Review

THE RELATIONSHIP BETWEEN QUERCETIN AND HEALTH FROM THE PERSPECTIVE OF EPIGENETICS

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ABSTRACT

Background: Research on free radicals has been one of the topics that have attracted scientific and medical attention for decades, especially about ageing, disease, and infectious and non-infectious diseases. Exposure to free radicals from daily pollution and unhealthy lifestyles accelerates bodily damage and aging. These factors are primary contributors to gene and chromatin dysregulation, leading to chronic diseases such as metabolic disorders, allergies, cancer, etc.

Scope and approach: In the present literature, quercetin has been shown to have the ability to neutralize free radicals, reduce the formation of inflammatory cytokines, induce histamine release, and induce cell damage. At the same time, they have been shown to inhibit the growth of some inflammatory bacteria in the body, reversing the epigenetic mechanism of the disease. Moreover, quercetin has also been shown to have the ability to improve the body's immune system, help the body stay healthy, and overwhelm health hazards from the external environment. These roles of quercetin in health are reviewed from the latest advances in epigenetics.

Key findings and conclusions: Quercetin plays an important role in the treatment of human diseases through epigenetic mechanisms. Quercetin's potential to reverse the epigenetic mechanism for pathology requires further investigation to obtain a general view.

Keywords: *epigenetic, quercetin, antioxidant, reactive oxygen species, autophagy*

I. INTRODUCTION

Free radicals are unstable molecules that have the potential to damage body cells and tissues. Free radicals are generated from many causes such as the mitochondrial electron transport chain, inflammatory reactions, enzymes such as xanthine oxidase, drug metabolism, smoking, exposure to X-rays and UV rays, etc. [1]. Free radicals have been linked to the risk of osteoporosis and eye diseases including cataracts, glaucoma, keratoconus, dry eye, myopia, macular degeneration, and pterygium [2, 3]. Free radicals and allergic disease are associated with dysregulation of epigenetic mechanisms. Plant-based diets provide the body with compounds including EGCG, curcumin, quercetin, and genistein that reverse the epigenetic mechanism involving DNMT and HAT enzymes [4]. Here we are mainly concerned with quercetin. In addition to being obtained from the diet, quercetin is also abundant in plants with traditional medicinal uses, such as *Physalis angulata* L., *Hibiscus sabdariffa* L., *Anoectochilus setaceus*, and *Psidium guajava* L.

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These plants are known for their roles in treating diseases, offering anti-inflammatory, antibacterial, anti-toxic, anti-cancer, and immune system-regulating properties [5-8]. Quercetin promotes the body to form endogenous enzymes, which neutralize free radicals and detoxify by the Nrf2 signalling pathway [9]. Quercetin protects hepatocytes, preventing excessive accumulation of lipid droplets in the nonalcoholic fatty liver via the IRE1a/XBP1s pathway [10].

In the process of synthesizing documents and proofs, several research areas are also mentioned and focused, including:

- Epigenetics is the study of the mechanisms by which behavioural and environmental factors can induce changes that affect gene regulation, including processes such as gene methylation, histone modification (acetylation), and micro RNAs (miRNAs) [11].

- Nutrigenomics and nutrigenetics study the effects of nutrition on gene regulation, the impact on individual health, and the risk of developing diseases [12]. In addition, nutrigenomics and nutrigenetics also help to better understand how components of the diet, directly or indirectly, affect metabolism and how gene regulation occurs in humans. More specifically, this research direction is also interested in effective ways to prevent diseases and reduce risks in disease treatment and medical costs [12].

II. METHODS

We conducted a thorough review of the existing literature on quercetin, genetics, epigenetics, and the relationship between dietary behavior and health at the molecular biological level. Relevant scientific literature was comprehensively examined and analyzed using keywords such as epigenetics, quercetin, antioxidant, reactive oxygen species, autophagy. Document sources are selected and used based on various reputable databases such as Google Scholar, Springer, PubMed, and ScienceDirect. The selected publications were published between 2002 and 2024. Based on 352 articles, we narrowed it down to 77 articles relevant to the problem we studied. The 275 removed articles were excluded because they were written in a language other than English or Vietnamese, were not related to the research problem, were not capable of being read and consulted for free, and the source version was not considered appropriate and reliable. In addition, we also searched for relevant reports in the libraries of many different organizations, including the World Health Organization, the World Bank, research institutes, universities and other organizations.

III. INTRODUCTION TO QUERCETIN

Quercetin is a compound found in many foods (see Table 1). Quercetin exists in several forms including quercetin-3,4'-O-diglucoside; quercetin-3-O-glucoside; quercetin-3-O-rhamnoside; quercetin-4'-O-glucoside; quercetin-3-O-rutinoside [13].

Quercetin is also found in many plants that act as a medicine for many diseases including *Physalis angulata* L., *Hibiscus*

sabdariffa L., *Anoectochilus setaceus*, *Psidium guajava* L.,v.v [5-8].

Physalis angulata L. is distributed mainly in tropical and subtropical regions including Asia, Central and South America, Africa and the Pacific Islands. *Physalis angulata* L. is an edible plant with therapeutic uses including anti-inflammatory, antibacterial, anti-toxic, anti-cancer and immune-modulating effects by phenolic acids (chlorogenic acid, caffeic acid, p-coumaric acid) and flavonoids (rutin, quercitrin, quercetin and kaempferol) [6].

Hibiscus (*Hibiscus sabdariffa* L.) is used as food and medicine. Their calyx is a rich source of flavonoids, especially quercetin and anthocyanin. Quercetin has an antibacterial role [5].

Guava (*Psidium guajava* L.) is distributed in tropical and subtropical regions such as Asia, Africa, South America and the Caribbean. In Viet Nam, *Psidium guajava* L. is very popular and is grown in many places but mainly in the Mekong Delta with an area of nearly 4500 ha. Guava leaves are also used as tea, the main phenolic compound in guava leaves was identified as quercetin-3-O-sulfate with anti-diabetic, antioxidant, anti-bacterial, anti-cancer, anti-diarrheal and anti-inflammatory effects [8].

Fenugreek (*Trigonella foenum-graecum*) is a herb that is widely grown in India, Pakistan and some Middle Eastern countries, with many useful medicinal effects such as antibacterial, antiviral, anti-tumour, anti-inflammatory and antioxidant. Both their leaves and seeds have been widely consumed as both food and medicine. *Trigonella foenum-graecum* is rich in nutritional value, providing vitamins, iron, β-carotene, etc. Fenugreek seeds contain a variety of alkaloids, flavonoids, saponins and carbohydrates, leaf analysis revealed the presence of two main flavonoids, quercetin and kaempferol [27].

