂,减少冠心病的发生,防治骨质疏松症,抗癌,并能止痛消肿。本文总结了近年来有关异黄酮医用价值研究的成果。
[关键词] 异黄酮类; 冠状动脉心脏病; 骨质疏松; 更年期综合征; 癌症; 镇痛药; 消炎药
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Medical value of isoflavones

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[ABSTRACT] Isoflavones as a kind of phytoestrogen exist in soy plant widely . With the advantages of estrogen, they can regulate endocrine function of the human body, reduce blood cholesterol, decrease the incidence of coronary heart disease, prevent osteoporosis, inhibit tumor growth, and relieve pain . This article summarized the investigations on the medical value of isoflavones in recent years .
[KEY WORDS] isoflavones; coronary heart disease; osteoporosis; menopause syndrome; cancer; analgesics; anti-inflammatory agents

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① 异黄酮是存在于豆类植物中的一类植物雌激素,具有类雌激素或抗雌激素样作用,被称为天然的选择性雌激素受体调节剂,对人体健康起重要保护作用。异黄酮有调整人体内分泌功能、防治妇女更年期综合征、降低血脂、减少冠心病的发生、防治骨质疏松症和抗癌等作用,并能止痛消肿。本文总结近年来有关异黄酮医用价值研究的成果。

1 冠心病

冠心病是绝经后妇女的“第一杀手”,亚洲居民冠心病的发病率远低于西方人,流行病学调查研究表明,这与亚洲居民习惯摄入豆类食品有关[1],大豆异黄酮在豆类植物中含量丰富,大量研究表明异黄酮可以降低冠心病的发生率。

1.1 降低血脂 Anthony 等[2]将猕猴分为 3 组:酪蛋白组、异黄酮大豆蛋白组、不含异黄酮大豆蛋白组。14 个月后发现,与酪蛋白组比较,异黄酮大豆蛋白组的低密度脂蛋白和极低密度脂蛋白分别下降了 30% 和 40%,而高密度脂蛋白上升了 50%,3 组中异黄酮大豆蛋白组的冠状动脉硬化发生率最低。Crouse 等[3]进行了一项有 94 名男性和 62 名女性参加的临床试验,受试者被分为酪蛋白组、不含异黄酮大豆蛋白组、异黄酮大豆蛋白组,其中异黄酮大豆蛋白组又分为 25 mg、42 mg、58 mg 3 组,结果发现随着异黄酮剂量的增大,受试者的总胆固醇及低密度脂蛋白逐步下降,尤以异黄酮 58 mg 组的作用最为显著。Potter 等[4]的临床试验也得出了同样的结论。

1.2 防止动脉硬化 1998 年 Anthony 等[5]报道经过 3 年临床观察,含异黄酮的大豆蛋白可以明显减少动脉粥样斑块的形成,而低密度脂蛋白氧化是动脉粥样硬化发生中的一个重要过程。Tikkanen 等[6]发现异黄酮可以阻止低密度脂蛋白的氧化。染料木黄酮(genistein)可与动脉血管壁上的雌激素受体结合,直接抑制血管内皮增生,减少动脉硬化的产生[7]。此外,低浓度的 genistein 能够抑制酪氨酸激酶的活性,防止血小板的活化和聚集,减少血栓形成[8,9]。

1.3 改善动脉顺应性 动脉顺应性是冠心病的危险指标。Nestel 等[10]报道绝经前及绝经后妇女每天摄入 80 mg 异黄酮 5 周后,全身动脉顺应性改善了 26%。

1.4 降低血压 Washburn 等[11]报道绝经后妇女服用异黄酮 34 mg/ 次,2 次/ d,连续 6 周后,舒张压

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有所降低。West 等[12] 进行的临床观察表明,与酪蛋白组比较,40～55 岁的男性摄入异黄酮 60 mg/ d 可以降低舒张压。

2　骨质疏松症

骨质疏松症被称为“悄无声息的杀手”,髋部骨折是其最严重的并发症。流行病学调查表明,亚洲地区居民的髋部骨折率明显低于西方国家。人们对异黄酮防治骨质疏松症的功效和机制进行了一系列的研究。

