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SIGNIFICANCE AND ROLE OF FOXO3 GENE IN HUMAN LONGEVITY AND VARIOUS DISEASES: A SHORT REPORT

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ABSTRACT

The aim of this report is to disseminate scientific knowledge about FOXO3 gene and its activation by phytochemicals. The Fork head box O (FOXO) transcription factor is composed of helix DNA. FOXOs are involved in metabolism, cell cycle arrest, apoptosis, energy, oxidative stress, immunity, inflammation, and stem cell maintenance. Aging symptoms occurs mainly by FOXO associated diseases by SIRT/FOXO signaling Pathway. Its FOXOs family consists of FOXO1, FOXO3, FOXO4 and FOXO6, but all of them are different from each other, among which FOXO3 gene involved in human longevity. FOXO3 proteins manage those genes that are associated with growth factors. To increase health span FOXO3 proteins are engaged in many physiological and pathological conditions like cardiovascular diseases, cancer, diabetes, chronic neurological diseases, and tumor suppressants. Phytochemicals, including polyphenols, seem to have potential for upregulation of the function of FOXO3. The literature for the described study was collected by various research engines like Google Scholar, PubMed, ResearchGate, etc. Our review-based study reveals that Phenols, Polyphenols and terpenoids were found to be effective regulators of the FOXO3 gene for human longevity.

***Keywords*:** FOXO3, Tumor suppressants, Polyphenols, Oxidative stress, DNA.

INTRODUCTION

Different humans have different attributes to human health and physiological condition. Unlike standard treat and symptoms alone, gene therapy addresses the underlying cause of inherited disorders offering a helpful cure **[1]**. Geroprotectors, that target aging-related processes, are becoming more widely acknowledged as a technique to prolong life expectancy in older people **[2]**. The FOXO gene is particularly significant since it is expected to play a significant role in the multifactorial attribute of longevity. The Fork head family of transcription factors, which includes FOXO proteins, serves as a common integration point for a variety of crucial physiological activities. Mammals have been found to contain the FOXO1, FOXO3, FOXO4, and FOXO6 family of FOXOs **[3]**. Scientists study the FOXO3 as a geroprotective gene, which may be crucial for understanding life span and good ageing. The study aims to improve body defenses and potentially provide remedies for various illnesses focusing on general health and life expectancy. Human longevity, lowered

disease risks, and even self-reported health are all associated with FOXO3 genetic variations **[2]**. The FOXO3 gene is located on chromosome 6 in humans **[4]**. According to a survey which is done in Lahore 45 (49.5%) were men and 46 (50.5%) were women there which contain foxo3 gene in Pakistan **[5]**. FOXO3 works via Insulin/IFG-1 signaling system pathway that controls FOXO3 activity through regulating aging rates. To preserve vascular homeostasis and delay vascular aging, FOXO3 is essential. Genes involved in cell cycle arrest, oxidative resistance, apoptosis, autophagy replication, DNA damage repair, and energy metabolism are among its transcriptional targets. Post-translational modifications control FOXO3 activity by modifying its subcellular localization and DNA binding affinity **[6]**. Through the stimulation of autophagy, activation of the Akt/foxo3 signaling pathway prevented oxidative stress-related cell death **[7]**. The function of FOXO3 shown in **[8]** (Figure 1). In this report, we will discuss the evident role of FOXO3 in human health. Foxo3 gene are involved in various pathological and physiological conditions and treats, many diseases like cancer , neurological disease **[9]** and various autoimmune diseases, etc. **[10]**.

METHODOLOGY

Literature search was conducted through electronic databases Google scholar, science direct, Springer, pub-med, sci finder. The search was implemented through key words like "FOXO, foxo3, human longevity, phytochemical". Articles were searched and screened after going through the abstracts of review. After that detailed reviews were done for included articles. The inclusion of articles in this review is based on the significance of foxo3.

RESULTS AND DISCUSSION

The research articles identify the significance of foxo3, Role of FOXO3 in diseases, Table 1 described the phytochemical reactions with the FOXO3 genes. Also, the human longevity through FOXO3 genes was also studied.

Phytochemical reactions with FOXO3 gene

In addition to primary or secondary metabolites, natural extracts, phenols, terpenoids, and other purified natural compounds, with more specific subgroupings of the secondary metabolites theoretically feasible, phytochemicals also aid in the activation of FOXO3 **[2]**. Among above Syringaresinol are polyphenol which also help in treating many diseases by activation of FOXO3 **[11]**. Some phytochemicals may interact with the FOXO3 gene indirectly through their effects on cellular signaling pathways and gene expression. These interactions can impact aging, longevity, and age-related diseases. Here are some examples of phytochemicals that have been studied in relation to the FOX3 gene and its associated pathways as shown in Table 1.

