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Applications of nutritional genomics and the study of the bioactive genetic repairing nutrients effect on supporting ever healthy diet

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Abstract:

The aim is to gather and apply the efficacy of genetic repairing bioactive nutrients in a diet called GAHD (genomics Application for a Healthy Diet) every one can use this diet for health optimization and minimization of genetic diseases by fixing shortage of genes and repairing DNA mutations which optimize health and decrease mortality and morbidity according to many researches on different nutrients that minimize all nutritional diseases and study all applications of nutritional genomics for continuous modification and optimization of that diet together with continuous development through food questionnaire for clinical follow-up and results confirmation and continuous development , another name for that diet will be HAMD (healthy Arab-Mediterranean Diet) where as the basic diet will be the most healthy Mediterranean diet which has been modified to be suitable for Arabian customs and traditions in food traditions in food according to Islamic legislation and what was referred to in the holly Quraan and the noble prophet's Sonnah , which was confirmed through the latest scientific research . This Diet should be applied in parallel with the continuous call for our societies to solve endemic nutrition and nutritional problems, together with continuous development and nutritional research which will shift the diseases concepts from traditional epidemiology and physiology to molecular biology, genetics , epigenetics and nutrigenomics which focus on deciphering the genomic, transcriptomics , proteomic and metabolomic effects of both nutrient deficiency and toxicity. From nutrigenomics point of view, nutrients are the potent signals/sensors that direct specific cells to undergo metabolic changes determining the result as a healthy or diseased individual. The varying cell sensing pattern towards a particular diet is known as 'dietary signature' that can be exploited for tailoring functional food and precision nutrition. 'Data mining' and various bioinformatics tools are helpful towards evidence-based intervention strategies by decoding nutrigenomics data as an ultimatum of which sound health is restored and diseases are prevented. This review is an attempt for the conglomeration of evolution of nutrigenomics, genome interaction and exploration of genomic tools to develop precision nutrition and food-based related disease suitable for private medicine and personal diet according to genetic diseases found in the patient's genetic map or expected to occur for more definite health precautions which will achieve highest degree of prosperity , progress and well-being.

Key words: HAMD/GAHD unified diet, scientific miracles of the holly Quraan , nutrigenomics , nutrigenetics , Epigenetics , bioactive foods, nutritional problems , nutrition

1. Introduction:

Adequate nutrition is important to the health of everyone as nutrition plays a vital role in health maintenance and prevention of genetic and nutritional diseases, The nutrients are able to interact with molecular mechanisms and amend the physiological conditions by influencing different molecular mechanisms in human body , The nutritional Genomics science focuses on the interaction between bioactive food components and the genome, which includes the interrelated fields Nutrigenetics and Nutrigenomics . The study of the influence of food nutrients on expression of genes in human body is called Nutrigenomics, while the diverse heterogeneous response of gene variants to food nutrients, dietary components and developing nutraceuticals is called nutrigenetics , this genetic variation affect food tolerances among human subpopulations and may also influence dietary requirements and raising the possibility of individualizing nutritional intake for optimal health and disease prevention on the basis of an individual’s genome , Nutrigenomics provides a genetic understanding for how common dietary components affect the balance between health and disease by altering the expression and/or structure of an individual's genetic makeup .Nutrigenetics describes that the genetic profile have impact on the response of body to bioactive food components by influencing their absorption, metabolism, and site of action , In this way, considering different aspects of gene–nutrient interaction and designing appropriate diet for every specific genotype that optimize individual health, diagnosis and nutritional treatment of genome instability, prevention and control conversion of healthy phenotype to diseases by specific diet of bioactive components of specific diet , on the other hand Globally, millions of people are suffering from malnutrition or diseases linked to food related deficiencies. Several diseases such as cardiovascular diseases, cancers, diabetes are intimately related to uneven intake of nutrients, leading to large number of deaths on national and global level (Organization 2003),we don’t take this old study enough interest in our countries and still spending much more money on treatment of malnutrition diseases instead of ending poverty and going on progress pathway like the researches in china which funded by National Natural Science Foundation of China (42171224), National Key R&D Program of China (2018YFB0505400),the Great Wall Scholars Program (CIT&TCD20190328), Key Research Projects of National Statistical Science of China (2021LZ23**) (Wang, Jia et al. 2022)**. Sufficient amount of minerals, vitamins, and proteins in human diet play indispensable role in maintaining the active metabolism for better human health. All the essential nutrients that are requisite for an individual's survival are acquired from plants as well as animals. Micronutrients and macronutrients directly influence the metabolic pathways and their deficiencies play a substantial role in development of manifold disorders. In addition to environmental factors, quality and quantity of foods are key factors in maintaining the human health. Transition from healthy to diseased state is concurrent with the pattern of gene expression that is largely influenced by nutrition and environment. A combined approach to study the influence of nutrition on expression of numerous genes can be well explored through nutrigenomic studies. Nutrigenomics includes studies wherein applied genomics is used to investigate nutritional science to understand the compartmentalization of genes that influence the cause of diet-related complications.**(Mir, Nazir et al. 2022)** , genetic variation is a result of different food diets ,environment ,diseases , chemical drugs , pollutants and even behaviors and believes in correlation to each other but the most dominant effect is of nutrition which play a pivotal role on genes.

1.1.Nutrient-Sensing Mechanism: The metabolic enzymes, regulatory kinases, membrane receptors, and transcription factors focus on sensing the quantity of fatty and amino acids along with glucose. Glucose plays an important role as a member of the nuclear receptor superfamily inthe nutrient-sensing pathways. Macronutrients and micronutrients are bound to nuclear receptors with their metabolites like fatty acids to PPARs, oxysterols to liver X receptors, and vitamin D to vitamin D receptors, allowing nutritional variations to be translated into genomic responses. Nuclear receptors in metabolic organs response to nutrients changes by activating the numerous target genes. Furthermore, nuclear receptors and their ligands activate the immune system's inflammatory and antigen responses. Additionally, nuclear receptors are transcription factors that come into play a key role in the management of the circadian system in both the CNS and peripheral organs. Essentially, all of our body's tissues and cell types have a functional molecular base, whose coordination is critical for optimal physiological metabolism. The selection of robust nutrition sensing mechanisms was influenced by periodic scarcity of nutrients. The direct binding of the macronutrient or micronutrient to its sensor and an indirect method based on the identification of a metabolite that indicates the nutrient's availability are both possibilities for this sensing process. The relevant sensor is a protein which binds nutrients with the affinity for variations in physiological concentrations. The release of hormones or other signalling molecules into the circulation may be triggered by the detection of nutrients, resulting in a coordinated response of the entire organism. Lipids are rarely encountered free in soluble form due to its non-polar behaviour, i.e., its insolubility in aqueous phase. They are either carried in lipoproteins and chylomicrons or coupled by albumin in serum. GPRs (G protein-coupled receptors) engaged with long unsaturated fatty acid chains, like those found in the membrane of pancreatic cells, and boost glucose-triggered insulin release in these cells. The binding of lipids to GPRs in enteroendocrine cells of the intestine results in the production of incretins (i.e., gastrointestinal hormones that amplify insulin secretion). The scavenger receptor binds fatty acids in the intestinal lumen and begins their absorption (Carlberg 2019). Figure 1 shows the nutrient-sensing mechanism in brief. Internal cholesterol levels must be accurately sensed in order to avoid activation of the energetically difficult cholesterol synthesis pathway and hazardous levels of free cholesterol in the cell in the event of plentiful external supply. SCAP is a protein that binds cholesterol. SCAP enhances its affinity for the INSIG1 (insulin-induced gene 1) protein, which anchors SCAP and the transcription factor SREBF1 (sterol regulatory element-binding transcription factor 1) within the ER membrane, when intracellular cholesterol levels are high. SCAP-SREBF dissociates from INSIG and shuttles to the Golgi apparatus, where SREBF is liberated, translocates to the nucleus, and activates genes involved in lipid anabolism, such as cholesterol production and lipogenesis. Further, the enzyme HMGCR (HMG-CoA reductase), that is also found in the ER membrane, catalyses a rate-limiting phase of cholesterol de novo synthesis at low cholesterol levels. High quantities of substrates in the cholesterol production pathway, such as lanosterol, on the other hand, cause HMGCR to bind to INSIG, resulting in the enzyme's ubiquitin-mediated destruction. High cholesterol levels activate LXRs, implying that the SREBF and LXR pathways function in concert to sustain cellular and overall cholesterol homeostasis. When amino acids are in insufficient supply, cellular proteins are employed as a reserve and destroyed by the proteasome or autophagy. Therefore, by maintaining cellular energy levels, this mechanism aids survival during hunger. In contrast, amino acids can be catabolized for the generation of glucose and ketone bodies during periods of protracted hunger and hypoglycaemia; i.e., they supply important energy sources for the brain. Hepatic gluconeogenesis elevates glucose levels within liver cells during hypoglycaemia, and plasma membrane protein exports glucose to the circulation. The enzyme glucokinase, which catalyses the initial phases in the storage and consumption of glucose, i.e. glycogen formation and glycolysis, is involved in intracellular glucose sensing. The glucokinase has a low insulin affinity than the other hexokinases; hence, it is only active at high sugar levels. As a glucose sensor, glucokinase works similarly to plasma membrane protein. This characteristic permits glucokinase to transport non-phosphorylated glucose from the liver towards the brain and skeletal muscles under lower glucose levels. The comprehensive research towards nutrient-sensing systems, particularly those mediated by nuclear receptors, would enable a more holistic understanding of our body's biochemical reactions to food components. This will include not just the cross-regulation of distinct nutrient-sensing pathways, but also other signalling pathways including those that control cellular development or mediate chronic inflammation (Carlberg 2019). 21 Nutrigenomics Research: A Review 363 Many extracellular growth factors and cytokines (signalling molecules) all seem to be hydrophilic and therefore cannot pass through cellular membranes, requiring interaction with membrane receptors to activate a signal transduction pathway that ultimately leads to changes in gene expression via the activation of a transcription factor. As a result, transcription factors act as sensors for a wide range of cellular changes. The signal transduction process is simpler in the case of lipophilic signalling molecules, like steroid hormones, because these molecules can pass through cellular membranes where it binds straightforwardly to the nuclear receptors which are the ligand-sensitive transcription factors. Nuclear receptors are a group of transcription factors that can bind to and be activated by small lipophilic molecules termed ligands. There are 48 nuclear receptors in humans. Micro- and macronutrients, as well as their metabolites, make up a large portion of these nuclear receptor ligands. It thus involves retinoic acid (vitamin A derivate), fatty acids, lipids, bile acids, oxysterols, and other hydrophobic food ingredients. The specificity of such nuclear receptors towards specific distinct ligands varies from 0.1 nM to greater than 1 mM and reflects normal molecular concentrations. As a result, few nuclear receptors act as real micronutrients and macronutrient sensors. Other nuclear receptors, such as the hepatocyte nuclear factor liver receptor and steroidogenic factors, bind nutritional derivatives like sterols, phospholipids, fatty acids, and haem, and the interaction does not fall under sensing. The sensor's heterodimers' correct and precise detecting nuclear receptors attach to certain nucleotide sequences. Other nuclear receptors, on the other hand, form homodimers or even touch DNA as monomers. Heterodimer complexes are found in the nucleus, where they do not disintegrate from the chaperone proteins to diffuse back into nucleus. This shows that the nucleus is where macro- and micronutrient sensing occurs through nuclearreceptors. Nutrients can thus operate as gene switches by causing a structural shift in the ligand-binding regions of certain nuclear receptors (Carlberg 2019). 364 S. Dey and Y. Kumar The immune system is made up of a variety of highly specialized cells which are all produced through a process known as haematopoiesis, which involves the differentiation of blood cells. Epigenetic pathways regulate cellular differentiation, and a number of developmental transcription factors play a critical role. Immune system cells have a high turnover rate, allowing them to respond to environmental changes as quickly as possible. The differentiation and subtype specification of immune cells such as T cells, macrophages, and dendritic cells is aided by lipid sensing and signalling via nuclear receptors. Notably, such cells seem to be mobile and can be found in various different subtypes almost anywhere in human bodies, including metabolic tissues and disease scenarios like obesity. Thus, alterations in the transcriptome profile and subtype specification of macrophages and dendritic cells, as well as their precursors, monocytes, coordinate metabolic, inflammatory, and general stress-response pathways show maximal adaptive environmental changes. Nuclear receptors play a crucial role in perceiving these endogenous and external stimuli, as well as modifying the immune cells' gene expression profiles (Carlberg 2019).**(Dey and Kumar 2022)**