Table 1. *Quercetin content in food, beverages and health studies on quercetin.*

Food and beverage	Quercetin	Research on quercetin for health	Ref.
Food (mg/100 g)			
Apple	4.01	Quercetin-3-glucoside (Q3G), coumaric acid, phloridzin, quercetin and phloretin are the major polyphenolic compounds that makeup apple pulp. Studies on HeLa cell lines show that Q3G inhibits the cell proliferation cycle in the S phase, promotes apoptosis by activating caspase 9/3, reduces the expression of BCL 2 anti-apoptosis protein, and upregulates the expression of BAX pro-apoptotic protein. The Q3G present in apple pulp holds promise as an anti-inflammatory and anticancer agent for the treatment of cervical cancer.	[13, 14]

Food and beverage	Quercetin	Research on quercetin for health	Ref.
Blueberry	5.05	The most abundant polyphenols detected in extracts of *V. myrtillus* were quercetin, kaempferol, phenolic acid, and gentisic acid. A study on the colorectal cancer cell line HCT-116 showed that quercetin and kaempferol have strong cytotoxic, antioxidant, and apoptotic effects.	[15, 16]
Garlic	1.74	Garlic oil contains 0.24 mg/g quercetin and 0.33 mg/g gallic acid. The study showed that garlic essential oil had antibacterial properties against *Staphylococcus aureus,* and the diameter of the growth inhibition zone increased from 20.20 ± 0.58 mm (37.5 mg/mL) to 31.70 ± 0.55 mm (300 mg/mL).	[17, 18]
Okra	20.97	Quercetin-3-gentiobioside (Q3G), quercetin-3-sambubioside (Q3S), rutin, quercetin-7-glucoside (Q7G), isoquercitrin (ISO), and quercetin-3-malonylglucoside (Q3M) are found in okra. The study showed that Q3G, Q3S, ISO, and Q3M significantly inhibited the proliferation of cell lines NCI-N87, A375, A549 (25- 100 μmol/ L), and HFLS-RA (200- 300 μmol/ L).	[17, 19]
Onions (*Allium cepa L.*)	20.30	Neuronal ischemia is the cause of neuronal damage and gliosis. Research has shown that onion extract (*Allium cepa L.*) and quercetin contribute to the amelioration of ischemic neuropathy, protecting hippocampal pyramidal cells in the CA1 region, simultaneously reducing 4-hydroxy-2-nonenal formation in a male Mongolian gerbil model (*Meriones unguiculatus*).	[17, 20]
Beverage			
Black tea	2.50 (mg/100 ml)	The study was based on venous blood samples from healthy adults (25-30 years old). Research has shown that BPA damages and causes swelling of red blood cells leading to hemolysis. Black tea extract and quercetin play a role in protecting red blood cells and significantly slowing down hemolysis caused by BPA.	[13, 21]
Red wine	3.16 (mg/ 100ml)	The skin cancer study on CD1 mice showed that red wine has 4 types of polyphenols including quercetin,	[13, 22]

Food and beverage	Quercetin	Research on quercetin for health	Ref.
		gallic acid, (+)-catechin, and trans-resveratrol that play a role in cancer prevention. Research indicates that trans-resveratrol is absorbed much more efficiently than (+)-catechin and quercetin after oral administration, concluding that trans-resveratrol may be the most effective anti-cancer polyphenol present in red wine when taken orally consumed by healthy human subjects.	
Lotus leaf tea	105.93 (mg/ 100 g)	Overdose of acetaminophen resulted in mitochondrial damage leading to leakage of damaging free radicals in hepatocytes of AML (ATCC CRL-2254) mice. The Nrf2 signalling pathway involved in the transcription of antioxidant and detoxifying enzymes including HO 1, NQO 1, and UGT 1A is activated by phenolic compounds (gallic acid, EGCG, myricitrin, rutin), ellagic acid, myricetin, quercetin, luteolin, kaempferol and apigenin), compounds extracted from lotus leaves act as inhibitors of DNMT and HDAC enzymes.	[9, 23]
Pomegranate juice	1.456 (mg/ 100 g)	60 strains of *Staphylococcus epidermidis* isolated from human eye infections were obtained from the Instituto de Oftalmología Conde de Valenciana, Mexico City. Half of the strains were resistant to multiple drugs and other compounds, such as ethidium bromide and benzalkonium chloride. Research has shown that pomegranate juice plays an antibacterial role against resistant bacteria *Staphylococcus epidermidis.*	[24, 25]
Prickly pears (*Opuntia spp.*)	4.86 (mg/ 100 g)	The study was based on four cancer cell lines: mammary (MCF-7), prostate (PC3), colon (Caco2) and hepatic (HepG2). Research shows that juice derived from Prickly pears (Opuntia spp.) plays a role in inhibiting the proliferation of cancer cells and fighting free radicals. *Opuntia violaceae* Moradillo contains the highest content of flavonoids and inhibits prostate and colon cancer cell proliferation. *Opuntia rastrera* Rastrero inhibits the growth of four cancer cell lines.	[17, 26]

3.1. Quercetin inhibits cancer

Cancer is currently a major burden on global health, is one of the most common dangerous diseases, and is the collective name for a group of similar related diseases. When cancer is present, the body's normal cells appear abnormal, divide, multiply uncontrollably, and invade surrounding tissues to form a mass of solid tissue. Normally, naturally, the body's cells grow and divide to form new cells, replacing old, ageing, or dead cells. With cancer, old cells do not die but continue to grow, continuously producing new cells. They multiply uncontrollably, form tumours, and can metastasize via the circulatory or lymphatic systems. Up to now, cancer drugs are being researched and developed, but the scientific community has not yet found a brand name for specific types of cancer as well as a commercial drug product to treat all types of cancer [28].

Bahare Salehi et al. (2020) identified quercetin as having potential therapeutic roles in treating various diseases, including diabetes, Alzheimer's disease, arthritis, parasitic infections, and cancer. For cancer, preclinical and clinical trials have examined quercetin's effects on pancreatic cancer, osteosarcoma, ovarian cancer, breast cancer, cervical cancer, colon cancer, and gastrointestinal cancer [29]. To help readers understand the bidirectional relationship between quercetin and epigenetics, its potential role in cancer treatment is discussed in sections 3.2 to 3.4.

Besides understanding quercetin-epigenetics, the author also points out challenges in applying quercetin in humans including poor water solubility, poor permeability, and instability in physiological environments (stomach and intestines), short biological half-life and first-pass metabolism in the liver before reaching the systemic circulation result in poor oral bioavailability [29].

3.2. Gastrointestinal cancer

Among types of cancer, gastrointestinal cancer has the highest proportion, accounting for 26.3% of the total 4.8 million new cases worldwide in 2018. Which, colorectal cancer accounts for the highest (10.2%), followed by stomach cancer (5.7%), liver cancer (4.7%), esophageal cancer (3.2%), and pancreatic cancer (2.5%) (see Figure 1) [30].