FOXO3 in human health

FOXO3a as a member of the FOXO subfamily of fork head transcription factors which mediate a variety of cellular processes including apoptosis, cell cycle progression, DNA damage, proliferation, and tumorigenesis. FOXO3a is frequently inactivated in cancer cell lines by mutation of the FOXO3a gene or cytoplasmic sequestration of FOXO3a protein. The function

of FOXO3a in both normal physiology as well as in cancer growth have showed a great challenge to preparing an effective therapeutic approach for cancer **[6]**.

Diseases related to FOXO3

FOXO3 plays a vital role in preventing diseases. It also regulates various processes in body such as cell growth, DNA repair and stress management. So, it contributes to longevity and it reduced risks of age associated diseases as shown in (

FOXO3a in disease development

FOXO3a and its role in non-neoplastic diseases

The dysregulation of FOXO3a has been involved in numerous pathological processes. FOXO3a play an essential role in neurological disorders such as Alzheimer's diseases, Parkinson's diseases, motor neuron disease and acute spinal cord injury. FOXO3a is also linked with the development of heart disease, muscle atrophy, and premature ovarian failure.

Effect of FOXO3a in carcinogenesis

It has been observe FOXO3a has a imperative role in apoptosis, cell proliferation, DNA damage and resistance to oxidative stress, and thus its deregulation of FOXO3a is highly related with a series of malignancies **[12]**.

Role of FOXO3a in human longevity

Foxo3a acts as key regulators of longevity by targeting various intracellular pathways involved in DNA repair insulin and insulin like growth factors, oxidative stress, and nutrients into specific gene expression programs. During aging DNA repair mechanisms became less efficient and an unrepaired DNA impairment can trigger genomic uncertainty and induce signaling cascades which leads to cell death. Foxo1 and foxo3 can also suppress members of the pro-growth mechanistic target of rapamycin or mTOR kinase pathway. mTOR is a key pathway of cellular metabolism that regulates cell metabolism by determining whether the cell needs catabolic or anabolic metabolism. Motor pathway has been shown to regulate lifespan through mediating various processes including proteostasis, autophagy, mitochondrial dysfunction, cellular death and decline in stem cell function. Suppression of the mTOR pathway delays the onset of age related pathologies there by increasing the life span and promoting healthy aging **[12]**.

Figure 3 describe the activation of longevity by increasing the expression of FOXO3 pathway

Traditional Chinese herbs, vegetables, and fruits contain phytochemicals that have been identified to control several molecular and signaling pathways. These compounds may one day be used to treat conditions like cancer, cardiovascular disease, and neurological disorders. Additionally, influencing cell division, migration, invasion, apoptosis, autophagy, and other biological processes are phytochemicals. For the first time, the effects of phytochemicals on RNA expression in a variety of chronic diseases, including cancer, were examined, together with the underlying mechanisms, to give a thorough theoretical foundation for using RNAs as a therapeutic target for chronic diseases **[13]**.

