Innovative nutritional prevention of osteoporosis : the polyphenol fisetin sustains bone health by controlling osteoblasts and osteoclasts differentiation

Laurent Léotoing[1], Jérôme Guicheux[2], Elisabeth Miot-Noirault[3], Yohann Wittrant[1], and Véronique Coxam[1]

-1.INRA, UMR 1019, UNH, CRNH Auvergne, F-63009 CLERMONT-FERRAND, FRANCE. Clermont Université, Université d'Auvergne, Unité de Nutrition Humaine, BP 10448, F-63000 CLERMONT-FERRAND, FRANCE

-2.Inserm, UMRS791, LIOAD, group STEP, F- 44042 NANTES, FRANCE. PRES LUNAM, Université de Nantes, UFR Odontologie, 1 Place Alexis Ricordeau, F- 44042 NANTES, France

-3.Inserm, UMR 990, F-63000 CLERMONT-FERRAND

Contact : UMR1019 INRA Université d'Auvergne – Unité de Nutrition Humaine - 63122 Saint Genès Champanelle, France – E-mail : veronique.coxam@clermont.inra.fr- Phone +33 (0)4 73 62 46 32 (+33 (0)6 32 32 09 92)

With the continuing demographic shift in population toward an older society, all industrialised countries face a growing prevalence of chronic age-related conditions. Among those diseases, impaired capacities of movement due to osteoporosis, are especially disabling. Indeed, osteoporosis is a major public health problem characterized by a reduced bone mass and disruption of bone architecture, resulting in increased bone fragility. While the social and economic burden of the disease is growing at an alarming rate, health professionals deplore the lack of prophylactic tools and the fact that only 10% of women with fragility fractures receive any osteoporosis therapy due to several side effects. Moreover, the poor access to treatments is compounded by poor adherence. This is why the authorities and the public health systems strongly advocate implementing new strategies of proven scientific value.

In this context, a growing body of evidence has contributed to stress the importance of nutritional preventive measures for bone health. However, so far, research has been limited to calcium and vitamin D. Consequently, the present work sought to develop an innovative science-based nutritional approach targeting new pathways involved in bone loss. We thus considered the putative interest of a new concept based of nutrients endowed with both antioxidant and anti-inflammatory properties. Using molecular and preclinical approaches, we demonstrated that a natural molecule, a polyphenol named fisetin, positively modulates bone physiology and prevents estrogen deficiency and inflammation-induced osteoporosis. Indeed, bone mineral density, micro-architecture parameters and bone markers were positively modulated by fisetin.

This very potent compound exhibits a dual role by promoting osteoblast and repressing osteoclast differentiation processes, both *in vivo* and *in vitro*. The complete mechanism of action was deciphered, starting from physiological-based evidences in experimental models to reach the most detailed mediating molecular pathways in bone cells : Consistently, fisetin promotes primary pre-osteoblasts differentiation and activity by stimulating Runx2 transcriptional activity. Moreover, it is able to repress RANKL-induced osteoclast differentiation; fusion and activity, as demonstrated by an inhibition of TRAP activity and differentiation genes expression. The signaling pathways NF-κB, p38 MAPK and JNK induced by RANKL, are negatively regulated by fisetin and key transcription factors such as c-Fos and NFATc1 expressions are decreased as well. Using shRNA stable cell lines, we further demonstrated that the potency of fisetin is mediated through MKP-1, the phosphatase that deactivates p38 and JNK. Thus, fisetin should be further considered as a bone protective agent.

The present work has a major interest for:
-The world of research: innovative scientific concept and strong scientific approach.
-The authorities and the public health systems: highly relevant targeted disease and lack of validated preventive strategies for prevention.
-The consumers: new options for prevention to improve both health and quality of life.
-The industry: very strong science based project in a booming market allowing applying for claims and convenient form of use.