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PREDICTING THE EFFECTS OF NUTRIENTS AND BIOACTIVE COMPOUNDS ON THE EXPRESSION OF LOW DENSITY LIPOPROTEIN RECEPTOR (LDLR) USING IN SILICO APPROACH

***[1]Ibrahim Suleiman Musa, [2]Hafsat Ibrahim Okuba and [3]Bilkisu Azores Musa**

[1]Department of Animal Science, Nasarawa State University, Keffi, Nigeria
[2]Department of Fisheries, College of Agriculture, Science and Technology, Lafia, Nasarawa State.
[3]Department of Science Laboratory Technology, College of Agriculture, Science and Technology, Lafia, Nasarawa State.

*Corresponding authors' email: dribmazara@yahoo.com

ABSTRACT

The objective of the study was to evaluate the effects of some nutrients and bioactive compounds on the expression of low density lipoprotein receptor using computational method. Low density lipoprotein accounts for 70% of circulating plasma cholesterol which is regulated by low density lipoprotein receptor. The evaluation of low density lipoprotein receptor expression was done using the Nutrigenome Data Base which is composed of manually curated differentially expressed genes from treatments with nutrients and bioactive compounds obtained from nutrigenomic experiments. Significant up regulation in the expression of low density lipoprotein receptor was associated with grape extract, quercetin, rosemary extract, tomato extract and sandal woods. Similarly, down regulation of LDLR expression was associated with yellow onion, cholic acid, gingerol and blackberry extract. It can be concluded that some nutrients and bioactive compounds present a great opportunity for the control of LDLR expression and hypercholesterolemia. Further studies on the use of locally available nutrients for the regulation of LDLR expression and hypercholesterolemia is recommended.

Keywords: Nutrigenomics, Low density lipoproteins, Gene expression, Prediction, Insilico

INTRODUCTION

Low density lipoprotein receptor is a cell surface glycoprotein that mediates the endocytosis of cholesterol rich low density lipoprotein, there playing a key role in cholesterol homeostasis (Nykjaer and William, 2002). Mutations in the LDLR encoding genes result in familial hypercholesterolemia. The plasma levels of LDL is maintained LDLR by endocytosis occurring mainly in the liver. Low density lipoprotein cholesterol receptor binds to ligands on the cell surface, followed by endocytosis of the ligand receptor complex thereby regulating the clearance and homeostasis of cholesterol (Namita and Jayanta, 2010). It is responsible for internalization of plasma LDL cholesterol.

Low density lipoproteins account for 70% of circulating plasma cholesterol which is predominantly regulated by LDLR (Golgstein & Brown, 2009). Regulation of low density lipoprotein receptor expression which is essential for normal cellular function is controlled primarily by sterol regulatory elements. The most important regulatory factor is the intra cellular cholesterol concentration. Serum levels of cholesterol have been attributed to the occurrence of cardiovascular disease. It was observed that total serum cholesterol and concentration of LDL cholesterol was associated with increased cardio vascular disease mortality, while high density lipoprotein cholesterolwas inversely associated with cardiovascular disease (Eujene et al,. 2022). The main function of lipoproteins is to transport fat molecules in cellular fluids. Low density lipoprotein is associated with atherosclerosis following accumulation of LDL cholesterol in the blood (Rose et al,. 2007).

Studies have indicated that nutrition may impact on health status by influencing gene expression and critical metabolic pathways (Panagiotou & Nielsen,2009). Dietary compounds can regulate cellular processes such as gene expression and protein synthesis.

Enhanced expression of low density lipoprotein receptor result in decreased levels of serum low density lipoprotein cholesterol, thereby providing a strategy for the control of hypercholesterolemia. The main objective of this study was to evaluate the effects of some nutrients and bioactive compounds on the expression of low density lipoprotein receptor using computational method.

MATERIALS AND METHODS

The effects of nutrients and bioactive compounds on the expression of low density lipoprotein receptor was evaluated using the Nutrigenome data base. The module is composed of manually curated differentially expressed genes from treatment with nutrients and bioactive compounds obtained from nutrigenomic experiments (Martin et al., 2019). The module can be quarried by multiple gene symbols to obtain differential gene expression values from nutrigenomic experiments. The results are linked to original data sources. Visual expression of specific genes are obtained using interactive line plot. The expression heat map functionality is based on differential expression of profiles built using cluster grammer web based tool using specific java scripts and python libraries (Fernandoz et al., 2017).

Experimental gene expression data was obtained from the data base by launching specific queries. Results were filtered by selecting gene expression data from homo sapiens as described by (Martin et al., 2019). The selection was based on cell assays (human cells) design with at least two replicates per treatment. The repository of nutrigenomic used for evaluation of gene expression patterns is composed of human cells cultured in vitro after treatment with nutrients and bioactive compounds.

RESULTS AND DISCUSSION

The results indicated that Grape extract, Quercetin and Rosemarry extract induced significant up regulation of low density lipoprotein receptor (LDLR) expression whereas, significant down regulation of LDLR expression was induced by blackberry extract, gingerol and cholic acid.

Effects of nutrients and bioactive compounds on the expression of low density lipoprotein receptor is shown in table 1.

