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NUTRIGENOMICS AND BIO-AVAILABILITY ENHANCERS AS A COMBINATION THERAPY FOR MYOSTATIN INHIBITION TO COPE WITH MUSCULAR DYSTROPHY

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Abstract

Nutrigenomics deals with epigenetic changes in human with respect to dietary intake and it can be influenced by Phyto-medicines and herbal drugs. Nutrition related complications are frequently seen in Muscular Dystrophies. Myostatin is an attenuator of skeletal muscle growth and plays a major role in muscular dystrophy, Myostatin inhibitors are being investigated as potential treatments for diseases such as muscular dystrophy. Phytochemicals such as isothiocyanates have potential to inhibit Myostatin, but phyto-drug absorption varies according to molecule structure. Bioavailability enhancers are molecules when used in combination, they enhance the absorption and bioavailability of the drug molecule in Human body. Many phytoconstituents such as Quercetin, Genistein, Piperine and Naringin exhibit bioavailability enhancer property. In this opinion article, we present Nutrigenomics and bioavailability enhancers as one of approach to target muscular dystrophy related diseases.

Keywords*: Nutrigenomics, Bio-availability Enhancers, Combination Therapy, Myostatin, Muscular Dystrophy.*

INTRODUCTION

Dietary intake and the environment are the two major factors affecting the health or illness of an individual. Studies in the nutritional area have increased the understanding of how to maintain healthy a group of individuals that live in different dietary conditions. Epigenomics can be defined as the study of the complete set of epigenetic modifications in a cell or in a tissue at a given time. Nutrition related complications are frequently seen in Neuromuscular Diseases (NMDs), NMDs represent a heterogeneous group of acquired or inherited conditions. Myostatin inhibition has shown to increase muscle mass and therefore might assist attenuating muscle fibrosis which is a hallmark of muscular dystrophy. Sulforaphane an isothicyanate obtained from a plant source has exhibited significant inhibitory action of Myostatin. Recently, there has been a global shift in the use of herbal medicines due to their therapeutic effects and fewer adverse effects. However, many herbal drugs and herbal demonstrate less or negligible in-vivo activity due to their poor lipid solubility or improper molecular size, resulting in poor absorption and hence poor bioavailability. Naringin pretreatment significantly altered the pharmacokinetic parameters of verapamil and the Ka, Cmax and AUC of verapamil were significantly ($p<0.05$ or $p<0.01$) increased in the pretreatment of naringin.

NUTRIGENOMICS

Nutrigenomics is a new branch of '-omics' which focuses on the role of nutrients on the genome,

proteome, and metabolome of Human. Epigenetic markers decides fate and destination of a cell, these are influenced by the surrounding environment, diet, phyto-medicines and determine the phenotype of human. In the present article, we propose Nutrigenomics and bioavailability enhancers as one of approach to target muscular dystrophy related diseases due to their high prevalence worldwide. Nutrigenomics applies molecular tools to search, access, and comprehend how the components of a particular diet (bioactive compound) may affect the expression of genes, which may have increased its potential or which can be suppresse. Nutrigenomics has become the biological tool used to understand gene expression and genome regulation using certain diet.

MYOSTATIN

MSTN, a transforming growth factor β (TGF-β) family member, is a negative regulator of skeletal muscle growth. Genetic mutation in MSTN resulted in increased musculature in vivo in mice, similar cases have been reported in sheep, dogs, cattle and humans. MSTN is present in serum or locally in an inactive state when bound to follistatin or the MSTN propeptide. MSTN is secreted into the extracellular matrix and binds to type Act RII, Ser/Thr kinase receptor. ActRIIB, combines with a type I receptor, either activin receptor-like kinase 4 (ALK4 or ActRIB) or ALK5 (TβRI), to induce phosphorylation of Smad2/Smad3 and activate a TGF-β-like signaling pathway. MSTN prevents Bone Morphogenetic Protein 7 binding to its receptors, suggesting that MSTN is an important regulator of adipogenesis. Attenuation of MSTN activity of antibodies, peptides, or pseudo-ligands have demonstrated to increase muscle mass in mice. MSTN enhances nuclear translocation of β-catenin and formation of the Smad3-βcatenin-TCF4 complex. The expression of myostatin was inhibited by RNAi silencing of β-catenin and over expression of dominant-negative TCF. Over expression of dominant-negative TCF4 inactivated Wnt signaling pathway in preadipocytes; when not inhibited these cells differentiate into adipocytes. Modern pharmacological studies have revealed ability of herbal medicines to enhance the bioavailability of various phytoconstituents and synthetic drugs when incorporated together.