2 .1　体外细胞培养　生理情况下,成熟的骨组织不停地进行改建,以适应体内外的环境变化。成骨细胞和破骨细胞是骨重塑的主要角色。Yoon 等[13] 报道 genistein 可以刺激成骨细胞增殖,增加碱性磷酸酶的活性和胶原的合成。Chen 等[14] 研究发现异黄酮可以抑制成骨细胞分泌白细胞介素 6 而刺激骨保护素表达的增高。白细胞介素 6 和骨保护素分别是骨吸收和骨形成的重要因子,说明异黄酮可以通过成骨细胞来调节破骨细胞的功能。在体外,异黄酮能够抑制破骨细胞形成、分化和吸收的活性[15～17],促进其凋亡[18],从而抑制骨的吸收。

2 .2　动物实验　1995 年 Anderson 等[19] 报道 genistein 对骨的作用具有两相性。他们以去卵巢的生长期和哺乳期大鼠作为研究对象,genistein 的干预量分别为 1 .0、3 .2、10 mg/ d。结果发现,生长期及哺乳期大鼠分别喂药 2 周和 5 周后,最低剂量 genistein 能有效地阻止去卵巢引起的骨量流失,与雌激素功能相近,而中、高剂量却不能够。1996 年 Arjmandi 等[20] 研究大豆蛋白对大鼠骨质疏松模型骨密度的影响。他们将 SD 大鼠随机分为 4 组:(1)假手术组;(2)去卵巢加酪蛋白组;(3)去卵巢加大豆蛋白组;(4)去卵巢加雌激素组。结果表明:右股骨骨密度以雌激素组为最高,而酪蛋白组最低,大豆蛋白组的骨密度低于假手术组及雌激素组,却显著高于酪蛋白组。大豆蛋白组第 4 腰椎的骨密度与雌激素组相似,显著高于酪蛋白及假手术组。该实验表明大豆蛋白对松质骨有较好的保护作用。1998 年 Arjmandi 等[21] 用相同模型,进一步阐明了大豆蛋白中所含异黄酮与其骨保护作用的关系。异黄酮含量高的大豆蛋白能够提高大鼠股骨密度,而异黄酮含量低的大豆蛋白则无效,说明大豆蛋白对骨的保护作用与其中异黄酮的含量有关。Ishida 等[22] 报道大鼠灌喂 daidzein 和 genistein 50 mg · kg^{-1} · d^{-1} 4 周后,能有效防止去卵巢引起的股骨密度、强度、灰重及钙磷含量的下降。Fanti 等[23] 给去卵巢大鼠皮下注射 genistein 后发现,每周 5 μg/ g 和 25 μg/ g 能显著改善骨量的减少,而每周 1 μg/ g 则无此效果。

2 .3　临床试验　1998 年 Potter 等[4] 报道了大豆异黄酮对绝经后妇女骨密度及骨矿含量的影响。实验采用随机双盲对照设计,66 名绝经后妇女分为 3 组,其中 2 组服用含有不同剂量异黄酮的大豆蛋白(40 g/ d)。低剂量组每克大豆蛋白含 1 .39 mg 异黄酮;高剂量组每克大豆蛋白含 2 .25 mg 异黄酮;另 1 组服用酪蛋白及脱脂奶粉。实验共进行 6 个月。结果发现,高剂量组妇女腰椎骨密度及骨矿含量上升,低剂量组保持不变,而酪蛋白组下降。Alekel 等[24] 报道经过 6 个月的随机双盲临床实验,发现大豆异黄酮能够防止围绝经期妇女腰椎骨矿含量及骨密度的下降,而大豆蛋白则不能。最近丹麦学者进行的一项为期 2 年的临床试验发现,异黄酮可以防止绝经期妇女腰椎骨密度的下降[25]。香港大学的 Mei 等[26] 对 650 名中国南方妇女进行的调查表明,与习惯性低异黄酮饮食者比较,高异黄酮饮食妇女的绝经后骨转换率低,腰椎及髋部骨密度高。

3　更年期症状

3 .1　潮热　流行病学资料显示,异黄酮含量丰富的膳食可以减少更年期的潮热症状,在西方国家潮热的发生率为 80%,而在中国为 20%[27]。Albertazzi 等[28] 进行了一项有 104 名绝经后妇女参加的随机对照双盲平行多中心临床试验,第 1 组病人服用含异黄酮的大豆蛋白,第 2 组病人服用酪蛋白, 12 周后发现第 1 组与第 2 组比较,潮热的次数明显减少。Upmalis 等[29] 的双盲对照临床试验结果则发现异黄酮可以减轻潮热的程度。