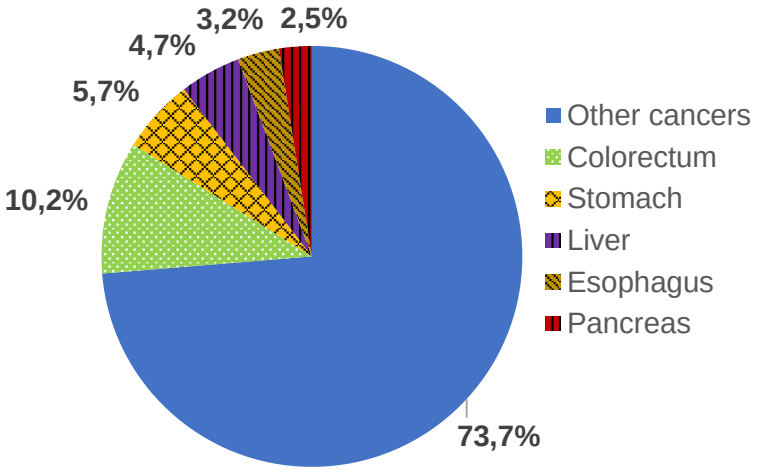

Figure 1. *Statistical data on the number of new cases of gastrointestinal cancer globally in 2018 out of a total of 4.8 million cases [30].*

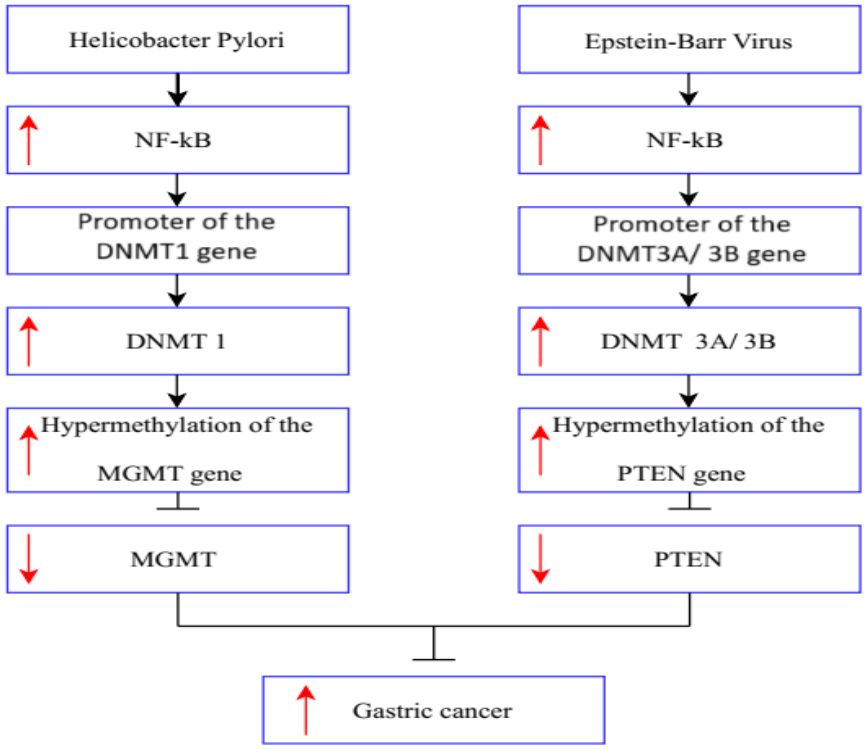

Figure 2. *Effect of Helicobacter pylori and Epstein-Barr virus on increased risk of stomach cancer.*

Regarding the mechanism of gastrointestinal tumour development, pathogens (such as viruses, bacteria, and parasites) have evolved over a long period, finding ways to efficiently enter the host and transform it into a host adaptive changes to increase their survival (e.g., *Helicobacter pylori* tolerating the acidic environment of the human stomach) [31]. Microorganisms host different pathologies such as exposure to *Helicobacter pylori* and Epstein-Barr Virus. *Helicobacter pylori* promote methylation of tumour suppressor genes including E-cadherin (CDH1), Heart and neural crest derivatives expressed 1 (HAND1), and multiple tumour suppressor 1 (p16 INK4A) [31]. Epstein-Barr virus promotes transcription and formation of DNA methyltransferase (DNMT) enzymes. These include DNMT 1, and DNMT 3A/3B formed by the transcription factor NF-kB. DNMTs involved in methylation of the tumour suppressor genes O-6-Methylguanine-DNA Methyltransferase (MGMT), Phosphatase and tensin homolog (PTEN) cause gastric cancer (see Figure 2) [32, 33]. In addition, smoking and alcohol consumption trigger inflammatory responses that lead to gastric damage, increasing the risk of exposure to *Helicobacter pylori* and Epstein-Barr virus [34, 35].

Conversely, quercetin compromises the integrity of the cell barrier, leading to cell lysis by peroxidation of the outer lipid membrane in gram-negative bacteria (*Escherichia coli*). At the same time, quercetin activates the kynurenine pathway, which depletes L-tryptophan stores leading to reduced growth of gram-positive bacteria [31]. Yali Liu et al. (2024) found that quercetin in liquorice

has anti-cancer effects by effectively inhibiting proliferation, reducing tumour volume, inducing cell cycle arrest, and promoting apoptosis. These effects are associated with increased levels of Cyt-C, caspase-3, and BAX, as well as decreased levels of BCL-2 and Ki67, a reduction in mitochondrial membrane potential, and induced mitochondrial damage. They are also associated with increased levels of Cyt-C, caspase-3, and BAX, decreased levels of BCL-2 and Ki67, a reduction in mitochondrial membrane potential, and induced mitochondrial damage [36].

Thus, quercetin has an antibacterial role in helping protect the stomach from being damaged by inflammatory reactions from external agents. In addition, healthy lifestyle changes, limiting the use of alcoholic beverages (alcohol, beer), and smoking contribute to reducing the risk of cancers of the digestive tract, stomach, etc.

3.3. Breast cancer

Breast cancer is a fairly common cancer in women worldwide with more than 2 million new cases in 2020 [37]. Breast cancer is the fastest-growing cancer in India and has now surpassed cervical cancer. The National Cancer Registry Program in 2018 estimated 162,468 new breast cancer cases and 87,090 deaths [38]. Breast cancer is known and documented in the "Edwin Smith Papyrus", about 3600 years ago (about 1600 BC). More recently, in the period of ancient Egyptian civilization, Hippocrates (460- 370 BC) suggested that the human body was an entity balanced by four types of humours including blood, phlegm, yellow bile, and black bile, representing respectively air, fire, earth, and water, help constitute all natural things. Breast cancer is the result of an imbalance, an excess of black bile, which causes tumours [39].