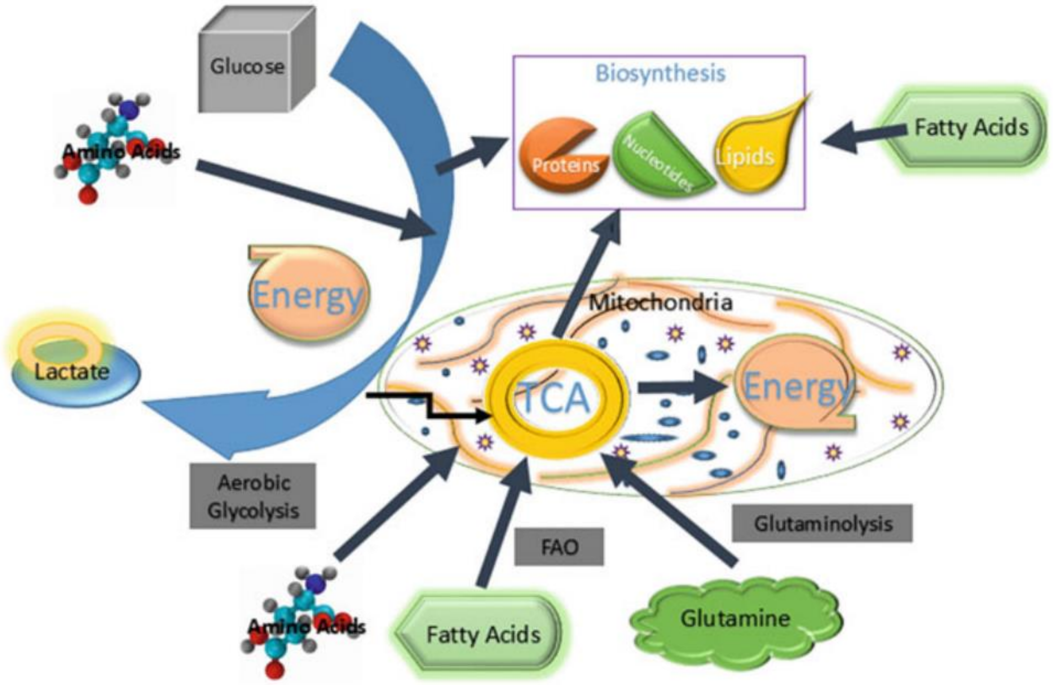


Fig.1 Nutrient-sensing mechanism

*1.2.Genome:*The genome is the haploid set of chromosomes (complete set of genes or genetic material) in each cell of a multicellular organism. It consists of DNA (or RNA in RNA viruses). A gene is a unit of heredity that is transferred from parent to offspring which determines some characteristic of the child. The genome includes both genes, and non-coding sequences of DNA/RNA. The genome is largely static within an individual . It is undeniable that the primary sequence of our genome encodes all the biological potential of what we can become. Rosalind Franklin's diffraction data, and subsequent modelling by Watson and Crick, identified the fundamental double helical structure of DNA, marking
the first association of genome structure with function. Since this time, we have studied the relationship between the primary sequences of DNA to gain information on the genes it encodes. With the Herculean effort of the Human Genome Project as well as the 1,000 Genomes Project, we have now begun to truly understand how this primary sequence provides the blueprint for all the biological potential within an organism. Within this code, we have natural variations that do not necessarily cause disease but changes how our biology responds to our ever-changing environment. A classical definition of nutrigenetics is the study of how genetic variations effect how our cells "interpret" nutrients and by extension the impact on health, disease, and lifespan (Figure 2). To fully appreciate 3-dimensional genome organization and its dynamics, we first need to review thefundamentalprinciples of genome biology. In eukaryotic systems, DNA is complexed with positively charged histone proteins to form chromatin. The most basic structure of chromatin is the nucleosome (Table 1); ~146 bp of DNA wrapped around a histone octamer (two of each H2A, H2B, H3, and H4) proteins . With the 3.6 billion base pairs of DNA measuring ~2 m in a single cell, some theories suggest that the primary driver for chromatin evolution was to allow for efficient packing. However, electron micrographs measuring the volume of the nucleus occupied by chromatin reveals that this is only ~16.5% of the total volume , indicating that compaction is not the primary driver. In addition, the association of DNA with histones actually increases the total volume occupied, further providing evidence against this theory. One possible explanation for chromatin evolution may be that the primary sequence of DNA alone does not contain sufficient functionality to guide gene regulation. Although the primary DNA sequence

contains essential sequence motifs for DNA binding proteins and transcription factors, this is only one critical step in gene regulation. As such, the tails of histones that protrude from the nucleosomal core likely evolved to provide the additional levels of regulation and structures for controlling gene expression. Modification of these histone tails by post-translation modifications provide information indicating if a gene is to be transcribed or repressed. These histone modifications, in combination with CpG island methylation and noncoding RNAs (not discussed here) constitute the epigenome. In contrast to the relatively stable nature of the primary DNA sequence, the epigenome is extremely dynamic and can change within minutes in response to cells receiving stimuli. Although epigenetic changes are central to mediating genome response to dietary compounds, there are several excellent review articles **(la Torre, Lo Vecchio et al. 2023)** discussing this topic, and we will focus on genome structure and organization.**(Fleming, Nelson et al. 2023)**

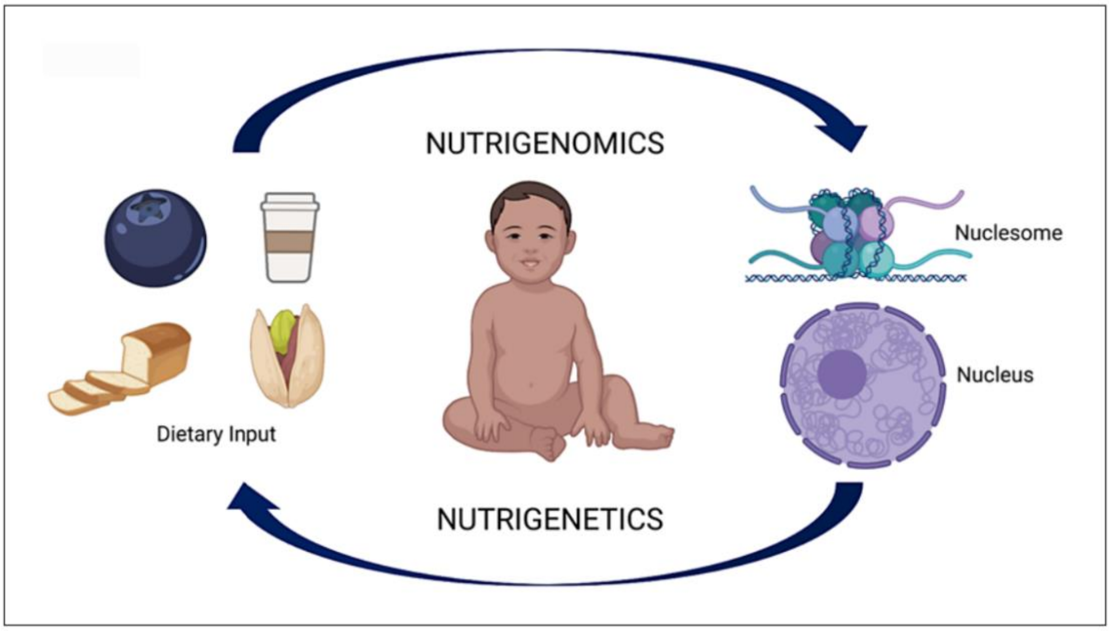
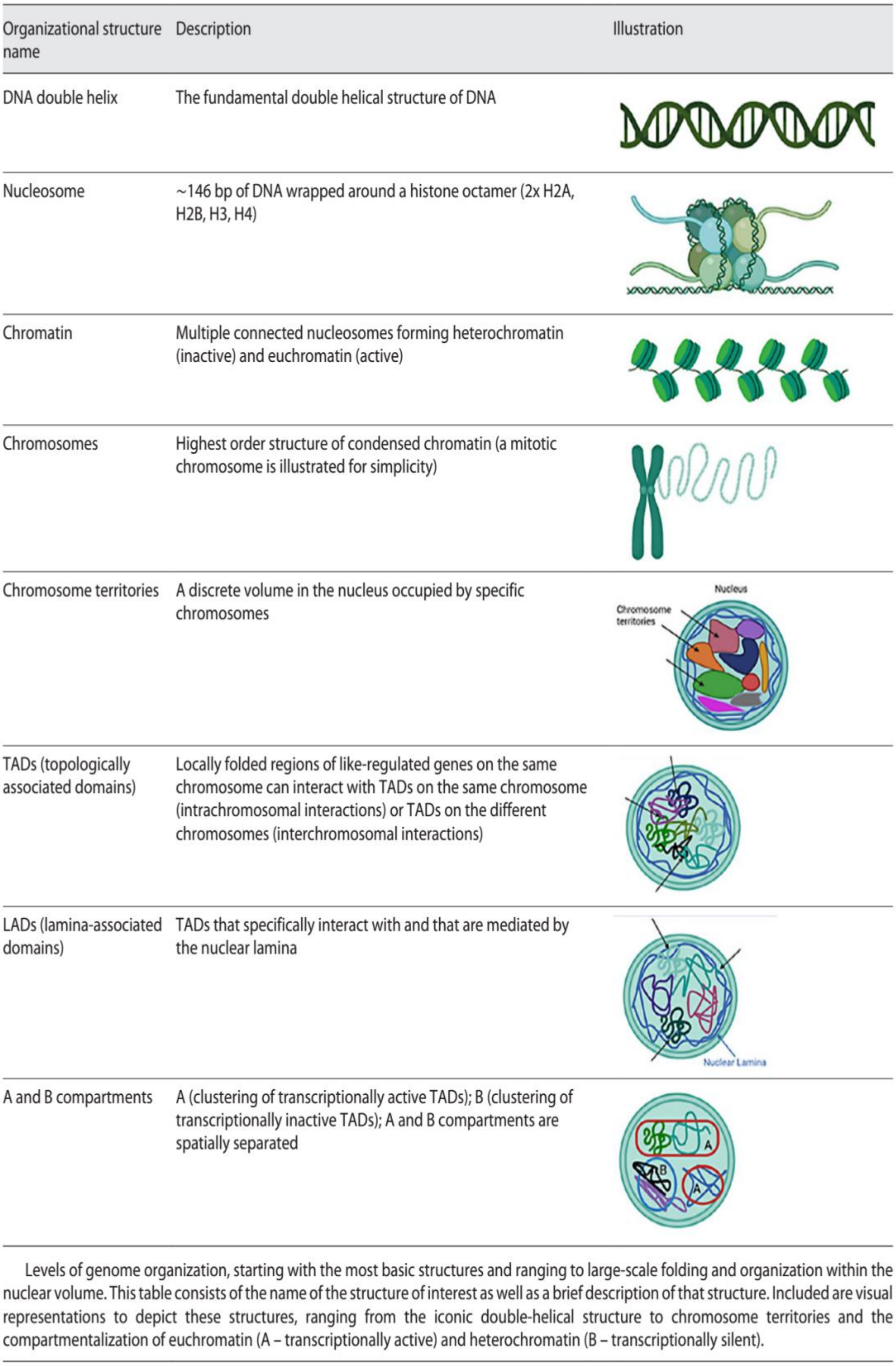


Fig.2. Nutrigenetics versus nutrigenomics. Nutrigenetics is the study of how genetic variation impacts how cells interpret/use essential and nonessential nutrients whereas nutrigenomics is the study of how these nutrients modulate the function of the genome through organizational changes.**(Fleming, Nelson et al. 2023)**



Organizational structure name	Description	Illustration
DNA double helix	The fundamental double helical structure of DNA	
Nucleosome	~146 bp of DNA wrapped around a histone octamer (2x H2A, H2B, H3, H4)	
Chromatin	Multiple connected nucleosomes forming heterochromatin (inactive) and euchromatin (active)	
Chromosomes	Highest order structure of condensed chromatin (a mitotic chromosome is illustrated for simplicity)	
Chromosome territories	A discrete volume in the nucleus occupied by specific chromosomes	
TADs (topologically associated domains)	Locally folded regions of like-regulated genes on the same chromosome can interact with TADs on the same chromosome (intrachromosomal interactions) or TADs on the different chromosomes (interchromosomal interactions)	
LADs (lamina-associated domains)	TADs that specifically interact with and that are mediated by the nuclear lamina	
A and B compartments	A (clustering of transcriptionally active TADs); B (clustering of transcriptionally inactive TADs); A and B compartments are spatially separated	

Levels of genome organization, starting with the most basic structures and ranging to large-scale folding and organization within the nuclear volume. This table consists of the name of the structure of interest as well as a brief description of that structure. Included are visual representations to depict these structures, ranging from the iconic double-helical structure to chromosome territories and the compartmentalization of euchromatin (A – transcriptionally active) and heterochromatin (B – transcriptionally silent).

Table 1. Summary of the levels of genome organization

1.3.Nutrigenomics: aims to identify the effects of several nutrients, including macronutrients and micronutrients on the genome **(Bakrim, Aboulaghras et al. 2023)** , and explores the interaction between genes and nutrients or food bioactives and their effects on human health **(Guest, Corey et al. 2022)**, Nutrigenomics also describes the use of functional genomics tools to study a biological system to understanding of how nutritional molecules affect metabolic pathways and homeostatic control. This branch of science will reveal the optimal diet form within a series of nutritional changes whereas Nutrigenetics will yield critically important information that assist clinicians in identifying the optimal diet for a given individual, i.e. personalized nutrition**(Casper and Ac 2023)**, also Nutrigenomics examines relationships among genes, diet, and health. Specifically, nutrigenomic research is "the study of how foods affect the expression of genetic information in an individual and how an individual's genetic makeup affects the metabolism and response to nutrients and other bioactive components in food.**(Greyvensteyn, Walsh et al. 2023)** Included among the aims of nutrigenomic research are to:
1-Identify genes and gene variants that may be significant in understanding genetic responses to diet.
2-Identify genotypes associated with diet-related disease.
3-Modify diet for the treatment or prevention of disease.
4-Improve dietary guidelines at group and individual levels.**(Rajasekaran and Davison 2023)**
Although there is growing expectation that nutrigenomic research will improve individual and group health through personalized nutrition.**(Casper and Ac 2023)** the field faces several methodological challenges, including:

- Defining and measuring dietary intake;
- Shifting outcomes of interest from actual disease to biomarkers indicating early stages of disease;
- Simultaneously analyzing genetic, molecular, clinical, phenotypic, and dietary data to account for the full effects of food;
- DNA and its functions present many unknowns, and new types of DNA continue to be discovered;
- Conducting longitudinal studies with large, diverse populations for adequate statistical power; and
- Addressing bias toward positive findings in the publication of NG research.**(Keijer, Escoté et al. 2023)**

These and other challenges contribute to inconsistent findings across genetic association studies and complicate the development of nutrigenomic interventions to improve individual health.**(Meyer, Appelbaum et al. 2023)** . Transcriptomics, proteomics, and metabolomics are also technologies that apply in Nutrigenomics research (figure 3) , According to numerous studies, nutrients can alter the expression of genes at the level of gene regulation, signal transduction, chromatin structure and protein function **(Fleming, Nelson et al. 2023)** , Dietary chemicals can affect gene expression directly or indirectly. At the cellular level nutrients may act as ligands for transcription factor receptors **(Zou, Ye et al. 2022)** or be metabolized by primary or secondary metabolic pathways, thereby altering concentrations of substrates or intermediates, and finally positively or negatively affect signal pathways **(Pencina, Valderrabano et al. 2023)** , Transcription factors (TFs) are one of the key molecules through with nutrients can alter the gene expression. One of the most important groups of nutrient sensors is PPARs TFs with 48 members in the human genome. The majority of receptors in this superfamily bind nutrients, their metabolites, and influences expression of specific genes involved in numerous metabolic process in the liver, including fatty acid oxidation, ketogenesis, gluconeogenesis, amino acid metabolism, cellular proliferation, and acute-phase response **(Jabeen, Malik et al. 2023)** , For example, the fatty acids palmitic (16:0), oleic (18:1n9), linoleic (18:2n6), and arachidonic acid (20:4n6) **(Wang, Chen et al. 2021)**, and the eicosanoids, 15deoxy-δ12, 14prostaglandinJ2 and 8-(S) hydroxyeicosatraenoic acid, are **ligands** for PPAR-δ **(Aldamarany, Taocui et al. 2023) ,** These nuclear receptors act as sensors for fatty acids. Lipid sensors usually heterodimerize with retinoid receptor, whose ligand is derived from another dietary chemical, vitamin A, and hyperforin, bind directly to nuclear receptors and influence gene expression (Table1).