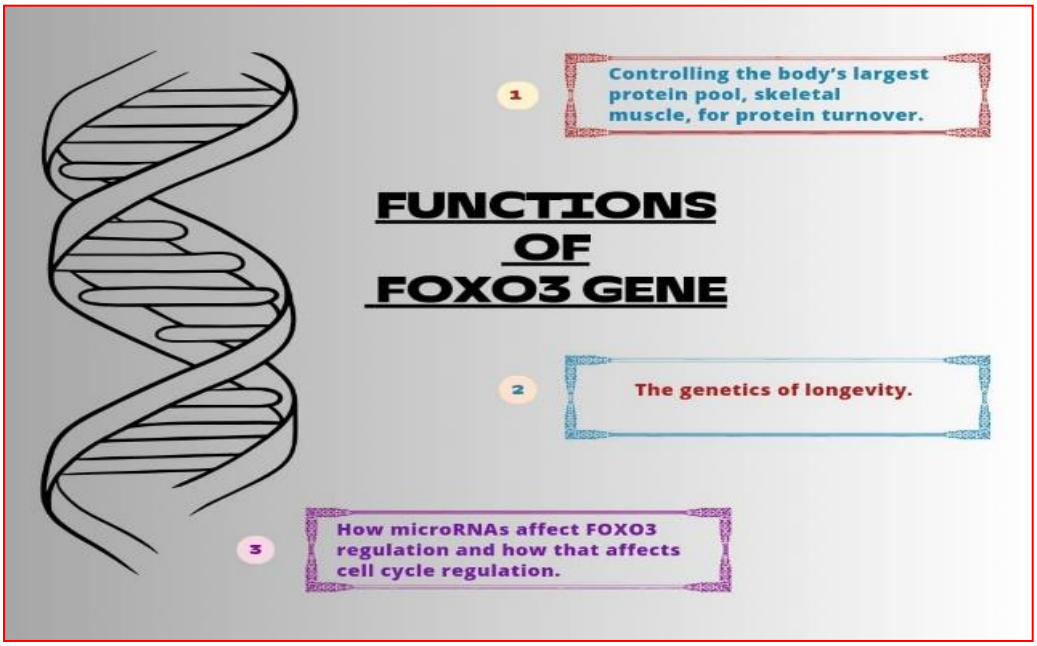

Figure 1.: Function of FOXO3

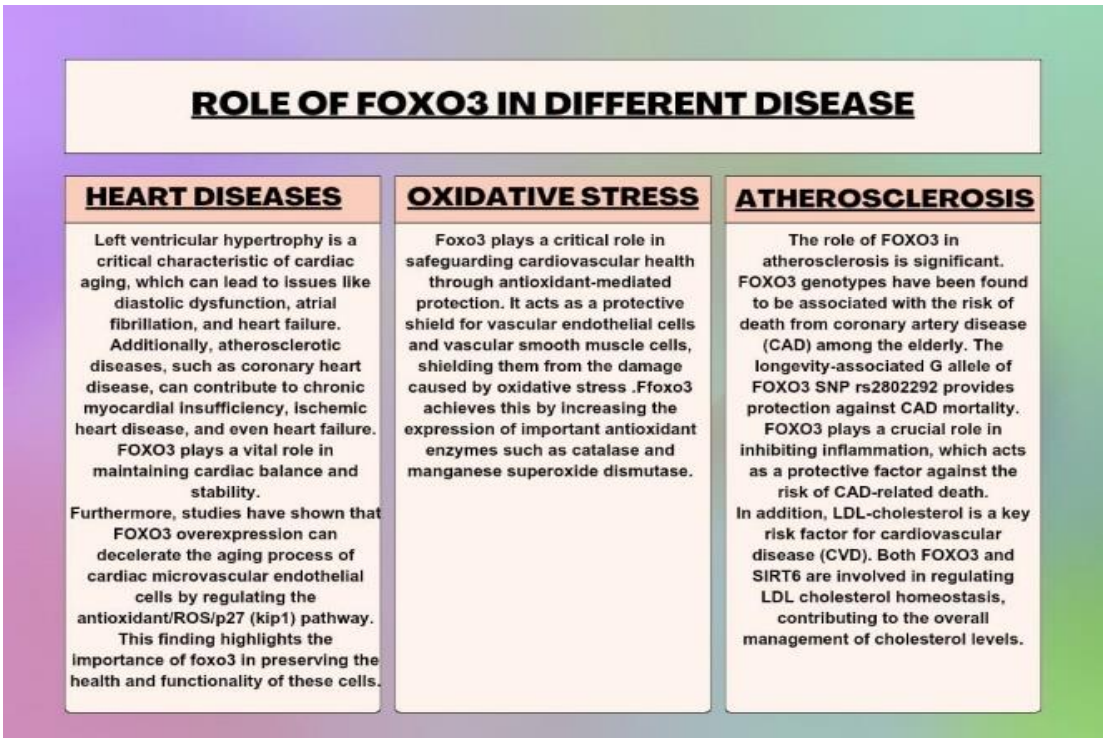

Figure 2: Role of FOXO3 in Various diseases

Table 1: Impact of FOXO3 gene with some phytochemical reactions

PHYTOCHEMICALS	IMPACT ON FOXO3 GENE
Quercetin	Quercetin is a flavonoid found in various fruits, vegetables, and teas. It has antioxidant and anti-inflammatory properties and may influence FOXO3 gene expression through its impact on the AMP-activated protein kinase (AMPK) pathway, which is known to regulate FOXO3.
Curcumin	Curcumin is the active compound in turmeric and has been studied for its anti-inflammatory and antioxidant effects. It may influence FOXO3 through its interaction with various signaling pathways, such as the PI3K/Akt pathway.
Epigallocatechin gallate (EGCG)	EGCG is a polyphenol found in green tea. It has been shown to activate the FOXO3 gene, promoting cellular stress resistance and potentially contributing to longevity
Sulforaphane	Found in cruciferous vegetables like broccoli and cauliflower, sulforaphane has been studied for its potential to enhance FOXO3 expression and promote antioxidant and detoxification pathway
Resveratrol	Resveratrol is a phytochemical found in red wine, grapes, and certain other plants. It has been shown to activate the SIRT1 gene, which in turn can activate the FOXO3 gene. This activation may play a role in promoting longevity and improving cellular stress response