From the perspective of modern science and epigenetics, tumour suppressor genes play an important role in inhibiting or regulating cell proliferation by encoding proteins that block the action of tumour cell proteins that promote cell proliferation. Tumour suppressor genes including *APC, BRCA1, Cyclin D2, GSTP1, p16, PTEN, RARβ, RASSF1A, ZMYND10*, etc. are among the important causes of breast tumours and are potential biomarkers in clinical applications, prognosis and early diagnosis of breast cancer [40].

Gene *BRCA1* is a tumour suppressor gene, which helps protect our body from uncontrolled proliferation of cells, leading to inhibiting the formation of cancerous tumours. Simultaneously, BRCA1, and BRCA2 together with MGMT and RAD 51 involved in the repair of the double-strand break of DNA [41]. Research shows that a diet low in folic acid and cobalamin increases the risk of tumour formation by increasing the rate of promoter methylation of the *RAR β* and *BRCA1* genes [42, 43].

Research by Sai Kundur et al. (2018) has shown that quercetin and curcumin enhance histone acetylation at the H3K9 position of the promoter of the *BRCA1* gene [44]. Inhibition of cell proliferation and activation of apoptosis in the MDA-MB-231 (ATCC, HTB-26) cancer cell line was observed at a concentration of 20 μM of quercetin reduced cell viability and increased programmed cell death. This medium and concentration also suppressed cell cycle progression through upregulation of the expression of FOXO3a by the JNK signalling pathway [45]. Tianyu Luo et al. (2024) proved that

quercetin inhibited breast cancer progression in chronically stressed C57BL/6J mice by regulating microglia M1 polarization by targeting the STAT1 protein [46]. Marta et al. (2020) , this study was performed on the docetaxel-resistant MCF7 breast cancer cell line. The results showed that quercetin inhibited Lef1 and reduced the expression of drug resistance-related proteins such as ABCG2, Vimentin, and Caveolin-1. Quercetin was tested in a phase I clinical study in 1996, which demonstrated that it could be used safely in humans without significant toxicity at doses up to 1700 mg/m². These findings support the feasibility of using quercetin as a safe adjuvant therapy in combination with docetaxel for the treatment of drug-resistant breast cancer, as it has the potential to enhance cancer cell sensitivity without posing significant risk to the patient [47].

From the above evidence, a quercetin-rich diet plays a very important role in breast cancer suppression through inhibition of cell proliferation, activation of apoptosis, and alteration of epigenetic mechanisms for suppressor genes tumour.

3.4. Cervical cancer

Cervical cancer is a common malignancy in women worldwide. An estimated 493,000 cases and more than 273,500 deaths annually worldwide. Methylation of the promoter of the tumour suppressor gene *RASSF1A* is associated with a variety of cancers including breast, liver, pancreas, prostate, kidney, brain, stomach, blood, skin, Hodgkin's lymphoma, etc. Compounds methionine, vitamin B12, resveratrol, curcumin, emodin, peperomin E, dioscin, mahanine and PEITC participate in the demethylation of the promoter of the *RASSF1A* gene [48]. Studies on HeLa cell lines show that quercetin and eugenol enhance the demethylation of the *RASSF1A* gene [49].

On the other hand, FADD and caspase 8 participate in apoptosis, inhibiting cervical cancer formation. HPV-E6 virus inhibits apoptosis through HPV-E6 binding and degradation of FADD leading to an increased risk of cervical cancer [50]. Flavonoid compounds (myricetin, morin, quercetin, kaempferol, galangin, etc.) act as inhibitors of the interaction between HPV-E6 and FADD, caspase 8 [51]. Motoki Murata et al. (2022) admitted that dietary quercetin enhanced the expression of cervical tumour-inhibiting miRNAs, including miR-26b, miR-126, and miR-320a, while simultaneously inhibiting the CTNNB1 gene, which encodes β-catenin, by upregulating miR-320a expression [52].

From the above evidence, it is shown that a diet rich in quercetin also plays a strategic role in inhibiting cervical cancer by activating apoptosis and altering the epigenetic mechanism of tumour suppressor genes.

IV. QUERCETIN FOR TYPE 2 DIABETES AND AGE

Advanced glycation end products (AGEs) are compounds formed from many different stages, AGE is generated at the last stage of the Maillard reaction through polymerization, oxidation, dehydration, and cyclization events, discovered by Louis-Camille Maillard (1878- 1936) [53].

Type 2 diabetes is recognized as a common disease in modern times, causing a heavy burden on global health, forecasting the number of cases in adults (20–79 years old) with 783.2 million cases in 2045 [54]. High blood sugar is responsible for endogenous AGE synthesis. AGE together with the RAGE receptor activates inflammatory responses (NF-kB, NOX1, ERKs, Janus kinases, MAPK) that damage cells leading to diseases including retinopathy, neuropathy, nephropathy, and atherosclerosis. Endogenous AGE comes from the cause of high blood sugar in patients with diabetes, but exogenous AGE originates from a typical Western diet with the characteristics of high-temperature food processing and cooking for a long time, low hydration, and high pH [53].