The liver X receptor-α (binding cholesterol metabolites), bind as a heteromers to specific nucleotide sequence (response elements) in the promoter regions of a large member of genes. During ligand binding, nuclear receptors undergo a conformational change that results in coordinated dissociation of corepressors and recruitment of coactivator proteins to prepare transcriptional activation**(Jabeen, Malik et al. 2023)**. Thereby, a number of genes are induced such as those involved in fatty acid oxidation or fatty-acid storage, depending on the cellular metabolic state (**Gaur and Kaur 2023)**. In metabolically active organs, such as the liver, intestine, and adipose tissue, these TFs act as nutrient sensors by changing the level of DNA transcription of specific genes in response to nutrients changes **(Jabeen, Malik et al. 2023).** Dietary chemicals indirectly regulate some of TFs. The sterol regulatory element binding proteins (SREBPs), for example, are activated by protease cleavage, an event regulated by low levels of oxy sterols and changes in insulin/glucose and PUFAS **(Alam, Ali et al. 2022)**. The carbohydrate-responsive element-binding protein (chREBP) is a large TF, activated in response to high glucose levels, and is regulated by reversible phosphorylation events **(Sakiyama, Li et al. 2022)**. This DNA binding protein servesas an effector of lipogenic gene expression **(Feng, Sureda et al. 2019)**. Moreover, dietary chemicals can directly affect signal transduction pathways. For example, green tea contains the polyphenol,11-epigallocatechin-3- gallate (EGCG) that EGCG inhibits tyrosine phosphorylation of Her-2/neu receptor and epidermal growth factor receptor that reduces signaling via the phosphatidyl inositol 3-kinase (PI-3)-AKt kinase-NF-kB pathway. Activation of the NF-kB pathway is associated with some types of breast cancer **(Alam, Ali et al. 2022).** PUFAs such as n-3 and n-6 are other micronutrients, which are also referred to as omega-3 and omega-6 fatty acids, may influence gene expression. Animal studies have demonstrated that PUFA intake can modulate the gene expression of several enzymes involved in lipid and carbohydrate metabolism. A significant interaction has also been shown for the PPARA Lue162Val polymorphism n-6 PUFA intake. Individuals with the less common V162 allele, increased n-6 PUFA intake is associated with a marked reduction in triacylglycerol concentration, whereas this association is not observed in L162 carriers. Conversely, in L162 and V162 carriers n-3 PUFA intakes results in triacylglycerol concentrations reduction **(Rajendiran, Lamarche et al. 2021)**. Approximately 40 micronutrients are needed in the human diet. Suboptimal intakes of specific micronutrients have been associated with CVD (Vit B, E, and carotenoids), cancer (folate, carotenoids), neural tube defects (folate), and bone mass (Vit D) **(Francis, Veeraraghavan et al. 2022)**. B6, B12 and folate deficiencies, for example, are associated with increased serum homocysteine levels. Hyperhomocysteinemia is a risk factor and marker for coronary artery disease. Deficiency of Vit B12, folic acid, B6, niacin, C or E, iron or zinc appears to imitate radiation in damaging DNA by causing single and double-strand breaks, oxidative lesions, or both **(Hameed, Ahmed et al. 2022)**, (Table 2). Nutrient deficiencies are more important than radiation because of constancy of exposure to milieu promoting DNA damage **(Saleem, Awad et al. 2022)**. For example, folate deficiency breaks chromosomes due to substantial incorporation of uracil in human DNA (4 million uracil/cell) **(Tagliamonte, BARONE LUMAGA et al. 2023)**. Amino acids can play the role of nutritional signals in the modulation of expression of particular genes. Studies have shown that cells can detect variants in amino acid levels and respond by mechanism as control of transcription, mRNA stabilization ,as well as by up or down regulation of translation initiation **(Okanishi, Ohgaki et al. 2022).** For example, in human cells amino acid L-tryptophan in supraphysiologic concentrations is a powerful inducer of collagenase gene expression at a transcriptional level. The increase in collagenase mRNA levels was reversible, time and L-tryptophan dose dependent **(Lu, Ma et al. 2022)**. Simple and complex carbohydrates have differential effects on blood glucose concentrations. Foods with a high glycemic index (GI) would increase insulin production and, decrease synthesis of insulin receptors. High glucose concentration also induces the transcription of several genes of the glycolytic and lipogenic pathways **(Meiliana and Wijaya 2020)**. Therefore, dietary chemicals are regularly ingested and are involved indirectly and directly in regulation gene expression, it follows that a subset of genes regulated by diet must be involved in disease initiation, progression, and severity **(Mirzaei, Afaghi et al. 2021)**.

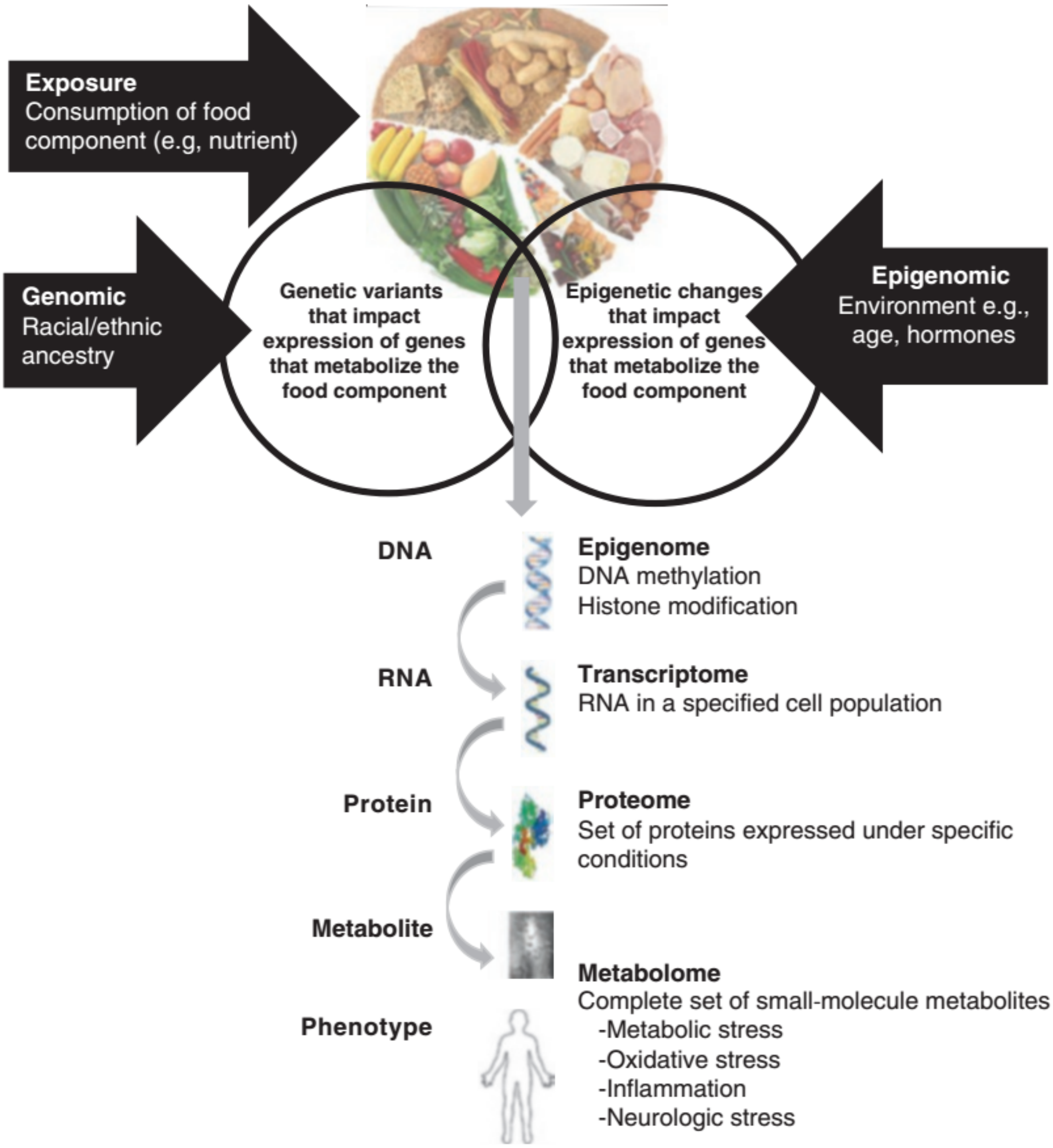
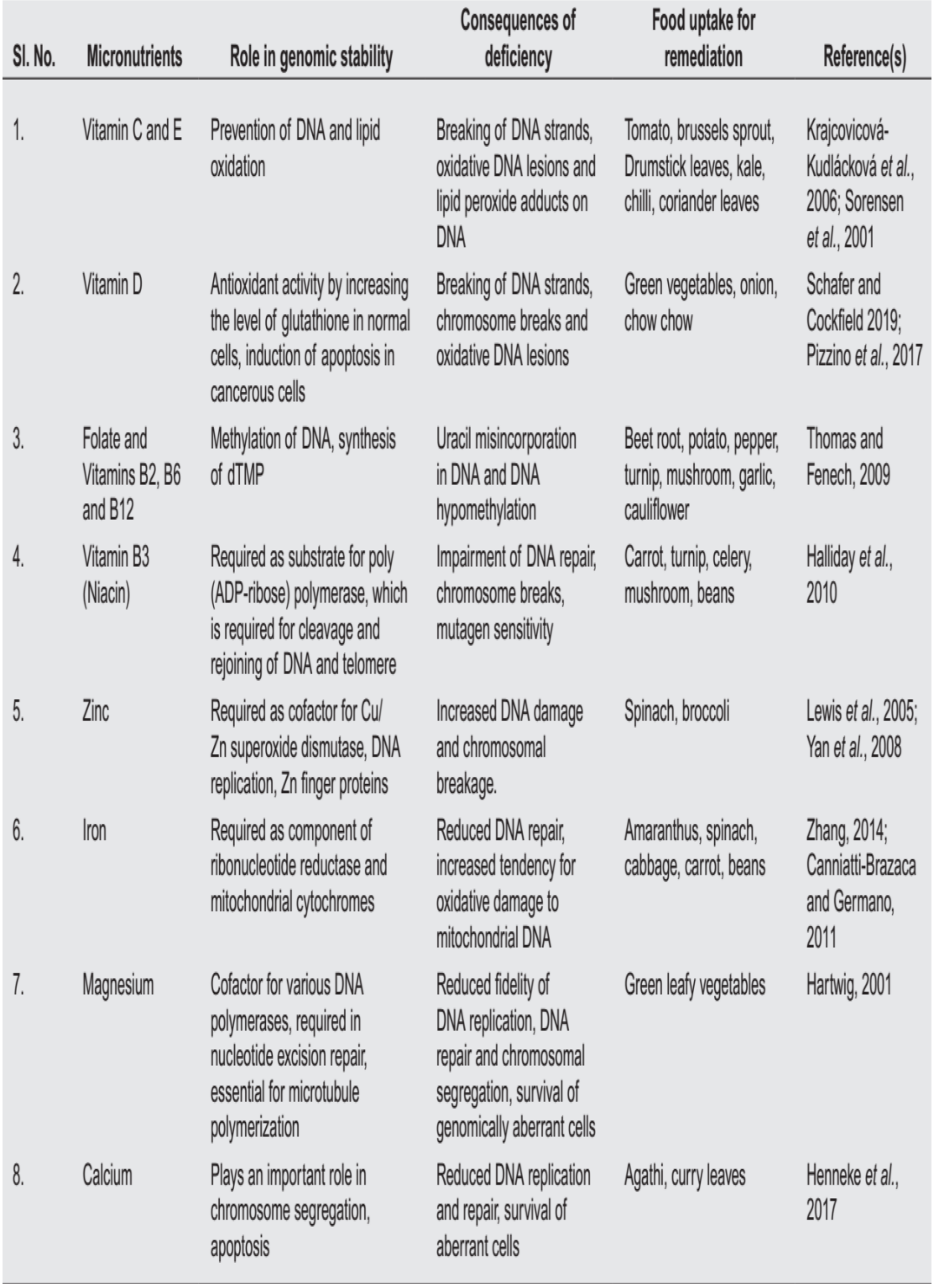


fig. 3 Diet–gene interactions. Adapted from **(Mullins, Bresette et al. 2020)**

Table 2: Role of micronutrients in maintaining genomic stability.**(Jabeen, Malik et al. 2023)**