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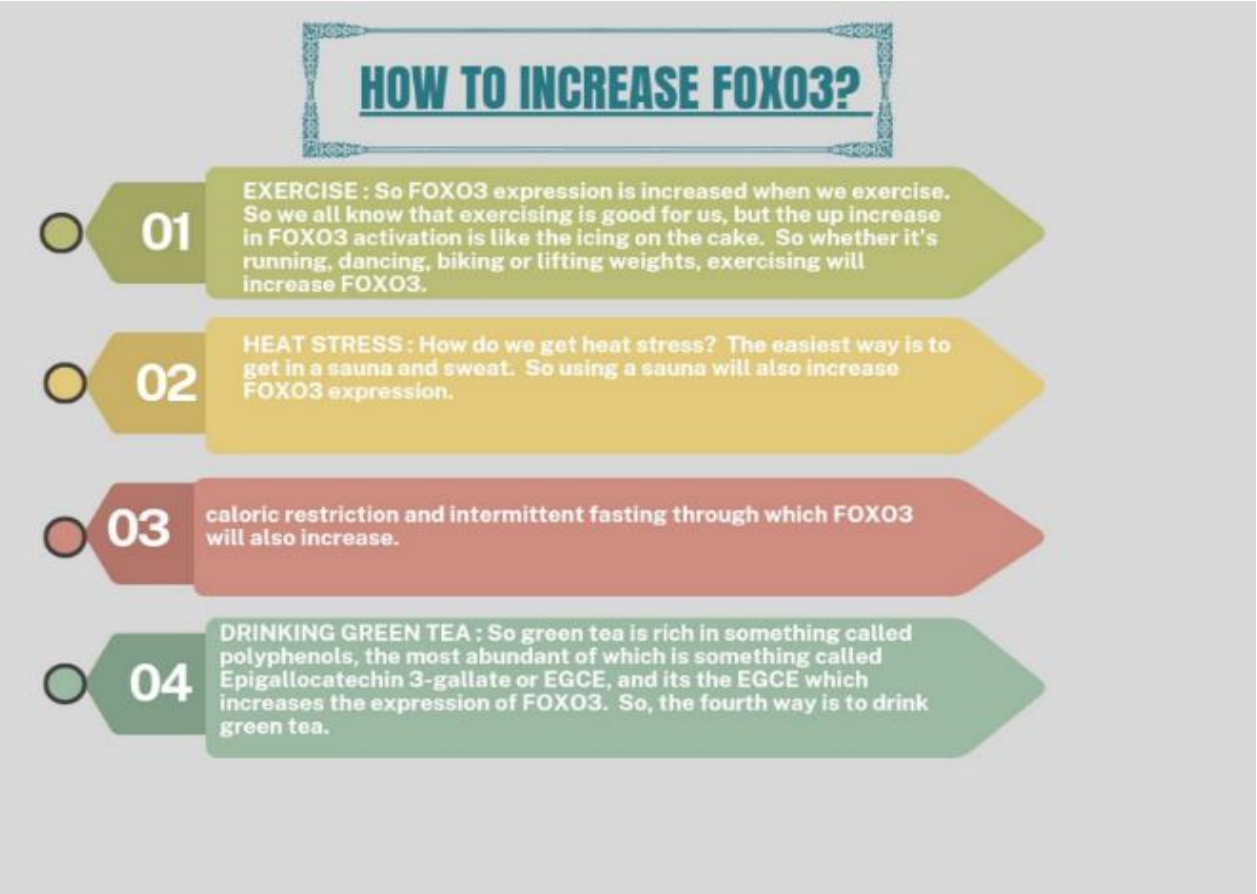

Figure 3. These are the following ways to increase FOXO3.

CONCLUSION

Foxo3 is a protein-based gene that plays a crucial role in life proliferation and delayed age-related diseases. It is active through phytochemicals, such as primary metabolites and secondary metabolites, and is involved in growth factors. FOXO3 proteins are involved in various physiological and pathological conditions, including cardiovascular diseases, cancer, diabetes, and chronic neurological diseases. Lifespan is dependent on cellular maintenance functions after the reproductive phase, and survival genes contribute to survival rather than longevity genes. More literature and studies are necessary to know the exact mechanism of FOXO3 and its function in human health.

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