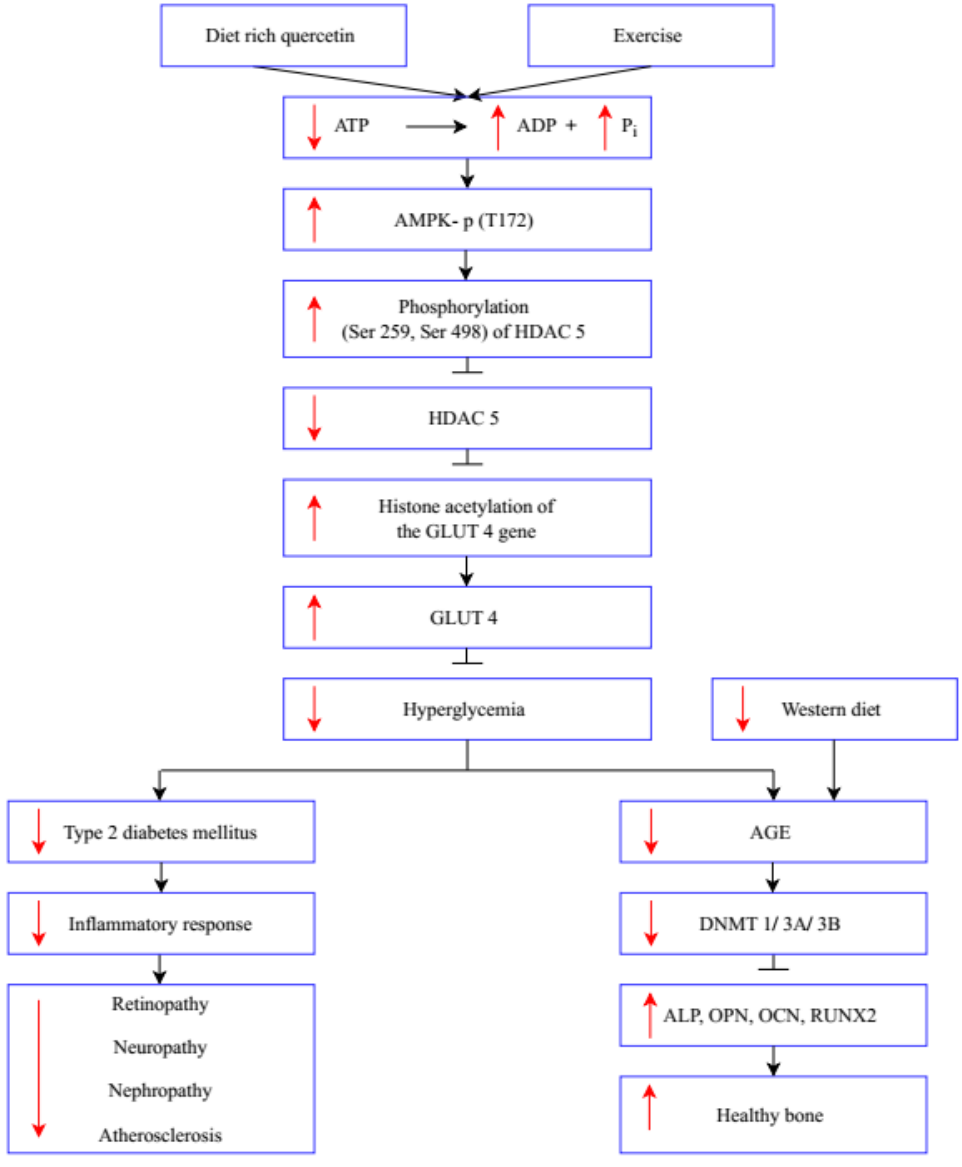

Figure 3. *Relationship between quercetin, and exercise for HDAC5 in promoting the enhancement of GLUT4 expression through histone acetylation in disease prevention.*

Exercise and a quercetin-rich diet have a major effect on phosphorylation at the Thr 172 site of AMPK. AMPK again activates phosphorylation at Ser 259 and Ser 498, leading to inhibition of HDAC5 enzyme activity. This development contributes to promoting histone acetylation, helping to untwist the chromatin of the GLUT4 gene in skeletal muscle cells, contributing to reducing blood sugar levels, and improving the condition in diabetics [55, 56]. Nuclear factor erythroid 2-related factor 2 (Nrf2), a key transcription factor, plays a crucial role in regulating antioxidant and anti-inflammatory responses, thereby protecting cells from oxidative damage and inflammation-induced injury. Quercetin ameliorated diabetic kidney disease by inhibiting ferroptosis and modulating Nrf2 in streptozotocin-induced diabetic rats [57]. AGE has been reported to inhibit osteoblastogenesis and bone mineralization, increasing the risk of osteoporosis by promoting the expression of DNA methyltransferase enzyme (DNMT1/3A/3B) leading to methylation of promoter regions in a gene such as Alkaline Phosphatase (ALP), Osteopontin (OPN), Osteocalcin (OCN), and Runt-related transcription factor 2 (RUNX2) (see Figure 3) [58].

From the above evidence, it is shown that diabetes is the cause of many other diseases due to inflammatory reactions by endogenous AGEs. In addition, limiting Western-style diets, reducing processing, and heating foods to high temperatures contribute to a reduction in exogenous AGE formation. Exercise and a diet rich in quercetin contribute to the activation of AMPK, which inhibits the HDAC5 enzyme leading to a reversal of the epigenetic mechanism that improves and reduces the progression of diabetes.

V. THE ROLE OF QUERCETIN IN AUTOPHAGY RELATED TO NAFLD AND TUBERCULOSIS

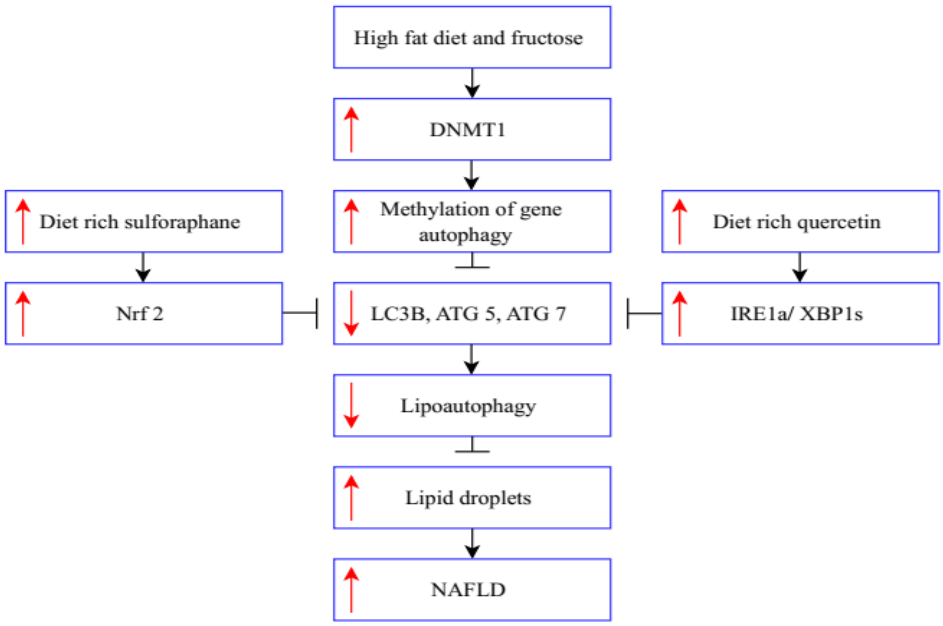

Figure 4. *Role of a diet rich in sulforaphane and quercetin-activating autophagy in the prevention of NAFLD.*

Autophagy is a process that plays a role in the degradation and reuse of substances inside the cell such as damaged organelles, misfolded protein molecules, lipid droplets, and killing pathogens [59]. Research by Rajat Pant et al. (2023) has shown that a high-fat and fructose diet significantly increases the number of Kupffer cells with an M1-dominant phenotype in mice leading to the activation of inflammatory responses. At the same time, the above diet also increased the expression of the DNMT1 enzyme leading to methylation of LC 3B, ATG 5, and ATG 7 genes, which disrupted the degradation of lipid droplets (lipoautophagy), causing them to accumulate excess in hepatocytes. This is the basic cause of non-alcoholic fatty liver disease (NAFLD) [60].