Sl. No.	Micronutrients	Role in genomic stability	Consequences of deficiency	Food uptake for remediation	Reference(s)
1.	Vitamin C and E	Prevention of DNA and lipid oxidation	Breaking of DNA strands, oxidative DNA lesions and lipid peroxide adducts on DNA	Tomato, brussels sprout, Drumstick leaves, kale, chilli, coriander leaves	Krajcovicová-Kudlácková *et al.*, 2006; Sorensen *et al.*, 2001
2.	Vitamin D	Antioxidant activity by increasing the level of glutathione in normal cells, induction of apoptosis in cancerous cells	Breaking of DNA strands, chromosome breaks and oxidative DNA lesions	Green vegetables, onion, chow chow	Schafer and Cockfield 2019; Pizzino *et al.*, 2017
3.	Folate and Vitamins B2, B6 and B12	Methylation of DNA, synthesis of dTMP	Uracil misincorporation in DNA and DNA hypomethylation	Beet root, potato, pepper, turnip, mushroom, garlic, cauliflower	Thomas and Fenech, 2009
4.	Vitamin B3 (Niacin)	Required as substrate for poly (ADP-ribose) polymerase, which is required for cleavage and rejoining of DNA and telomere	Impairment of DNA repair, chromosome breaks, mutagen sensitivity	Carrot, turnip, celery, mushroom, beans	Halliday *et al.*, 2010
5.	Zinc	Required as cofactor for Cu/Zn superoxide dismutase, DNA replication, Zn finger proteins	Increased DNA damage and chromosomal breakage.	Spinach, broccoli	Lewis *et al.*, 2005; Yan *et al.*, 2008
6.	Iron	Required as component of ribonucleotide reductase and mitochondrial cytochromes	Reduced DNA repair, increased tendency for oxidative damage to mitochondrial DNA	Amaranthus, spinach, cabbage, carrot, beans	Zhang, 2014; Canniatti-Brazaca and Germano, 2011
7.	Magnesium	Cofactor for various DNA polymerases, required in nucleotide excision repair, essential for microtubule polymerization	Reduced fidelity of DNA replication, DNA repair and chromosomal segregation, survival of genomically aberrant cells	Green leafy vegetables	Hartwig, 2001
8.	Calcium	Plays an important role in chromosome segregation, apoptosis	Reduced DNA replication and repair, survival of aberrant cells	Agathi, curry leaves	Henneke *et al.*, 2017

1.4.Nutrigenetcs: Nutrigenetics term was used first time by Dr R.O Brennan in 1975 in his book Nutrigenetics **(Simopoulos 2010).** Nutrigenetics points to understanding how the genetic background of an individual impact to the diet **(Casper and Ac 2023)**. The study of gene-nutrient interaction is a developing area of science. This idea that adverse diet/genome interaction can cause disease is not new and the unsuitable diet for any individual genotype could be a risk factor for monogenetic and polygenetic disease **(Blampied, Bell et al. 2020)**. Genetic polymorphisms can influence response to environmental elements, such as enzymatic activities changes that affect circulating concentrations and ultimately the effectiveness of chemicals and their metabolites **(Rajasekaran and Davison 2023)**. Furthermore, metabolic disorders are other examples of influence of the genetic variations to diet such as PKU defects associated with long chain fatty acid oxidation, iron absorption (haemo-chromatosis), which can be reasonably well managed with dietary restrictions **(Bobo, Magdy et al. 2022).** As mentioned earlier SNPs study can be categorized in the field of Nutrigenetics. Some specific examples of the association between SNPs and specific food components such as enzymes deficiency are reviewed in this article. For example, different mutations in galactose-1-phosphate uridyltransferase (GALT) gene **(Bobo, Magdy et al. 2022)**, phenylalanine hydroxylase gene and Glucose-6-phosphate dehydrogenize (G6PD) gene **(Assmar, Keypour et al. 2018)** resulted in Galactosemia, Phenylketonuria (PKU), and Favism diseases, respectively. Other examples of enzymes polymorphisms include Lactase-phlorizin hydrolase gene (LPH) polymorphisms that showhow SNPs alter gene expression. This polymorphism is in the upstream of the lactase-phlorizin hydrolase gene (LPH) associated with hypolactasia and changes tolerance to dietary lactose (milk sugar, LPH hydrolyzes lactose into glucose and galactose) and allows different expression of the LPH **(Mir, Nazir et al. 2022)**. Glutathione peroxide gene polymorphism is another example. The association between selenium supplementation and reduced incidence of liver, colon, prostate, and lung cancer in human has been shown. However, no individuals may respond equally. Glutathione peroxide is a selenium-dependent enzyme that acts as an antioxidant enzyme. Polymorphism at codon 198 of human glutathione peroxides results in a subsituation of proline to leucine amino acid, and has been associated with an increase risk of lung cancer. Investigators shown that persons with (Pro/Lue) genotype were at 80% greater risk for lung cancerand (Lue/Lue) genotypes were at 130% greater risk compared risk those with the (Pro/Pro) genotype. The leucine-coding allele was less responsive to increased activity because of selenium supplementation as compared with the prolin containing allele **(Roosan, Wu et al. 2023)**.Manganese super oxide dismutase (MnSOD) is a mitochondrial enzyme that plays a key role in detoxification of reactive oxygen species. A polymorphism valine to alanin subsituation in in this enzyme alters its transport into mitochondria which has been associated with increased risk of breast cancer **(Roosan, Wu et al.)**. Methylen tetrahydrofulate redoctase (MTHFR) enzyme catalyzes the reaction that produces 5-methyl tetrahydrofolate. The one-carbon units are carried on N-5 or N10 of tetrahydrofolate. One-carbone metabolism is needed for the denovo synthesis of purine nucleotides and thymidilate and for the remethylation of homocyisteine to methionine. With methionine adenylation S-adenosylmethionine (SAM) is formed, which is a co-factor for numerous methylation reactions such as DNA methylation that affect gene regulation **(Bobo, Magdy et al. 2022).** For the MTHFR gene tow important SNPs has been well recognized: C677T (cytosine-tothymidine subsituation resulting in the conversion of an alanine to valine) and A1298C (adenineto-cytosine subsituation resulting in the conversion of an alanine to glotamic acid). The C677T polymorphism is the most common variant that occurs as homozygous T/T in 5-10% of the and as heterozygous C/T genotypes up to 40% general population **(Rogulska, Strońska et al. 2021)**. The presence of C677T or A1298C mutations is associated with reduction in MTHFR enzyme activity and impairs folate accumulation, which may cause increases homocysteine concentration in plasma, a risk factor for venous thromboembolic and ischemic arterial diseases **(Subbiah 2007)**.Another polymorphism of

MTHFR gene is Ala222Val that affects folate metabolism. It increases the conversion of dUMP to dTMP and leads to more folate-dependent thymidine biosynthesis and folate deficiency **(Bobo, Magdy et al. 2022)**. This polymorphism is a risk factor for spontaneous abortionsand decreased fetal viability, thus maternal folate supplementation can be useful for individuals with this polymorphism **(Stover 2006)**. MTHFR is also involved in maintenance genomic CpG methylation patterns and prevention of DNA strand breaks, these mutations are associated with increased risk of neural tube defects and some types of cancer **(Kiani, Dhuli et al. 2022)**. Changes in the concentration of folate (the MTHFR substrate) and riboflavin (the MTHFR cofactor) can modulate the activity of MTHFR gene **(Farhud and Yeganeh 2010).** Generally, folic acid supplementation can help the negative health effect of these SNPs with decrease in plasma homocysteine levels. Enzymes that utilize and metabolize vitamin B12 have been associated with NTDs, increased risk of Down syndrome and colon cancer. For example, a common polymorphism in the HFE gene (Cys282Tyr) is associated with iron storage disease hereditary haemochromatosis, leading to an iron accumulation in the liver, heart and endocrine glands. This protein is an important regulator of cellular iron homeostasis and has role in intestinal iron absorption by regulating the interaction of the transferrin receptor with transferrin .Cytochrome P450s (CYPs) enzymes play a central role in the oxidative biotransformation of steroids, prostaglandins, nutrients, drugs, chemicals and carcinogens. Several dietary factors can alter the expression of CYP isoforms. CYP1A2 plays an essential role in the metabolism of wide range of drug and chemical substances. For example, CYP1A2 activates dietary carcinogens such as aromatic amines, but also detoxifies compounds such as caffeine. Low-activity CYP1A2 genotype with an increased risk of myocardial infarction suggests that this enzyme detoxify a substance, which may be an important risk factor in the population. Indeed, individuals with a low-activity CYP1A2 genotype are at a greater risk of coffee-associated heart disease. As caffeine is the main substance in coffee and is detoxified by CYP1A2, it may be an important risk factor for heart disease in certain population . Glutathione S transferase (GST) enzyme is a superfamily of enzymes that play an important role in the detoxification of several dietary compounds. GSTM1, GSTT1 and GSTP1 are isoforms of this enzyme. The GSTM1 and GSTT1 null genotype have been associated with both an increased and a decreased risk of some types of cancers such as breast cancer . Some components such as dietary isothiocyanates that are found in cruciferous vegetables are eliminated with GSTs enzymes. Indeed, protective effect of the GSTM1 null genotype on colon and lung cancer has been related to lower urinary excretion of glutathione conjugated phytochemicals indicating they are not rapidly excreted. GSTT1 plays a similar role to GSTM1 in eliminating beneficial phytochemicals found in cruciferous vegetables. Moreover, in vegetables rich in phytochemicals such as isothiocyanates the expression of GSTs is increased conjugating them to more water-soluble forms that are easily excreted . Endothelial nitric oxide synthase (eNOS) is synthesized from the amino acid L-argenine by NO synthase (NOS). The eNOS is expressed in the endothelium and produces NO that diffuses to vascular smooth muscle cell, where it increases the concentration of cGMP, leading to vascular relaxation. NO has central role in the pathogenesis of coronary spasm and atherogenesis. Several polymorphisms of eNOS may be associated with specific phenotype. For example, a Glu298Asp polymorphism in the eNOS gene has been associated with ischemic heart disease, myocardial infarction, and coronary spasm . Genetic polymorphisms in catechol-O-methyltransferase, sulfotransferase, and UDP-glucuronosyltransferase result in differences in enzymatic activity. These enzymes metabolize some of dietary compounds. For example, green tea was associated with a lower risk of breast cancer only in women with the low-activity allele for catecholO-methyltransferase. This enzyme catalyzes the methylation of catechins (a polyphenolic antioxidant plant secondary metabolite) in green tea making them more quickly eliminated . Apolipoprotein E (ApoE) gene has three different alleles (ε2, ε3, ε4). Persons with ε4 variant respond to a high-fat diet negatively with an increased risk for coronary heart disease (CHD). In these individuals, low-fat diet should be useful (2). Moreover, there is an important relationship between allelic variants in the ApoA1/C3/A4/A5 genes and the effect of dietary fats on lipoprotein metabolism and CVD (cardio vascular diseases) risk. Linkage disequilibrium within Apo A1/C3/A4/A5 cluster has been represented to affect plasma lipid concentration and CVD risk. Apolipoprptein A-1 is and is a key component of high-density lipoprotein particles (HDL). The locus of gene encoding APOA-1 is on chromosome 11q and highly polymorph and has a specific SNP in its promoter region . An Adenin/Guanin subsituation in the promoter region (-75bp) of the ApoA1 gene is common in different populations. The presence of A allele (A/A and A/G) has been associated with incresed HDLcholesterol. Moreover, mild increase in APOA-1 concentrations in subjects with the G/G genotype was observed . APOA-5 gene is also an important regulator of triglyceride (TG)-rich lipoprotein (TRL) metabolism . One of the Vitamin D receptor (VDR) polymorphism is Fok1. Individuals with F allele have three amino acids more than those without F allele in their VDR. The Ff or ff genotype is associated with 51% and 84% greater risk of colorectal cancer, respectively. Individuals that consumed low calcium and fat diet have more than double risk of colorectal cancer, specifically in persons with ff genotype rather than Ff genotype . VDR polymorphisms have been also associated with childhood and adult's asthma . Peroxisome proliferator-activated receptors (PPARs) are nuclear receptor supper family that plays an essential role in fatty acid oxidation, glucose, and extracellular lipid metabolism. PPARs are the best-known fatty-acid-regulated nuclear receptors. One of the three members of the PPARs family regulates many genes involved in fatty acid metabolism. PPR-α (PPARA) plays a central role in lipid oxidation and inflammation, whereas PPAR-γ is involved in adipocytes differentiation, glucose and lipid storage, and inflammation. PPAR-δ (also known as PPAR-β), may has a crucial role in development, lipid metabolism, and inflammation. These receptors bind to fatty acid and regulate the expression of genes involved in fatty acid transport and metabolism. PPARs family also involve in activation of about 300 genes . The PPAR-α gene has a polymorphism at codon 162 (Lue162Val) that has been associated with changes in total cholesterol, LDL-associated cholesterol, and Apo B concentrations. The less common V162 allele is associated with significantly higher serum concentration of total cholesterol, LDL cholesterol, Apo B, and Apo C-III than in carriers of L162 allele, especially in men . For individuals with the common L162 allele, increased intake of polyunsaturated fatty acids (PUFAs) had little effect on fasting triacylglycerol concentrations. In those with the less common V162 allele, however, fasting triacylglycerol concentrations fell abundantly with increasing PUFA intake **.(Farhud and Yeganeh 2010)**