MUSCULAR DYSTROPHY

Cachexia is a life-threatening disease with estimated 1.5–2 million deaths per year. Cachexia is characterized by extreme weight loss resulting mainly from the depletion of skeletal muscle; it has shown connection to Myostatin (MSTN), nuclear factor κB, and dystrophin glycoprotein complex pathway. A study suggests that MSTN is an attenuator of skeletal muscle growth in adult men and plays major role in muscle wasting in HIV-infected individuals. Duchene's muscular dystrophy (DMD) is the most common X-linked neuromuscular disease and is estimated to affect 1 in 3500 newborn males. DMD is characterized by progressive and severe muscle loss that leads to loss of ambulation. One of the approaches to treat DMD includes increasing the strength of muscles (Myostatin inhibitors), reducing muscle fibrosis, and decreasing oxidative stress.

BIOAVAILABITY ENHANCERS

Bioavailability enhancers increases production of digestive juices, thereby stimulating digestion and enhancing bioavailability and bioefficacy of drug. There are many bioavailability enhancers, are being used viz. Curcumin, Diosmin, Embelin, Genistein, Glycyrrhizin, Lysergol, Menthol, (-)-Epicatechin, Naringin, Nitrile glycosides, Peppermint oil Piperine, Quercetin, Sinomenine etc.

are reported to have bioavailability enhancer properties.

NARINGIN

Naringin (C27H32O14) is the major flavonoid glycoside found in grapefruit. Narinigin exerts a variety of pharmacological effects such as antioxidant, blood lipid lowering and anticarcinogenic activities. Also, naringin was reported to inhibit and CYP3A1/2 and P-glycoprotein in rats. Oral naringin was pretreated 30 min before intravenous administration of paclitaxel (3 mg/kg) and after intravenous administration of paclitaxel, the AUC was significantly improved (40.8% and 49.1% for naringin doses of 3.3 and 10 mg/kg, respectively). Hence, we can assume that Naringin can act as bioavailability enhancer and help in uptake of other phytochemicals like Isothiocyanates (ITC). Ayurvedic Medicine has identified more than 300 diseases that could be cured with the different parts of M. oleifera, such as leaves, roots, bark, flowers and seeds. *M. oleifera* is reported to enhance a broad range of biological functions including anti-inflammatory, anti-cancer, hepatoprotective, and neuroprotective functions. In addition, many studies have revealed its therapeutic value including anti-diabetes, anti-rheumatoid arthritis, anti-atherosclerosis, anti-infertility, pain relief, anti-depression, and diuretic and thyroid regulation. Sulforaphane (SFN) and moringin (GMG-ITC) are edible isothiocyanates present as glucosinolate in *Moringa olifera* Lam. Known Sulforaphane (SFN) is ITC obtained from cruciferous vegetables significantly with MSTN inhibitory action.

ITC are derived from naturally occurring, biologically inactive precursors called glucosinolates, via an enzymatic hydrolysis. Myrosinase is physically segregated from glucosinolates in the plant cell and is released upon chopping or chewing, thus, hydrolyzing glucosinolates to a variety of products, including ITCs. Alternatively, if myrosinase has been thermally destroyed during food processing the thioglucosidases in animal and human gut microflora may also hydrolyze consumed glucosinolates to ITCs. Herbal medicines are good source of ITC's such as Allyl isothiocyanate (*Armoracia rusticana* P.Gaertn., *Brassica nigra* (L.) K.Koch, B.Mey. & Scherb and *Eutrema japonicum* (Miq.) Koidz.). Iberin extracted from Brassicaceae family Moringin (*Moringa oleifera* Lam), Phenethyl isothiocyanate (*Nasturtium officinale* R.Br.), and Benzyl isothiocyanate (*Tropaeolum majus* L.). There is great promise for the improvement of muscle performance in livestock and for the therapy of muscle pathologies in humans by the targeting of MSTN in this cell population.

CONCLUSION

Nutrigenomics has opened new dimensions in the field of nutritional science and given insight how food interferes with the genetic code and how the organism responds to these interferences. Personalized nutritional counseling has opened new frontiers not only to change dietary habits, but also to a better diagnostic for certain diseases, and play vital role in the treatment of others. Many allopathic and herbal formulations despite their impressive in vitro findings demonstrate less or negligible in vivo activity due to Poor lipid solubility, improper molecular size; resulting in poor absorption, decreasing its bioavailability etc. Naringin shows promising bioenhancer property for the Nutrigenomics used for treating Muscular dystrophy. This combination in the form of therapy can contribute to Nutrigenomics research and guide development of new tools that can assist on a better quality of life and healthy diet to the population.

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COMPETING INTERESTS
The authors report no conflicts of interest.

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