A diet is rich in plant-derived sulforaphane, which activates the Nrf2 signalling pathway. The transcription factor Nrf2 is involved in the transcription of genes involved in autophagy including LC 3, ATG 5, and ATG 7 in hepatocytes [61]. A diet rich in quercetin suppresses the progression of atherosclerosis by enhancing autophagy activity in the foam cells of RAW 264.7 macrophages [62], preventing excessive lipid droplets accumulation in the nonalcoholic fatty liver via the IRE1a/ XBP1s pathway (see Figure 4) [10].

From the above evidence, it is shown that a diet rich in fat and fructose disrupts autophagy in hepatocytes through DNMT1 leading to NAFLD disease. Diets rich in sulforaphane and quercetin contribute to the enhancement of autophagy through the Nrf2 and IRE1a/ XBP1s pathways.

Tuberculosis (*Mycobacterium tuberculosis*) is a common host-borne bacterium worldwide with nearly 10 million new cases and 1.2 million deaths each year. Patients will develop symptoms including a persistent cough and can spread the disease through airborne particles containing Tuberculosis [63]. Tuberculosis has been reported to increase its ability to survive and spread to the host through epigenetic and hibernating mechanisms [63, 64].

In an epigenetic mechanism, *Mycobacterium tuberculosis* inhibits and disrupts autophagy by enhancing the activity of G9a, EZH2, and HDAC3 enzymes. G9a participates in the methylation of the histone tail H3K9 (H3K9 me2/3) and EZH2 participates in the methylation of the histone tail H3K27 (H3K27 me3), while reducing acetylation in the histone tails H3K9 (H3K9 ac) and H3K27 (H3K27 ac) by HDAC3. These processes lead to chromatin closure, transcriptional inhibition, and reduced expression of ATG 5 and ATG 7 genes involved in autophagy in RAW 264.7 macrophages (see Figure 5) [64].

Under favourable environmental conditions, with adequate nutrients, glucose participates in glycolysis and the TCA cycle leading to the breakdown of glucose into ATP, providing energy for the life of Tuberculosis [63].

Under nutrient-deficient conditions, the enzyme Isocitrate lyase plays an important role in converting isocitrate to glyoxylate of the glyoxylate cycle, which plays an important role in lipid anabolism via the gluconeogenesis pathway. Here lipid acts as an energy source for hibernation. Due to the flexibility in the process of adjusting metabolic pathways

from favourable to harsh environments, Tuberculosis can resist agents from antibiotics (antibiotic resistance) leading to easy transmission to a human host and increasing the chance of survival, so takes a long time to treat and is easy to re-infect [63]. An important finding was that Isocitrate lyase inhibition by quercetin bound to the N-terminus resulted in the inhibition of Tuberculosis bacteria growth at concentrations of 3.57 µM(IC_{50}) [65].

From the above evidence, autophagy plays an important role in protecting the host from disease in macrophages. Tuberculosis increases survival by evading host defences through epigenetic dysregulation and hibernation. Quercetin plays an important role in inhibiting the growth and survival of Tuberculosis during dormancy by targeting the Isocitrate lyase enzyme.

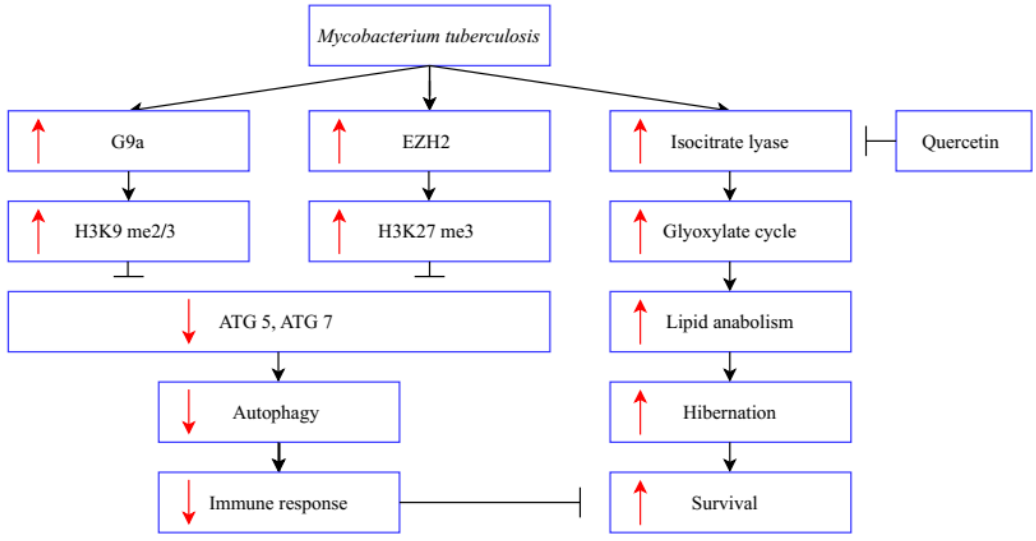

Figure 5. *Mycobacterium tuberculosis enhances survival by disrupting autophagy and hibernation, with quercetin playing a protective role against infectious disease.*

VI. QUERCETIN PROTECTS THE BODY FROM RADICALS

Free radicals are atoms, molecules, or ions with unpaired electrons that are highly active in chemical reactions with other molecules. In biological systems, free radicals are usually derived from oxygen (ROS), nitrogen (RNS), and sulfur (RSS) [1]. Reactive oxygen species (ROS) are formed from many sources including mitochondrial electron transport chains, inflammatory responses, enzymes such as xanthine oxidase, drug metabolism, smoking, exposure to X-rays and UV rays, etc. [1]. According to Liangping Li et al. (2021), ROS indirectly enhances the activity of the DNA-methyltransferase 3 beta enzyme leading to methylation of the promoter of the Kruppel-like factor 5 (*KLF5*) gene, inhibiting the wingless/int-1 (Wnt) signalling pathway, reducing the ability to differentiate osteoblasts leading to an increased risk of osteoporosis [3]. ROS damages the eye organs including the lens, cornea, anterior chamber, retina, ocular surface, optic nerve, and macula leading to eye diseases including

cataracts, glaucoma, keratoconus, dry eye, myopia, macular degeneration, and pterygium. Ultraviolet rays (UV), light-emitting diodes (LED), and electronic devices increase eye diseases [2]. Myopia is a common eye disease affecting approximately 1.6 billion people worldwide in 2000, GSTP1 and TXNRD2 enzymes participate in the neutralization of free radicals, contributing to the protection of the lens epithelium to help protect the lens from the risk of cataracts in highly myopic eyes. ROS promotes methylation of the GSTP1 and TXNRD2 promoter genes by the enzyme DNMT1, leading to reduced formation of free radical-neutralizing enzymes [66, 67]. A plant-based diet consisting of ascorbic acid, α-tocopherol, β-carotene, lutein, zeaxanthin, and quercetin protects the eyes from free radicals [2, 68].