1.5.Epigenomics: The epigenome is involved in regulating gene expression, development, tissue differentiation, and suppression of transposable elements. The epigenome can be dynamically altered by external environmental factors, whereas the underlying genome is not.**(Casper and Ac 2023)**, when you ever wonder how a cell with the same genomic make up could differentiate into the extensive array of cell within an organism? The answer is epigenomics where the complete set of epigenetic modifications of the genome of an organism is studied , environmental factors play a monumental in the field of epigenomics , one major environmental factor that humans are exposed to from preconception to death is diet , the field of nutritional epigenomics , nutriepigenomics , studies how diet impact human health through epigenetic mechanism , previous studies suggest that during embryogenesis , global genomic alteration are erased , however after implanting of the embryo epigenetic marks begain to be reestablished , over time environmental factors can cause modifications to occur on top of the genome, which regulates gene silencing or activation, genome regulation is mediated by DNA methylation , histone modification and non-coding RNAs or RNA-based modifications , which contribute to changes in the gene expression independent of changes to the DNA code. Epigenetic marks may be global or tissue-specific , and can also be inherited from parent to offspring through the germline , in essence inheritable transmission of phenotype can occur in the absence of the causative stimuli , past studies have linked epigenetics with diseases such as cancer , however recent studies include depression , obesity , cardiovascular disease , metabolic disease and more , its important to note that diet has been implicated in the regulation of these epigenetic adaptations and considered a key contributor of human health and disease (fig.4)**(Ferguson 2019)** . Nutritional epigenomics has highlighted diet as a critical factor with thepotential to influence both healthspan and lifespan. Novel insights into how perturbations in 1-carbon metabolism influence DNA methylation and data from epigenome-wide studies of nutrition interventions offer promising insights to understanding how diet impacts the methylome during healthy aging and disease.**(Amenyah, Ward et al. 2020)**

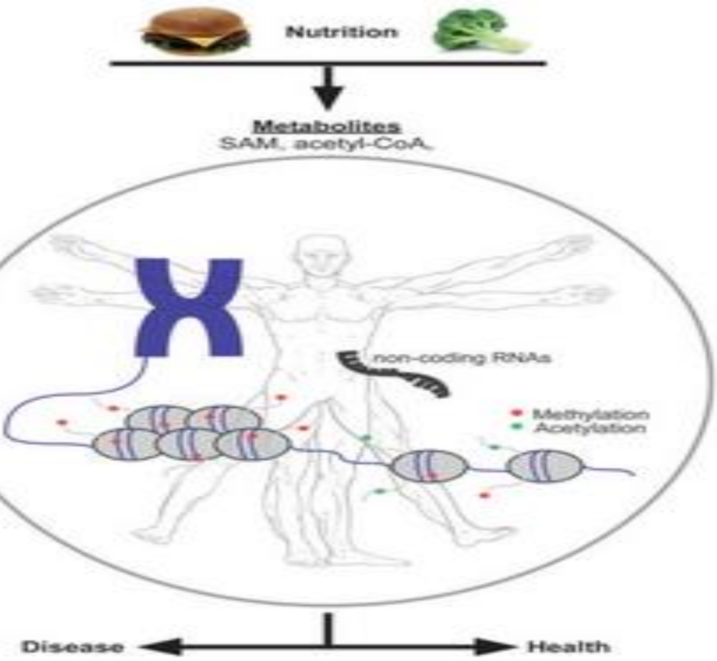


Fig.4 Diet and dietary metabolites impact the epigenome in manner that can promote health or disease

1.6.1 Epigenetics: Epi-genetics (the prefix ‘epi’- from Greek: above, outside of, around) is the study of external or environmental factors that turn genes on and off, and affect how cells interpret and express genetic code. Dynamic alterations in the transcriptional potential of a cell may or may not be heritable. Transcription is the first step of gene expression, in which a particular segment of DNA is copied into RNA. Unlike genetics based on changes to the genotype, changes in gene expression of epigenetics have other causes (i.e., external or environmental). The genes contained in DNA are provided by both parents, and are copied and inherited across generations. Physical traits like eye color, height, weight, blood type, etc. are the result. DNA is passed on to new cells during development and when reproduced within the body. Epigenetics is the study of how inherited traits are changed by influences other than a change to the DNA sequence. Non-genetic or inherited factors can cause genes to express themselves differently by modifying or changing their expression. This is done by activation, or silencing, of specific genes through abnormal methylation processes.**(Casper and Ac 2023)**

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1.6.2.Nutritional Epigenetics and Signalling: Numerous studies in humans, animals, and cell cultures have validated that macronutrients (e.g., fatty acids and proteins), micronutrients (e.g., vitamins), and naturally occurring bioreactive chemicals (e.g., phytochemicals such as flavonoids, carotenoids, coumarins, and phytosterols, and zoochemicals such as eicosapentaenoic acid and docosahexaenoic acid) regulate gene expression in various methods. The essential agents through which vitamins affect gene expression are transcription factors. Among the most vital team of nutrient sensors is the nuclear receptor superfamily of transcription factors, with 48 contributors in the human genome. Numerous receptors in this superfamily bind vitamins and their metabolites (Müller and Kersten 2003). For example, nuclear receptors, such as peroxisomeproliferator activator receptor-α (PPAR α) (binding fatty acids) or liver X receptor α(binding cholesterol metabolites), bind as heterodimers collectively with retinoid Xreceptor to unique nucleotide sequences (response elements) in the promoter regions of a giant wide variety of genes. During ligand binding, nuclear receptors endure a conformational exchange that outcomes in coordinated dissociation of corepressors and recruitment of coactivator proteins to allow transcriptional activation. In metabolically energetic organs, such as the liver, intestine, and adipose tissue, these transcription factors act as nutrient sensors with the aid of altering the stage of DNA transcription of specific genes in response to nutrient changes. Nuclear receptors have necessary roles in rules of numerous processes, including nutrient metabolism, embryonic development, and cell differentiation. Not surprisingly, nutrients, by way of activating these receptors, are able to have an impact on a broad array of cell functions. As an example, the PPAR team of nuclear receptors acts as nutrient sensors for fatty acids and influences expression of particular genes. One of the three PPAR isoforms, PPAR α is current chiefly in the liver (Mandard et al. 2004). The more than 3000–4000 target genes of PPAR α are concerned in several metabolic processes in the liver, which includes fatty acid oxidation, ketogenesis, gluconeogenesis, amino acid metabolism, cellular proliferation, and the acute-phase response (Mandard et al. 2004). Hepatic PPAR α is mainly important throughout fasting, when free fatty acids are launched from adipose tissue. These fatty acids then journey to the liver, where they undergo partial or entire oxidation. However, these fatty acids additionally bind PPAR α, which then increases expression of a suite of genes via binding to precise sequences in their promote regions. Fasted PPAR α null mice (mice that lack functional PPAR α) suffer from a range of metabolic defects, which include hypoketonaemia, hypothermia, multiplied plasmafree fatty acid levels, and hypoglycaemia (Mandard et al. 2004; Kersten et al. 1999). Recently, it has been verified that PPAR α directly regulates expression of genes involved in hepatic gluconeogenesis and glycerol metabolism (Mandard et al. 2004; Afman and Müller 2006). Because fatty acids are ligands for PPAR α, the latter mechanism may want to provide an explanation for the stimulatory effect of improved plasma-free fatty acids on hepatic gluconeogenesis and glucose output. In addition to its important feature in the physiological response to food deprivation or starvation, the role of PPAR α in obesity is much less clear, however most likely relevant to our perception of the obesity-linked pathophysiology of kind 2 diabetes (Patsouris et al. 2004; Afman and Müller 2006). Visceral weight problems are linked to increased free fatty acid degrees and, interestingly, these molecules might also be recognized by means of the liver as “hunger” or “in want of glucose” signals, ensuing in improved gluconeogenesis in a PPAR α-dependent manner, especially beneath prerequisites of hepatic insulin resistance (Moller and Kaufman 2005). 21 Nutrigenomics Research: A Review 367 In addition to the group of sensing transcription factors that without delay have interaction with DNA by using binding to unique response elements, the importance of corepressor and coactivator proteins became extra evident because a tremendous issue of gene manipulate is directed at the expression of coactivators. Coactivatorsgenome. Numerous receptors in this superfamily bind vitamins and their metabolites (Müller and Kersten 2003). For example, nuclear receptors, such as peroxisome proliferator activator receptor-α (PPAR α) (binding fatty acids) or liver X receptor α (binding cholesterol metabolites), bind as heterodimers collectively with retinoid X receptor to unique nucleotide sequences (response elements) in the promoter regions of a giant wide variety of genes.

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Recent facts on two coactivators of PPARγ, known as peroxisome proliferator-activated receptor-gamma coactivator-1 (PGC-1α and PGC-1β), are fascinating (Afman and Müller 2006). PGC-1 α has been related with electricity homeostasis, diabetes, and lifespan legislation. Polymorphisms in the genes encoding PGC-1α and PGC-1β have been related with development of kind 2 diabetes. Recently, high-fat feeding in a mouse mannequin has been shown to set off hyperlipidaemia and atherogenesis and to stimulate expression of PGC-1β in liver. Through molecular studies, the authors linked this mechanism to accelerated lipogenesis and very low-density lipoprotein excretion because of enhancer outcomes of PGC-1β on gene transcription ruled by using the transcription elements sterol regulatory issue binding protein 1 and liver X receptor α (Ling et al. 2004; Patti et al. 2003). From these results, a mechanism has been proposed by using which dietary saturated and transfatty acids can stimulate hyperlipidaemia and atherogenesis (Lin et al. 2005). This find out about demonstrates sensitivity of contemporary microarray evaluation and is an instance of nutrigenomics lookup due to the fact it permits simple detection of profound adjustments in hepatic gene expression patterns because of an adaptive response by the organism to modifications in dietary macronutrient composition (Afman andMüller 2006).368 S. Dey and Y. Kumar The 3-dimensional complex of genomic DNA and nucleosome-forming histone proteins is known as chromatin (Carlberg and Molnár 2014). It is classified into much less densely packed euchromatin, which without difficulty on hand to transcription elements and other nuclear proteins, and compact heterochromatin, which is a functionally repressed country (Beisel and Paro 2011) (Figure 5). Posttranslational histone modifications and DNA methylations as nicely as modifications of the third-dimensional structure signify functionally relevant chromatin levels. Euchromatin is placed closer to the centre of the nucleus, and in this open form of chromatin, histone proteins are frequently acetylated and genomic DNA is unmethylated. In contrast, heterochromatin is determined closer to the nuclear membrane, and in this closed chromatin form, both nucleosomes and genomic DNA are methylated. Epigenomics studies chromatin differences that do not contain adjustments to the genome (Carlberg 2019). Epigenome changes, additionally referred to as epigenomic programing, are very outstanding during embryogenesis, the place totipotent stem cells beget a number pluripotent traces of the embryo, which in turn act as precursors of terminally differentiated cells (Perino and Veenstra 2016). This differentiation manner restricts the access to an increasing quantity of genomic regions and genes that they are controlling, so that terminally differentiated cells are capable to focal point on their specialized functions. Thus, chromatin accessibility performs a necessary function in regulating gene expression. There is dynamic competition between nucleosomes and transcription factors for crucial binding regions within genomic DNA, such as enhancers and promoters. Chromatin dynamics are influenced by using a large set of chromatin modifying and redesigning enzymes, which interpret (“read”), add (“write”), or put off (“erase”) posttranslational histone modifications or DNA methylation (Carlberg and Molnár 2014). Interestingly, the pastime of many of these chromatin modifiers significantly relies upon on intracellular ranges of key middleman metabolites, such as NAD+, acetyl-CoA, and α-ketoglutarate (Gut and Verdin 2013). In this way, environmental inputs, such as the availability of power substrates, have direct effects on the epigenome and, via this, on gene expression. This implies that chromatin modifiers act as sensors of metabolic information, such as cells being in a fasting or feeding state. The subject of dietary epigenomics describes numerous connections between diet-derived metabolites and the epigenome. For example, a wide variety of secondary metabolites from fruits, vegetables, spices, teas, and medicinal herbs, such as resveratrol, genistein, curcumin, and polyphenols, affect the endeavour of chromatin modifiers and transcription factors. Vitamin D and different micro- and macronutrients have an effect on by means of their nuclear receptor sensors of chromatin accessibility; i.e., they belong to area of dietary epigenomics (Carlberg 2017). Importantly, in distinction to epigenomic programing for cell fate selections during cellular differentiation, which is largely irreversible, diet-induced epigenomics changes are dynamic; i.e., they are frequently transient and reversible (Carlberg 2019).**(Dey and Kumar 2022)**

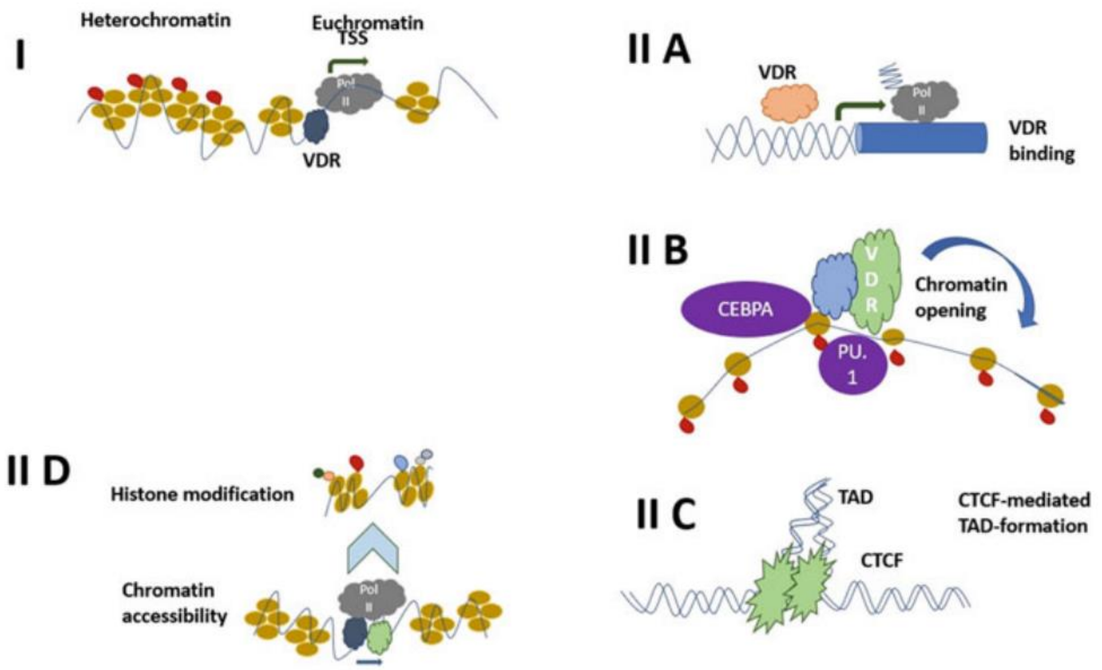


Fig.5 Vitamin D and the epigenome. Chromatin is segregated into non-accessible heterochromatin and euchromatin, where VDR can find its genomic binding sites. (I) Vitamin D can influencethe epigenome in multiple ways. (II) Such as increasing genomic VDR binding (A) affecting thebinding of pioneer transcription factor (B) influencing CCCTC binding factor (CTCF) binding andthe formation of topologically associated domains (TADs) (C) and changing histone modification and chromatin accessibility (D) **(Dey and Kumar 2022)**