3 .2　阴道干涩　Dalais 等[30] 进行的双盲随机对照临床试验表明,异黄酮能够促进阴道细胞的成熟,改善阴道的干涩状况。

4　癌　症

流行病学调查表明,东方居民乳腺癌、前列腺癌和结肠癌等的发病率比西方居民要低得多,这与东方人习惯摄入植物性尤其是豆类食品有关[31]。

4 .1　异黄酮抗癌机制　genistein 抗癌的功效及机制是研究的热点。大量研究显示,genistein 能够在分子水平发挥多途径的防癌抗癌作用。genistein 能够抑制酪氨酸激酶的活性,调节蛋白磷酸化,从而阻碍生长因子与受体结合后的信号传导,影响肿瘤细胞的生长增殖[32]。genistein 能够抑制 DNA 修复酶-拓扑异构酶 Ⅱ[33],具有抗氧化作用[34],能阻止 DNA 的氧化损伤。genistein 能促进细胞分化从而

预防癌症的发生[33]。genistein 抑制肿瘤内新生血管的生成,使肿瘤组织生长受阻[35]。此外,genistein 在体外可以升高转化生长因子β的浓度,抑制肿瘤的生长[36]。genistein 发挥上述功能的有效浓度为 5～100 μmol/L,远高于正常人体受试者的血浆浓度(约 0.4 μmol/L)。

4.2 乳腺癌 乳腺癌是妇女最常见的肿瘤之一,遗传因素占其发病原因的 10%～15%,环境因素例如化学物质、营养、生活方式等是发病的主要原因。1991 年 Lee 等[37]报道,经常食用豆制品的亚洲妇女乳腺癌患病率低。在体外,genistein 可以抑制乳腺癌细胞系的增殖[38,39]。Coral 等[40]研究发现,genistein 可以上调未发育成熟大鼠乳腺上皮细胞的因子表达,从而促进细胞分化,预防乳腺癌的发生,而在出生前及成年后进食 genistein 并无抗癌作用。因此,何时接触 genistein 至关重要。乳腺癌的发生很大程度上取决于卵巢激素水平及月经周期的长短。临床研究表明,genistein 可以升高绝经前妇女的性激素结合球蛋白,降低血中游离的雌激素水平,从而延长月经周期,降低患乳腺癌的机率。

4.3 前列腺癌 在体外,genistein 能够抑制前列腺癌细胞的生长[41],并可抑制生长因子引起的前列腺癌细胞系的增殖,产生这种效应的 genistein 的浓度需大于 50 μg[42]。在不同的大鼠前列腺癌模型中,genistein 均可抑制肿瘤生长,减少肿瘤数量和减小肿瘤体积[43～45]。最近的一项临床试验结果显示,前列腺癌患者服用 genistein 6 个月可以降低前列腺特异性抗体的水平,表明其可用来稳定前列腺癌患者的病情[46]。

5 止痛消肿

异黄酮具有抗炎作用,能够抑制胃肠道炎症[47],减少绝经后妇女骨关节炎的发生[48]。其中槐苷能同时抑制由巴豆油诱导的大鼠耳水肿和交叉胶引起的爪水肿[49],以 20 $mg \cdot kg^{-1} \cdot d^{-1}$ 给大鼠腹膜内注射,可明显抑制炎症过程中的增生及渗出[50],在槐苷、染料木苷和染料木素中,槐苷作为白细胞介素 5 的抑制剂,显示了最高的抑制活性[51]。这种止痛消肿作用对治疗骨质疏松症显然是有益的。

6 其他功效

除上述疾病外,人们发现异黄酮还可减缓中枢神经的退化,增强记忆,从而预防和治疗阿尔茨海默病等老年痴呆症[52,53];异黄酮可以减少由紫外线引起的皮肤细胞 DNA 的损伤,具有抗氧化的作用,能有效地清除氧化自由基以保护皮肤[54,55]。

7 安全性

随着研究的逐步深入,人们越来越关注异黄酮是否会对人体尤其是对婴幼儿产生不利的影响。Strom 等[56] 2001 年发表在 JAMA 上的文章表明,婴幼儿进食含有异黄酮的食品不会影响他们成年后的健康。男性服用异黄酮后,血中性激素水平及精子质量没有改变[57]。异黄酮对子宫内膜无明显刺激作用[58]。genistein 虽能够抑制甲状腺过氧化物酶的活性,但由于存在其它酶的代偿作用,因此并不产生甲状腺功能的低下[59]。最近,美国的一项研究表明,genistein 能够抑制鼠的胸腺,减少血中 T 淋巴细胞的数量,由此推断 genistein 可能影响婴儿及成人的免疫功能,由于种属的不同,这种假说尚待进一步的研究证实[60]。

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