Table 1: Effects of nutrients and bioactive compounds on the expression of low density lipoprotein receptor

Log 2 FC	Average expression	R-Value	Nutrient/ Bioactive compound
1.5	4.5	0.039	Grape extract
0.9	6.4	0.001	Quercetin
0.5	9.4	0.001	Rosemarry extract
0.4	8.8	0.008	Tomato extract
0.3	2.6	0.032	Sandal wood
0.2	8.4	0.137	Ishikawa genistein
-0.2	10.1	0.053	Caffeic acid
-0.3	8.2	0.203	Oleic acid
-0.3	11.1	0.036	Yellow onion
-0.3	10.8	0.007	Cholic acid
-0.3	7.6	0.019	Gingerol
-0.4	11.4	0.026	Blackberry extract

Log2 FC=1 when fold change =2

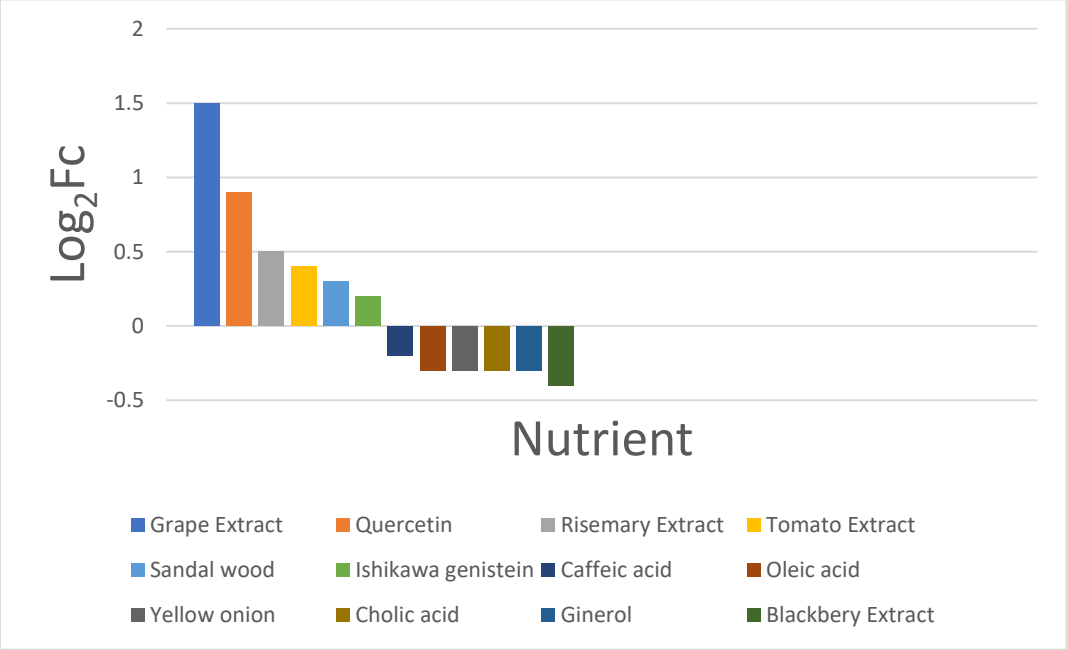

Figure 1: Low density lipoprotein receptor gene expression chart

Discussion

Our findings indicated significant up regulation of low density lipoprotein expression following treatment with grape extract, quercetin, rosemary extract and sandal woods, while significant down regulation of LDLR expression was associated with yellow onion, cholic acid, gingerol and blackberry extract.

Dietary saturated fatty acids in meat and dairy products was reported to increase serum levels of LDL cholesterol and HDL cholesterol resulting from decrease hepatic LDL clearance and increase production of LDL due to decrease in hepatic LDL receptor expression (Feigngold, 2024). Free cholesterol in the endoplasmic reticulum regulate activation of sterol receptor binding proteins (SREB), which enhances the activation of LDLR (Horton *et al* ., 2002). Activation of SREBs is inhibited by elevated cholesterol levels in the endoplasmic reticulum. Esterification of free cholesterol into cholesterol esters result in activation of SREB and up regulation of LDLR expression. Dietary saturated fatty acids have been shown to decrease the formation of cholesterol esters leading to increase free cholesterol which may result in down regulation of LDLR expression (Dietschy, 1998).

Mediteranean diet was reported to result in significant increase in HDL cholesterol levels and a decrease in both LDL cholesterol and triglycerides levels (Estruch, 2006). Polyunsaturated fatty acids appear to have a neutral effect on cardiovascular disease except where it replaces saturated fatty acids resulting in decrease plasma cholesterol leading to decrease cardiovascular events. Poly unsaturated fatty acids also increases cholesterol ester formation thereby decreasing the level of free cholesterol leading to up regulation of LDLR expression. Flavonoids found in green plants are reported to up regulate the expression of LDLR resulting in decrease incidence of cardiovascular disease and improved longevity (Anderson and Markham, 2006).

Coronary heart disease is reported to be a major cause of human mortality globally, extensive studies indicated that cholesterol carrying low density lipoprotein is a significant causative factor (Goldstein and Brown, 2015). Mutations resulting in decrease levels of LDLR are associated with elevated incidence of heart diseases. Arteriosclerotic heart attacks due to occlusion of coronary arteries are linked to elevated levels of low density lipoprotein cholesterol (Lavy, 2012). The incidence of heart diseases can be significantly reduced by lowering the serum levels of low density lipoprotein cholesterol.

Diet is an important lifestyle factor affecting cardiovascular health through body weight and other metabolic pathways.

The beneficial effects of reduced calorie intake, increased consumption of fruits and vegetables and decreased processed meat on cardiovascular health have been documented (Edward *et al*, 2019). Tree nuts and pea nuts are rich in unsaturated fats and bioactive compounds, these include walnuts, almonds and cashews. A consistent negative association between nuts consumption and cardiovascular disease risk have been documented.

CONCLUSION

Up regulation of LDLR expression using nutrients and bioactive compounds present an opportunity in the control of hypercholesterolemia and cardiovascular diseases.

RECOMMENDATION

Evaluating the effects of varying doses of locally available nutrients and bioactive compounds on the expression of low density lipoprotein receptor expression is recommended.

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