2.HAMD/GAHD unified diet components:

2.1.Medeterranian diet:

2.1.1.introduction: The Mediterranean Diet (MedDiet) is a term used to identify a dietary pattern that has caught the attention of clinicians and researchers worldwide. The MedDiet originated from the unique multi-millennial interplay between natural food resources and the eating practices of people living in the Mediterranean basin . It has been widely acknowledged that the MedDiet encompasses many aspects beyond nutritional behavior, including social, cultural, economic, and environmental features. The respect for seasonality, biodiversity, and food varieties, preferring local and fresh products, is a cornerstone of the MedDiet. The association of these cultural and nutritional features with physical activity is woven into the MedDiet model, making it widely considered to be a healthy lifestyle rather than a dietary Pattern.**(Finicelli, Di Salle et al. 2022)**. on the other hand the Seven Countries Study was the first to observe that the people of Japan and Mediterranean countries have a low risk of cardiovascular diseases (CVDs), which may be due to the cardioprotective effects of their diets. The UNO in 1998 certified that the Japanese diet could be a crucial factor for their longevity and healthy life expectancy. In Mediterranean countries such as Greece, Southern Italy, and Spain, people consume a traditional Mediterranean diet, which is protective against CVDs, diabetes, and cancer . In addition to these diets, the DASH diet has been developed and found to be protective against CVDs . It seems that there are both similarities and discrepancies in the consumption of foods and nutrient intake, in particular antioxidant and w-3 fatty acid intake, which could be a determinant of the effectiveness of these diets . A traditional Japanese diet shares several similarities with a traditional Mediterranean diet, as both are based on a foundation of plant foods such as rice, vegetables, grains, legumes, and fruit. Fish is consumed regularly, more in Japan than in Mediterranean countries, while red meat is consumed more sparingly. The majority of fat consumed in Japan is rice bran oil, whereas in Mediterranean countries, it is olive oil and from unsaturated sources . It has been found that all special types of diets may safeguard against the risk of CVDs and type 2 diabetes mellitus (T2DM) . The Japanese diet is naturally rich in fish, seaweed, green tea, soy, fruits, and vegetables and low in added sugar, fat, and other animal protein. However, the Indo-Mediterranean diet is higher in whole grains, spices, and mustard oil, in addition to fruits and vegetables and fish to nonvegetarians. The Indo-Mediterranean diet has been found to be protective against CVDs . It is proposed that whole grain content, in particular antioxidants in various diets, may explain, at least in part, the differences in the cardioprotective potential of these diets. This article aims to highlight the differences in the efficacy of these diets.**(Singh, Fedacko et al. 2022)**

2.1.2. The MedDiet: Definition and Composition

The term MedDiet commonly refers to the dietary pattern of the people living on the Mediterranean Sea coast, in particular Greece, southern Italy, and southern Europe**.(da Silva and Batista 2023)**.Although these Mediterranean countries show some eating habit differences, the common features characterizing the MedDiet are defined as (a) daily consumption of non-refined cereals and other products (e.g., whole grain bread, whole grain pasta, and brown rice), fresh fruits, vegetables, nuts, and low-fat dairy products; (b) olive oil as the principal source of lipids; (c) moderate intake of alcohol, preferably red wine, with meals; (d) moderate consumption of fish, poultry, potatoes, eggs, and sweets; (e) monthly consumption of red meat; and (f) regular physical activity.**(Franco, Interdonato et al. 2023)**. Besides these characteristics, the beneficial impact of the bioactive molecules in the essential individual components of the MedDiet has also been considered. In this section we provide a brief overview of the principal elements and clinical implications recognized for the significant features of the MedDiet (Figure 5). Marine omega-3 fatty acids are the most important bioactive molecules in fish and seafood consumed in the MedDiet (e.g., sardines, mackerel, mussels, octopus, salmon, squid, and tuna). Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are the major n-3 fatty acids recognized for their cardioprotective effects.**(Wang, Enssle et al. 2022).** In a meta analysis of a randomized controlled trial (RCT), EPA and DHA supplementation reduced the risk of coronary heart disease (CHD) in higher-risk populations.(**Karageorgou, Rova et al. 2023)** . Analogously, the high intake of fish is accountable for the beneficial effects on HDL cholesterol and triglycerides levels , Olive oil (OO), and especially extra virgin olive oil (EVOO), is the primary source of fat in the MedDiet. Monosaturated fatty acids (MUFAs) are the most representative ,OO fatty acids (FA), ranging from 55–83% of the total FA content . Saturated fatty acids (e.g., palmitate) impair mitochondrial respiration by causing an increase in both total cellular ROS and mitochondrial ROS, contrary to MUFAs, such as oleate from OO .Nevertheless, controversies still exist on the beneficial effect of MUFA on human health.

On the other hand, much attention must be given to the lesser components of OO (2% of the total weight), consisting of polyphenols or other secondary plant metabolites (e.g., oleuropein, tyrosol, hydroxytyrosol, secoirodoids, and lignans).**(Farhan, Al-Maleki et al. 2023).** Overall, these molecules contribute to the beneficial effects of OO and EVOO on human health. A meta-analysis of 32 observational studies revealed that OO consumption decreased the risk of stroke, CHD, and diabetes and improved some metabolic and inflammatory biomarkers . The consumption of OO enriched in phenolic compounds seemed to reduce the urinary levels of DNA oxidation (8-OHdG) and inflammatory (IL-8, TNF-α) markers in an opportune population cohort .. The regular intake of 15 mg/day of HTyr resulted in modification of body composition parameters and modulated the antioxidant profile, the expression of inflammation and oxidative stress-related genes in atherosclerosis.

Fruit and vegetable consumption is emphasized in the MedDiet. Oranges, pomegranates, berries, figs, and grapes are the most frequently consumed fruits and a source of dietary fiber, potassium, vitamin C, polyphenols (mostly flavones), and terpenes.**(Mantzorou, Mentzelou et al. 2023)** . Vegetables are mainly seasonal and field-grown. The most representative vegetables are fresh greens, tomatoes, eggplants, cabbages, radishes, garlic, onions, spinach, and lettuce. Although these foods are an essential source of nutrients (e.g., dietary fiber, potassium, copper, magnesium, folate, vitamin-A, -B6, -C, -E, -K), the phenolic compounds (mainly flavonoids) are the most important bioactive molecules.. Several studies demonstrated that high consumption of vegetables or fruit resulted in lower risk for all-cause mortality, CHD, stroke, T2D, colon rectal cancer (CRC), and adiposity . Legumes, grains, and nuts are regularly consumed in the MedDiet. Grains appear both as a single food (e.g., rice and oatmeal) and as ingredients of processed foods (e.g., bread, pasta, cereal, and crackers). Common MedDiet nuts include almonds, hazelnuts, walnuts, and pistachios. Among legumes, the most representative is lentils, beans, and chickpeas. Overall, these foods are a valuable source of fiber, folate, vitamin B6, magnesium, potassium, and copper . In particular, nut intake is crucial because these foods are unique fortheir MUFAs and polyunsaturated FA (PUFAs) content, especially linoleic, linolenic acid, phenols, flavonoids, isoflavonoids, and phytosterols . The beneficial effect of nut consumption primarily impacts the incidence of CVD, diabetes, and MetS . The beneficial effects of legumes and grains on CVD, body weight, and cholesterol (total and LDL-C) have also been described. Of note, grain consumption has also been associated with a lower risk of T2B and CRC . grapes , blue berry juices/red wine is routinely consumed with MedDiet meals. Resveratrol is the most abundant Polyphenol in red wine/ grapes, blue berry juices . Besides the acknowledged effect of this molecule on several chronic diseases (e.g., cancer, myocardial infarction, and brain disorders), evidence supports its role in protecting against the development of some MetS features, also we can found Resveratrol in grapes /berries juices and its preparations instead of red wine,**(Kavgacı, Yukunc et al. 2023)**, **(SEYHAN, YALCIN et al. 2023)** to avoid alcohol side effects and its addiction with excessive drinking .**(Teese, Van Doorn et al. 2023)**. Although this body of evidence demonstrates the role of nutrients and foods in the pathophysiology of numerous diseases, the mechanisms by which the MedDiet exerts its favorable effects are not fully understood. However, the five most important influences induced by adherence to the MedDiet can be summarized as (a) lipid-lowering effect, (b) anti-oxidative and anti-inflammatory action, (c) modification of key molecules (hormones and growth factors) involved in the pathogenesis of cancer, (d) inhibition of nutrient-sensing pathways, and (e) gut microbiota-mediated production of metabolites influencing metabolic health . The current research focuses on the MedDiet pattern as a whole. The overall combination of MedDiet foods and their components' additive or synergistic effects seems to provide more consensus regarding health benefits . Moreover, food production, consumption, cooking techniques, and eating behaviors are also emerging as innovative variables used to assess the beneficial effects of the MedDiet . Accordingly, research must go beyond the common links between foods and nutrients and consider other aspects characterizing the MedDiet as a healthy lifestyle.**(Finicelli, Di Salle et al. 2022)**

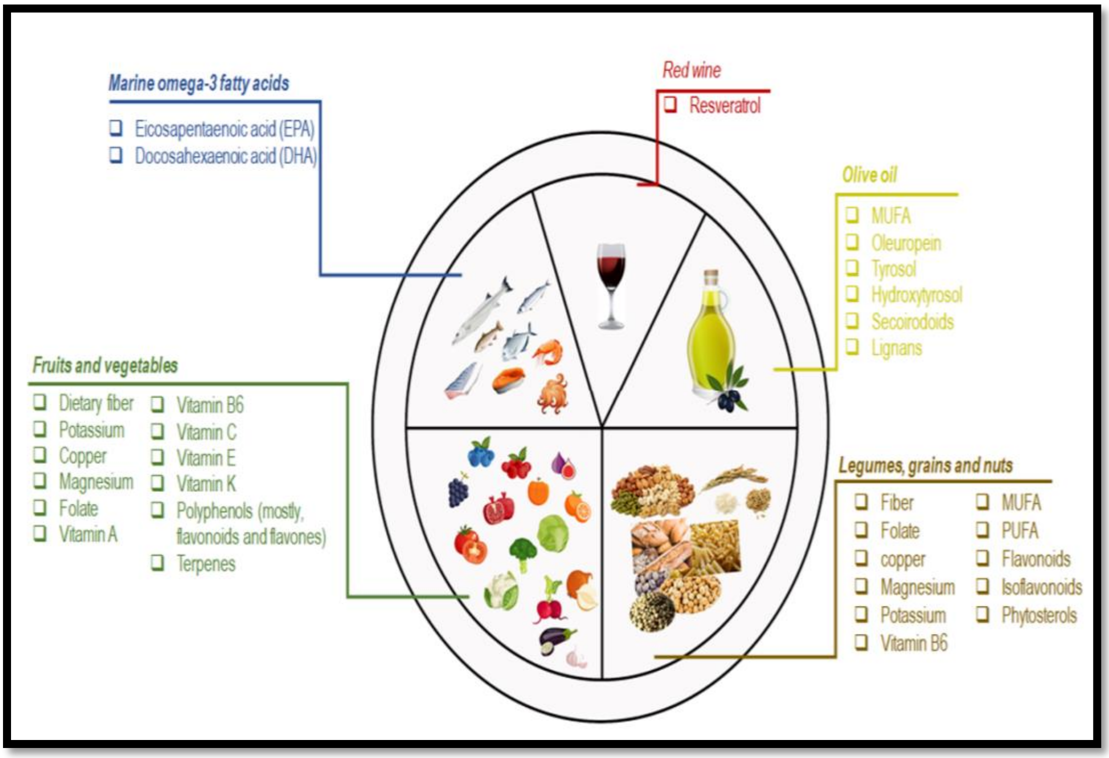


Fig.6 schematic representation of the nutritional and bioactive characteristics of principal components of MedDiet.