According to Zheng-Yuan Su et al. (2022), paracetamol (acetaminophen, APAP) is a common pain and fever reliever, their use in overdose damages mitochondria leading to leakage of free radicals that cause hepatocyte damage. The Nrf2 signalling pathway involved in the transcription of antioxidant and detoxifying enzymes including HO 1, NQO 1, and UGT 1A is activated by phenolic compounds (gallic acid, EGCG, myricitrin, rutin, ellagic acid, myricetin, quercetin, luteolin, kaempferol, and apigenin). Compounds extracted from lotus leaves act as inhibitors of DNMT and HDAC enzyme activity (see Figure 6) [9].

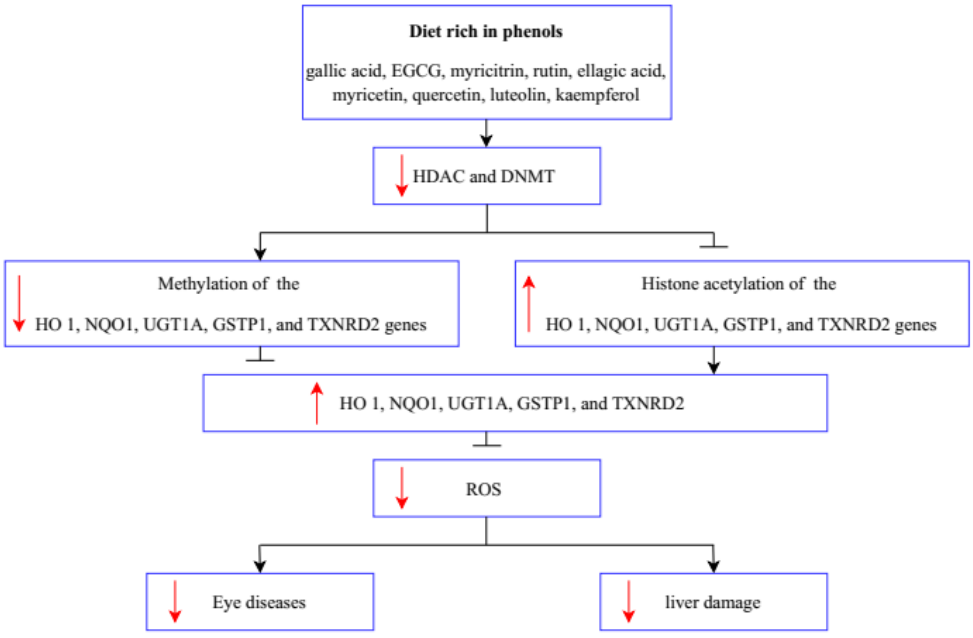

Figure 6. *The role of a phenol-rich diet that inhibits HDAC and DNMT enzymes in protecting the body from ROS in the prevention of diseases.*

From the above evidence, free radicals are the main cause of epigenetic disorders, eye diseases, and liver damage caused by paracetamol overdose. Diets rich in phenols including gallic acid, EGCG, myricitrin, rutin, ellagic acid, myricetin, quercetin, luteolin, kaempferol, and apigenin plant-derived contribute to Nrf2 activation involved in the transcription of endogenous enzymes

(antioxidant and detoxifying) through inhibition of HDAC and DNMT helps to protect eyes, liver, and other organs in the body from free radical damage.

VII. QUERCETIN PROTECTS NEURONS FROM TRAUMATIC BRAIN INJURY

Traumatic brain injury affects more than 10 million people worldwide each year. Traumatic brain injuries caused by external forces (traffic accidents, falls, attacks) damage the brain and the blood-brain barrier. Trauma causes disturbances of a multitude of biochemical and metabolic functions that affect brain cell homeostasis and lead to temporary or permanent impairment of consciousness, neuromotor disabilities, and psychological disturbances [69].

The study noted traumatic brain injury disrupted the epigenetic mechanism and enhanced histone acetylation of the *HMGB1* gene by the enzyme HAT. HMGB1 binds to microglia's Toll-like receptors (TLRs) leading to activation of the inflammatory response (NF-kB) signalling pathway, which damages nerve cells and worsens the disease [70, 71]. A diet rich in omega 3 activates the SIRT 1 enzyme, SIRT 1 enhances the expression of HDAC enzyme involved in histone deacetylation of the *HMGB1* gene and HMGB1 protein, which contributes to inhibiting the inflammatory pathway of HMGB1/ NF -kB (see Figure 7) [70, 72].

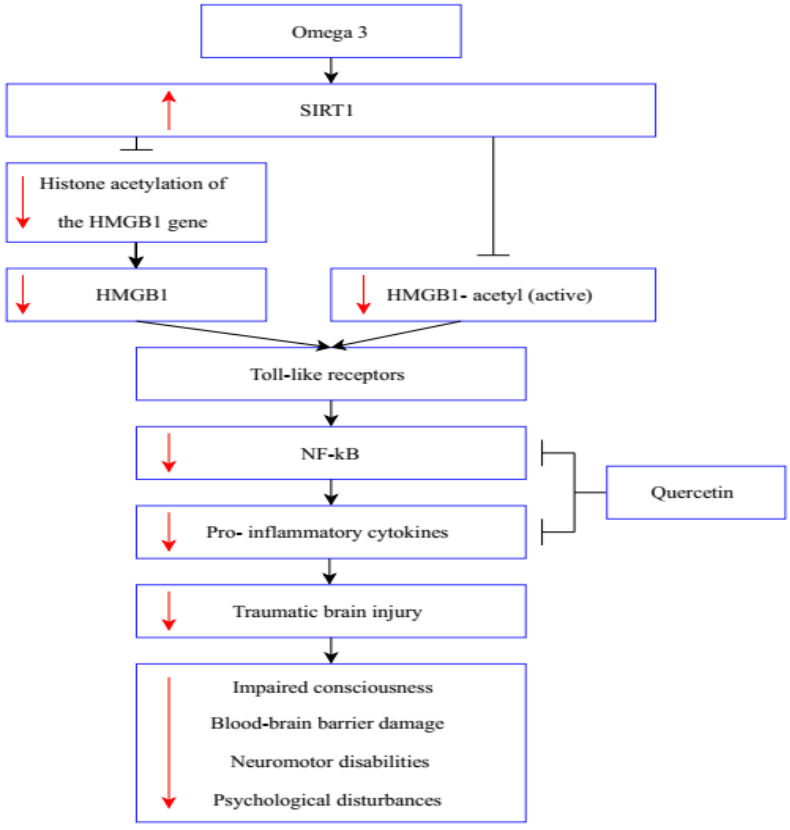

Figure 7. *The role of omega 3 and quercetin in protecting the brain from traumatic brain injury.*

Traumatic brain injury damages mitochondria, which leak free radicals that lead to the activation of inflammatory responses that damage nerve cells. Compounds including glutathione, N-acetylcysteine, ascorbic acid, flavonoids, coenzyme Q10, carotenoids, resveratrol, omega 3, α-tocopherol, and more help neutralize free radicals [69]. Quercetin plays an anti-apoptotic role, neutralizing free radicals through activation of Glutathione Peroxidase (GSH-Px), Superoxide Dismutase (SOD), and Catalase (CAT) enzymes and reducing inflammatory cytokines caused by traumatic brain injury [73]. Hitler Kom et al. (2019) admitted that quercetin treatment reduced the level of lipid peroxidation and increased SOD, CAT, and GSH-Px activities in the cortical area compared to the inflamed group. These findings suggest that dietary quercetin may help mitigate neuroinflammation-induced oxidative stress as well as associated behavioural and histological changes [74].