2.1.3. Epigenomics and Nutrigenetics of the Mediterranean Diet

The MD, in comparison with the other diet regimens in the world, has all the characteristics of being one of the examples of the "Environment-Livings-Environment" relationship. Similarly, at the biomolecular level, the MD could be described as a patchwork in which several biological and non-biological disciplines are interconnected in a network promoting human health. Moreover, the presence of some genotypes in consumer MD for genes of nutrient metabolism can be considered for a personalized diet that consolidates/corrects healthy/unhealthy habits. By remembering that oxidative stress and DNA methylation feature a common denominator, the one carbon cycle **(Andreo-López, Contreras-Bolívar et al. 2023)**, we may assume the existence of this chain:

dietary antioxidant → minor ROS → minor DNA damage → normalization of DNA methylation and the opposite one:

endo/exo-oxidants → greater ROS → greater DNA damage → hypomethylation of DNA for defence

On the basis of these chains, we can recognize the master strength of the MD: a diet with a high antioxidant and nutrigenomic modulation power. The traditional MD, unlike other diet regimens in the world, provides in the main daily meals of an individual an organized succession of foods and drinks (called first course, second course with side dish, fruit, wine), most of which have a high nutrigenomic value, sometimes summative of more single effects. Thus, a MD consumer daily assumes a wide range of foods, each in smaller quantities, but containing all together a large amount of antioxidants and molecules with nutrigenomic properties (Figure7)

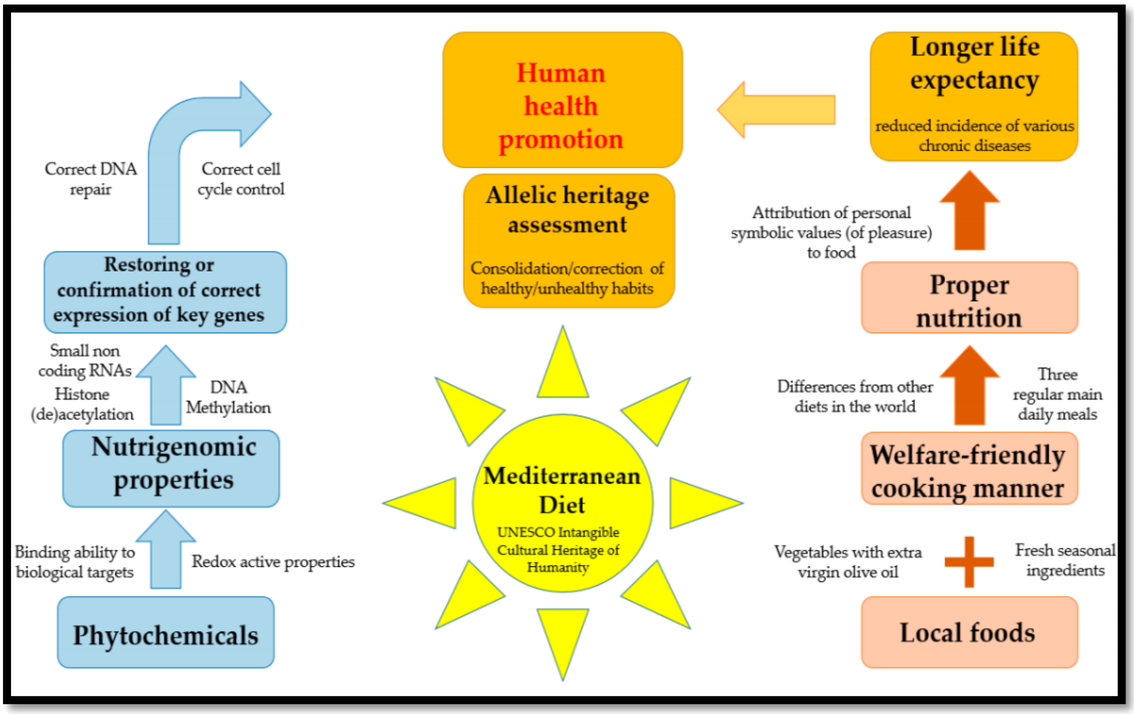
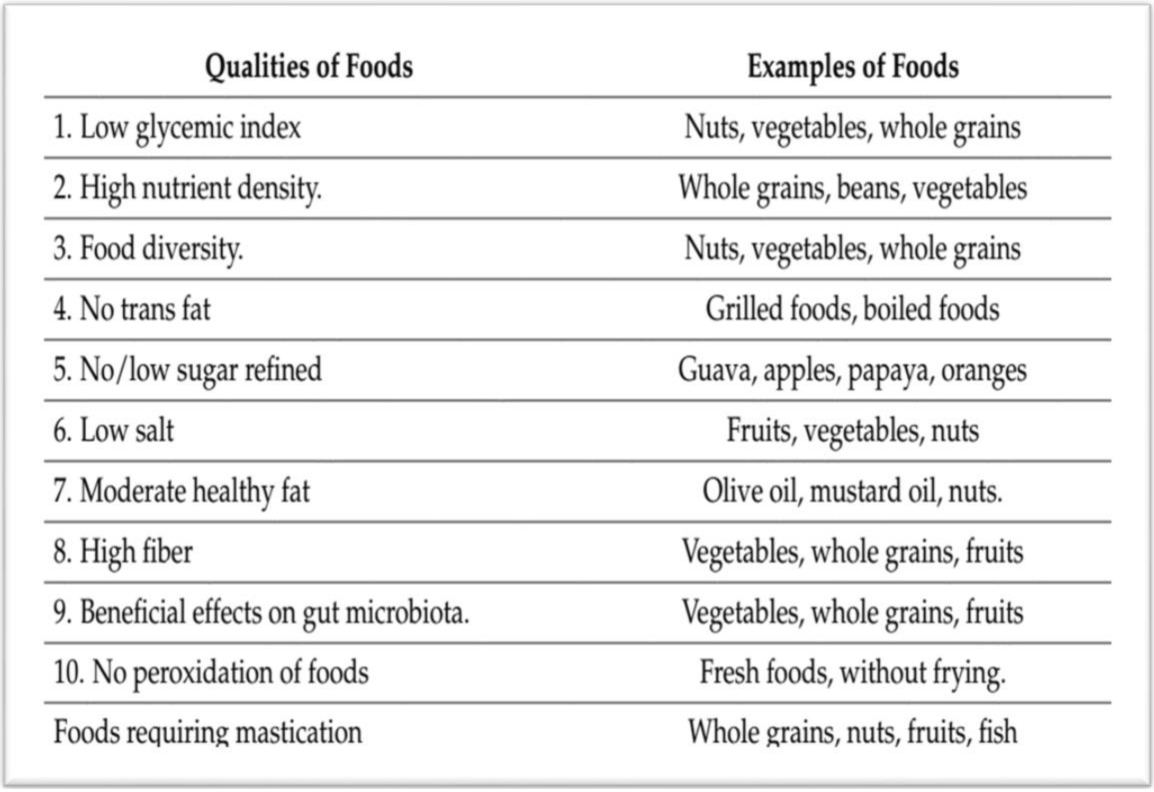


Fig.7. Patchwork expressing the whole concept of MD healthy properties , the left block of the diagram shows peculiar biological flowcharts , the right one displays selected non-biological points . The MD, interconnecting with both the blocks and taking advantage of an allelic assessment represents a network promoting human health

2.1.2. Best protein recommendations & Healthy advices:

2.1.2.1. Diet recommendations: It seems that the healthiest diet should have all the ten qualities of the diets and it shouldalso involve mastication **(Singh, Isaza et al. 2023)** (Table 3).

Table 3. Ten qualities of high-quality foods



Qualities of Foods	Examples of Foods
1. Low glycemic index	Nuts, vegetables, whole grains
2. High nutrient density.	Whole grains, beans, vegetables
3. Food diversity.	Nuts, vegetables, whole grains
4. No trans fat	Grilled foods, boiled foods
5. No/low sugar refined	Guava, apples, papaya, oranges
6. Low salt	Fruits, vegetables, nuts
7. Moderate healthy fat	Olive oil, mustard oil, nuts.
8. High fiber	Vegetables, whole grains, fruits
9. Beneficial effects on gut microbiota.	Vegetables, whole grains, fruits
10. No peroxidation of foods	Fresh foods, without frying.
Foods requiring mastication	Whole grains, nuts, fruits, fish

2.1.2.2.Protein best choices: The Holly Quraan referring to lean meat of the fish and sea foods and specified birds meat as the best food in the heaven and red meats as a religious rites for feeding on the general public level where large numbers of people suffice , That's why we recommend in GAHD/HAMD unified diet to eat birds meat twice or three times a week depending on the possibility of diversity and two to three times a week from sea food for best results , next studies confirm that .

1. All the five egg species in this study contained all the essential amino acids in significant quantities, hence the statement that "egg protein is a complete protein." Out of the 20 naturally occurring amino acids, 18 were present in the eggs—the 9 EAA and 9 NEAA. Two "neutral" amino acids—glutamine and asparagine (nonessential)—were not found in eggs, and this is confirmed by other similar studies such as Ismail et al. and Lewis et al. . It is also important to note that eggs have no limiting amino acids, unlike incomplete proteins, with one or two limiting amino acids such as methionine and cysteine . A lack of essential amino acids (EAA) like those found in eggs, a well-known animal protein source, may slow development and cause various health issues in humans . It was found that phenylalanine, isoleucine, lysine, isoleucine, valine, and threonine in the complete edible sections of eggs from various egg sources had varied patterns. Eggs' general protein digestibility is 1.0, which should be noted (same as casein, whey protein, and soy). Guinea fowl eggs had the highest TAA and TEAA content. As a result, it also had the highest AAS making its protein of the highest quality among the five egg species in this study. The values of the TEAA of the eggs were lower than the value of 45.2 g/100 g protein of the egg reference protein except for that of guinea fowl egg. This is similar to the findings of Adeyeye , which showed the guinea fowl egg as scoring 0.99 based on the whole hen egg's profile. The ratio of EAA to TAA in the samples was much higher than the 39 per cent deemed sufficient for protein foods for newborns, 26 per cent for children, and 11 per cent for adults . Compared to other animal protein sources, the proportion of EAA/TAA in the samples was favourable: 48.6% in guinea fowl , 51.1% in domestic fowl , and 50% in whole hen egg .However, most animal proteins are low in cystine (Cys), for example (Cys/TSAA—total sulphur-containing amino acid)%: 35.5% in *Archachatina marginata* ; 27.3%–32.8% in female freshwater crab body parts ; 23.8%–30.1% in three different Nigerian fishes ; 26.0–26.5% in turkey meat ; and 44% in domestic fowl . The present Cys/TSAA% results, such as 46.9% (turkey egg) and 56.8% (exotic chicken egg), differ from these literature observations except for that of guinea fowl (20.4%), which was low like that reported by Adeyeye [20]. This means that egg protein has a good cystine content, unlike some animal proteins. Numerous vegetable proteins have much more cystine than methionine (two sulphur-containing amino acids), such as 62.9% in coconut endosperm and 44.5% in entire Bambara groundnut seeds . Cystine positively affects mineral absorption, particularly zinc . The three branched-chain amino acids (BCAA), leucine, isoleucine, and valine, were also present in reasonable amounts, as seen in the amino acid scores. Guinea fowl eggs had significantly higher amounts of all three BCAA, and their AAS were relatively high. The BCAA are essential for muscle protein synthesis and can also be oxidized in the muscles during exercise for energy. A study by Blomstrand et al. showed that an intake of BCAA improved both mental and physical performances during athletic events. It is also important to note that boiling the eggs did not reduce the AA content of the eggs. Instead, an increase in the AA values was generally observed in both the EAA and NEAA. This is similar to Amaechi et al. , who reported that processing methods, mainly roasting, increased the AA composition of some flours. The situation is different if the eggs were boiled for more prolonged periods; however, those in this study were boiled following standard procedures for 10 mins. Furthermore, results from similar studies state that "the difference in protein and AA patterns of various eggs could be attributed to the impact of the diet composition on the level of crude protein and amino acids" . This implies that if the birds consume high protein feeds, their protein content and quality may be enhanced. These findings are consistent with

those reported by that regular raw eggs laid by free-range village hens (which were not allowed to roam outside but were allowed to roam in a building or open area) and nutrient-enriched eggs from poultry have different amino acid patterns, with lysine, leucine, isoleucine, and valine having the highest concentrations in the eggs. Limiting EAA for humans (which cannot be generated in sufficient amounts by human cells), phenylalanine, methionine, lysine, leucine, isoleucine, valine, threonine, and tryptophan were all present in the eggs, unlike some other plant-sourced proteins. Furthermore, due to their physiological requirements, histidine, arginine, cysteine, and tyrosine are considered EAA for newborns and developing children . Biochemically, variations in the amino acid patterns of egg proteins may be ascribed to the kind and proportion of protein in the egg white and egg yolks, such as ovalbumin, ovotransferrin, lysozyme, immunoglobulin Y, and ovomucin . More than fifty per cent of the protein in egg albumen is ovalbumin ; it is the predominant protein. From the results of this study, cystine (1.40 AAS) was the most significant amino acid in eggs, while (0.34 ASS) was the lowest. In a study by Attia et al. , eggs included more significant arginine, serine, cysteine, and isoleucine amino acids than soy protein, beef, casein, wheat flour, and egg white. This research showed that the five egg species under study had nine essential amino acids in significant amounts and nine nonessential amino acids. Guinea fowl egg had higher amino acid score than the standard reference (hen’s egg). In terms of heating, it was observed that boiling the eggs for just 10 mins under standard conditions did not reduce the amino acid content of the eggs; instead, a slight increase was observed in almost all the AA values of the boiled samples. In addition, the results show that not all eggs are the same in protein quality and certain varieties may be better recommended for frequent consumption by children who have higher protein requirements for growth and development. Consumption of less popular varieties such as guinea fowl and quail eggs should also be promoted due to their relatively higher nutritional value**.(Onyenweaku, Akah et al. 2022).**

2.Marine alkaloids derived from tryptophan constitute a valuable class of compounds being abundant in nature and displaying a broad range of biological activities. Regarding their antimicrobial potential, several tryptophan rich marine alkaloids isolated through the years have shown strong activity, namely against bacteria, fungi, and virus.**(Almeida, Resende et al. 2021)** .