From the above evidence, it is shown that traumatic brain injury disrupts the epigenetic mechanism, enhances histone acetylation of the *HMGB1* gene by the HAT enzyme, and promotes the activation of the inflammatory pathway of HMGB1/NF-kB. A diet rich in glutathione, ascorbic acid, flavonoids, coenzyme Q10, carotenoids, resveratrol, omega 3, α-tocopherol, quercetin, etc contributes to the neutralization of free radicals caused by mitochondrial damage. Diets rich in omega 3 play a role in reducing brain damage by reversing epigenetic mechanisms.

VIII. QUERCETIN PROTECTS THE BODY FROM ALLERGIES

Allergic diseases include allergic rhinitis, asthma, food allergies, drug allergies, atopic dermatitis and urticaria, and angioedema. These different allergic diseases have in common associated with an individual's hypersensitivity to foreign agents leading to overactivity of the immune system. Immune system overactivity is associated with epigenetic dysregulation of the DNMT1 enzyme with an emerging role in allergic diseases [75].

Polyphenol compounds (EGCG, curcumin, quercetin, genistein) reverse the epigenetic mechanism involving DNMT and HAT enzymes of the immune system. EGCG inhibits DNMT1 and HDAC enzymes, curcumin inhibits the HAT enzyme, quercetin activates the HAT enzyme and inhibits the HDAC enzyme, and genistein activates the HAT enzyme and inhibits the SIRT enzyme [4].

8.1 Allergic rhinitis

Quercetin is a bioactive compound implicated in reducing the progression of human diseases, such as malignancies, metabolic syndrome, and autoimmune, and allergic diseases. In particular, allergic rhinitis is a common inflammatory condition that affects a large number of people around the world. The mechanism of allergic rhinitis is quite complex. Th2 cells are IL-4 and IL-5-releasing agents, which facilitate the release of allergenic, IgE by Mast cells. In addition, Th17 cells promote inflammatory responses, while Treg regulates anti-inflammatory responses. The imbalance between Th1/Th2 and

Treg/Th17 is the cause leading to allergic rhinitis. Quercetin plays a role in balancing the immune system by reducing Ig E, Ig G1, and histamine and increasing Ig G2 in serum, enhancing the expression and activity of FOXP3 and IL 10 which contributes to the reduction of inflammation [76].

8.2 Food allergies

Food allergy is an immune-mediated adverse reaction involving two classical mechanisms, IgE-mediated and non-IgE-mediated responses to symptoms involving the skin, gastrointestinal tract, respiratory tract, and cardiovascular system. Almost any food can cause an allergic reaction, but 90% of recorded food allergies are caused by 8 food groups including eggs, milk, fish, shellfish, peanuts, soybeans, tree nuts, and wheat [77].

Th1/Th2 epigenetic dysregulation has been implicated in neonates. After birth, Th2 predominance is attenuated and Th1 is gradually increased, accompanied by demethylation leading to enhanced IFNγ and IL10 expression for Treg. Abnormal changes that disrupt epigenetic regulation leading to disruption of the normal development of the immune system are involved in the phenotype of allergic disease (see Figure 8) [77].

From the above evidence, it is shown that epigenetic dysregulation leads to disruption of the normal development of the immune system related to the phenotype of allergic disease. Plant-based diets rich in polyphenols (EGCG, curcumin, quercetin, genistein) have an impact on DNMT and HAT enzymes that reverse the epigenetic mechanism of the immune system, contributing to the immune system balance between Th1/Th2 and Treg/Th17 resulted in decreased inflammation and decreased IL 4, IL 5, Ig E and histamine.

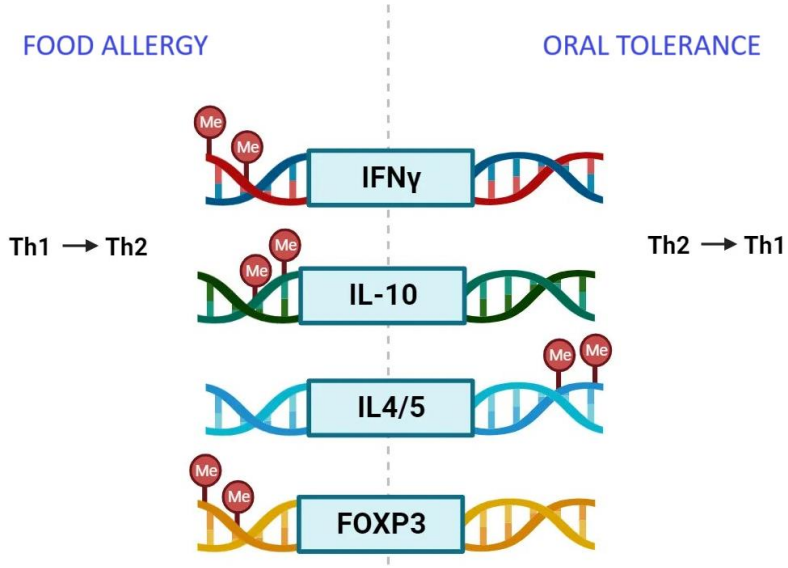

Figure 8. *Epigenetic dysregulation of IFNγ, IL10, IL4/5, and FOXP3 genes related to the balance of Th1/Th2 related to the phenotype of allergic disease [77].*

IX. CONCLUSION

A diet rich in fruits, vegetables, seeds, beans, whole grains, and juices contains high levels of biological compounds including quercetin that may prevent cancer, minimize the formation of harmful free radicals in the body, prevent eye diseases, osteoporosis, cancer, anti-inflammatory, anti-allergic (histamine, IL 4/5, IgE), inhibiting gram (+), gram (-) bacteria, reversing Epigenetic mechanisms of the disease, enhanced autophagy to prevent nonalcoholic fatty liver disease.

A plant-rich diet not only benefits human health but also contributes to environmental protection, saving resources, reducing pollution, and conserving biodiversity. Therefore, we should give priority to eating foods from nature, limiting foods of animal origin, industrial foods, high-temperature processing, and increasing exercise to improve quality. the quality of his own life and that of humanity as a whole.

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