3.The essential amino acid tryptophan (TRP) is discussed as a potential protective factor for physical and mental health. Besides positive effects via the microbiota of the gut on many physiological processes, TRP is the precursor of the neurotransmitter serotonin (5-HT), thereby playing a role for affective disorders. The present study investigated the effects of a TRP-rich diet on depressiveness and on one of its endophenotypes, impaired social cognition, Moreover, the habitual TRP intake was measured. It was hypothesized that a low-TRP diet is associated with higher depressiveness and worse performance in the social cognition tasks. The main hypotheses could be supported. However, contrary to the expectations, the effect of TRP on social cognition was not mediated by depressiveness. Results show that a tryptophan-rich diet is a potential protective factor against depression and is positively related to functioning in social cognition.**(Reuter, Zamoscik et al. 2021)**. Not only a diet rich in tryptophan but also a diet rich in antioxidants can have a positive impact on mood and cognition. This could be of special relevance for individuals who present with low grade inflammation conditions**.(Strasser, Gostner et al. 2016)**. the lower dose of fish (18% of protein) relative to meat (41% of protein) in the experimental diets. Fish intake had a significant effect on most NIR_{AA}s in plasma and RBCs, and the largest effects were seen in plasma NIR_{Leu} and NIR_{Glx}. Meat intake had a significant effect on many plasma NIR_{AA}s, but the largest effects were seen in different AAs than in fish: plasma NIR_{Ala} and NIR_{Val}. NIR_{AA}s were overall better at identifying of fish intake relative to meat intake. The plasma NIR_{Leu} was the most accurate classifier of fish intake, and the RBC NIR_{Pro} was the most accurate classifier of meat intake. These findings suggest that NIR_{AA}s have promise as biomarkers that can differentiate fish from meat intakes**. (Johnson, Shaw et al. 2022)**

2.2. Functional food specified for HAMD/GAHD unified diet:

2.2.1.Milk &Milk products: It's menthioned twice in the Holly Quraan ,one for Drinking it in our worldly life and other time about the rivers of milk in the heaven on the other life , also our prophet Mohammed peace and God prayer's upon him told us that it's the best drink ever

2.2.1.1 probiotic/prebiotic properties:

Probiotics are viable microorganisms that provide health benefits to the host when ingested in adequate concentrations . Fermented foods that contain live probiotic microorganisms are regarded as functional foods . Probiotics have therapeutic effects including anti-cancer , anti-cholesterol , prevent intestinal infections , antioxidant, immunomodulatory, hypoglycemic properties, and antihypertension characteristics . They have also been shown to help prevent a variety of digestive disorders such as necrotizing enterocolitis, anti-biotic associated diarrhea, and irritable bowel disease . Lactic acid bacteria (LAB) from the Lactobacillus, Bifidobacterium, Enterococcus,Streptococcus, and Pediococcus genera as well as the yeast from the Saccharomyces genera have all been utilized as probiotics in both humans and animals. Lactic acid bacteria also secrete lactic acid and bacteriocins that act as antimicrobials that hinder the growth of spoilage and pathogenic microorganisms, hence preserving the food and rendering it safe ., the L. plantarum EGER41 isolate had demonstrated technological properties such as acid production and clotting during milk fermentation. This study further demonstrated L. plantarum EGER41 isolate as an excellent probiotic candidate and gave insights on the potential of the isolate. The isolate exhibited probiotic potential owing to its high resistance to phenol, good growth at 30 °C and 37 °C, and tolerance to low pH. The isolate also displayed strong antagonistic activity towards human pathogens; E. coli, Salmonella enterica serovar Typhi, S. aureus and Candida albicans. The cumulative benefits of the L. plantarum EGER41 isolate indicate that it could potentially be recruited to produce safe functional foods. However, more probiotic parameters, in vivo activity, and whole-genome sequencing of the isolate should be investigated to validate its immunomodulatory, nutritional, and health benefits and determine if it harbors antimicrobial resistance genes.**(Katiku, Matofari et al. 2022) .** We isolated Lactobacilli from goat milk and identified API 50, CHL, and 16sRNA. Probiotic properties were determined according to bile salt and acidic tolerance, hydrophobicity, hemolytic activity, antibiotic sensitivity, antagonistic effect, and exopolysaccharide production. In addition, the cholesterol assimilation and folate production of cultures were determined , *L. plantarum* GM-12 and *L. plantarum* GM-15 showed the highest folate production and the highest cholesterol assimilation.These two strains are strong candidates for use as potential probiotics and starter cultures.**(Tulumoğlu, Kariptaş et al.)**

2.2.1.2.Other Health effects: the present study indicated that camel milk mixed with cow milk and camel milk alone influenced the beneficial effect much more than cow’s milk, and probiotic starter culture had a significantly stronger effect than traditional yogurt culture. Camel milk fermented with ABT-5 significantly reduced risk of dyslipidemia associated with the metabolic syndrome in hypercholesterolemic rats, lowering body-weight gain and serum triglycerides and LDL while boosting serum HDL. Biomarkers of kidney function (urea, creatinine) also increased dramatically, but total protein content in serum and serum albumin dropped moderately. Camel milk fermented with probiotic bacteria significantly ($p \leq 0.05$) improved the lipid levels and intuitive lipid buildup in hyperlipidemic rats. These metabolic improvements were accompanied by a reduction in tissue damage (liver, kidney). Results verified that feeding on the fermented milk with ATB-5 strains enhances the body's production of inhibitors that lower cholesterol levels and improve liver and kidney functions. Camel milk is superior to cow milk in this respect. This study encourages the consumption of fermented camel milk, as obesity and dyslipidemia are widely spread in the Arab countries.**(Alharbi, El-Zahar et al. 2022)**

2.1.3.Chemical Composition of Various Fermented Milk : An initial experiment was carried out to prepare a mixture of fermented camel and cow's milk in different proportions (25:75, 50:50, and 75:25% v/v), and then, fermented milk was produced by using ABT-5 probiotic strains and assessed the organoleptic characteristics and the level of consumers' accessibility to it. It was found that the best mixing ratios for camel and cow's milk was (50: 50% v/v), which was followed in the biological experiment to estimate the effect of probiotic bacteria as well as the effect of camel milk on the lipid profile in rats fed on a high-fat diet (results not showed). Results summarized in showed that the fat content in probiotic-fermented milk increased slightly in comparison with the fermented milk produced with the traditional starter culture. The amount of lactic acid produced increased with a concomitant drop in pH with an increase in fermentation time. The pH of fermented camel milk with ABT-5 was greater than that prepared by using traditional starter cultures. However, the combination of L. bulgaricus and S. thermophilus (1:1) resulted in a lower pH and higher acidity than probiotic starter cultures. In addition, fermented milk manufactured with the traditional starter was higher in acidity than probiotic-fermented milk. These results are in accord with the results reported by Ibrahem , which reported an increase in acidity up to 50% when storing fermented camel milk for 24 h after coagulation. This increase in acidity may be due to the difference in the metabolic activities of microbial species used as starters in the fermented milk manufacturing. The decrease in total protein in fermented milk samples occurred as a result of protein hydrolysis by the starter culture. These results agree with the results obtained by Galeboe . Protein degradation in all treatments increased due to the limited hydrolysis of milk proteins by lactic acid bacteria.**(Alharbi, El-Zahar et al. 2022)**

2.2.2. Honey: Like milk it's mentioned twice in holly Quraan and ther's a river's of honey in the Heaven , and Allah tell us that we should use it for healing & protection against any disease . Honey is a natural product produced and marketed worldwide by stingless bees and Apis bees. Both these types of honey contain unique and distinct compounds of variable nutritional and biological importance.**(Ávila, Beux et al. 2018)**, Among the 200,000 species of animals that serve as pollinators , only a tiny fraction feed exclusively on floral resources throughout their entire life cycles, due to the ecological and physiological challenges associated with consuming these foods. Specialization for consumption of floral foods, particularly nectar, has reached a pinnacle in Apis mellifera, the western honey bee, achieved with a suite of extraordinary adaptations that involve both food processing and storage. Biologically active constituents of honey. That honey making by A. mellifera involves incorporation of multiple materials other than nectar from environmental and internal sources is inconsistent with the longstanding conviction that honey serves as little more than a carbohydrate source for bees . As Erler & Moritz (47, p. 391) remarked, "It is the ability to store the huge variety of foraged antimicrobial substances that lends the honeybee colony an enormous advantage not just within the bee pollinators but also over many other social insects that require animal protein in their diet. The capacity to store food provides the honeybees with an opportunity to selectively choose among the variety of stored products in an adaptive way dependent on their own or the colony's health status." Honey bees, however, do more than just store food—bees process both nectar and pollen extensively before storing them.**(Berenbaum and Calla 2021)**

2.2.2.1 ORIGINS OF ANTIOXIDANTS OF HONEYS AND LONGEVITY ENHANCEMENT: The phytochemical content of honey may enhance longevity through its antioxidant activity. Among theories of aging in social insects, particularly A. mellifera , most relevant to differential longevity in workers is the oxidative stress theory of aging, which posits that irreversible accumulation of oxidative damage leads to senescence. Whereas order-of-magnitude differences in longevity of queens relative to workers appear to be independent of antioxidant gene expression , differential longevity of workers conforms to tenets of the oxidative stress hypothesis.Winter bees live up to 24 weeks as adults, whereas summer foragers have a life expectancy of three to four weeks . In summer workers, the transition from hive tasks to foraging is the central variable for honey bee aging, although chronological age, irrespective of behavioral state, contributes to aging as well . Associated with lifespan extension is a reduction in the abundance of peroxidizable (polyunsaturated) fatty acids and, concomitantly, a reduction in oxidative damage . The influence of honey constituents on longevity occurs via regulation of genes associated with lifespan. In several studies , p-coumaric acid ingestion by honey bee larvae upregulated forkhead (FOXO) 2.38-fold; FOXO has been implicated in bee longevity because its homolog in Caenorhabditis elegans downregulates life-shortening genes and upregulates antioxidant enzymes (catalase, superoxide dismutase) in Culex pipiens. In addition, D. melanogaster FOXO, when overexpressed in fat body, increased female lifespan . Chrysin, found in both honey and propolis (88), added to the diet of adult D. melanogaster increased the median lifespan of females by up to 12% and the maximum lifespan by up to 22% but had no longevity-enhancing effects on males (80). In female flies consuming diets to which chrysin was added, Hsp70 expression levels were reduced by up to 82% compared with flies on unamended diets. Although Hsp70 is thought to be geroprotective, the lower level of Hsp70 expression after chrysin consumption could be a biomarker of younger biological age given that flies with lower levels of Hsp70 reported live longer than do flies with higher levels. Honey constituents may also enhance longevity directly through their antioxidant activity. Many antioxidant phenolics in honey may be capable of neutralizing reactive oxygen species that damage proteins, DNA, and fatty acids, leading to cell death. Honey antioxidant capacity depends on nectar source; in the first study to examine this relationship, Frankel et al. found 20-fold variation in antioxidant capacity across 14 monofloral honeys. Interest in honey as a functional food for humans increased markedly with recognition of its antioxidant content; a search of the Web of Science core collection (March 3, 2020) yielded nearly 400 papers with titles including the words “antioxidant” and “honey.” Of these, however, only 38 included “Apis mellifera” as a topic; the preponderance concern human health and nutrition (e.g., 2), and the significance of antioxidant activity in honey to honey bee longevity (or any other health benefits) is not well known. Curiously, studies examining whether honey itself, rather than isolated constituents, can enhance longevity are more often conducted on parasitoid wasps than on the honey bees that produce it; most such studies are aimed at improving mass rearing of parasitoids for biological control. Harvey et al. compared life history attributes of Gelis agilis (Ichneumonidae) reared on honey, a honey-sugar mimic, or glucose. G. agilis females consuming honey produced twice as many offspring as those reared on other diets; female longevity was reduced only on the honeysugar mimic diet, suggesting contributions of constituents of honey other than sugars in increasing longevity and reproduction. Effects of individual honey constituents with high antioxidant capacity on lifespan have been more frequently evaluated in adult honey bees than has intact honey. Liao et al. (84) conducted a series of longevity assays with bees on a sugar-casein protein diet formulated with p-coumaric acid, quercetin, and the two phytochemicals together. Diets with p-coumaric acid increased longevity by 17.6%, and those with quercetin increased longevity by 6.2%; bees consuming the two phytochemicals together did not, however, experience longevity enhancement. Similar effects were reported by Wong et al. with the same phytochemicals; bees consuming p-coumaric acid lived longer than bees consuming the control diet, although bees consuming diets containing both pcoumaric acid and quercetin experienced reduced longevity. Bernklau et al. demonstrated that four phytochemicals—caffeine, gallic acid, kaempferol, and p-coumaric acid—enhanced longevity in adult bees at ecologically appropriate concentrations. Although all of these phytochemicals occur in honey, caffeine is less widely distributed and is known primarily from nectar of Citrus and Coffea . Few if any studies exist on the colony-level effects of honey antioxidant content on worker longevity or colony health.**(Berenbaum and Calla 2021)**

2.2.2.2.Phenolic compounds: Aglycones and glycosides Phenolic compounds have an aromatic ring with one or more hydroxyl groups in their structures, varying from a simple to a complex molecule phenolic polymer of high molecular weight (Bravo, 1998). Their structures can be classified into different categories and divided into two main groups: non-flavonoids (phenolic acids, lignans, and stilbenes) and flavonoids (flavonols, flavones, isoflavones, flavanones, anthocyanidins, and flavanols) (Etcheverry, Grusak, & Fleige, 2012). Regarding SBH, flavonoids and phenolic acids are the main polyphenols studied . Such compounds may be attached to one or more sugars (glycosides) or in their native/ free forms (aglycones) (Bravo, 1998). In this sense, flavonoid glycosides are widely distributed in nature (Bartnik & Facey, 2016); for instance, rutin, which is one of the most known quercetin glycoside derivatives (Frutos, Rincon-frutos, ´ & Valero-cases, 2019). In summary, glycosides are water-soluble compounds comprised of an aglycone attached to a sugar, in which the aglycone (non-sugar) is the lipophilic moiety (Bartnik & Facey, 2016). In general, glycosides are poorly absorbed by the digestive tract; thus, microbial activity in the distal ileum or large bowel may release the less polar aglycone moiety, making its absorption into the bloodstream possible (Bone & Mills, 2013). Besides, the chemical stability of these compounds is directly dependent on their structural characteristics, like the number of hydroxyl groups. That is, a greater degree of hydroxyl groups reduces compounds' stability (Biesaga, 2011), e.g., myricetin that has 3 OH groups in the B ring is less stable than quercetin (2 OH groups) and kaempferol (1 OH group), respectively (Biesaga & Pyrzynska, ´ 2013; Odriozola-Serrano, Soliva-Fortuny, & Martín-Belloso, 2008). Moreover, glycosidic bonds (linkage between aglycone and glycone) are unstable and susceptible to hydrolysis by acids or specific enzymes. However, they seem resistant to hydrolysis in the digestive tract, presenting low absorption (Bartnik & Facey, 2016). Nevertheless, they must be hydrolyzed through the action of enzymes present in the gastrointestinal tract to release their corresponding aglycone (lower polarity) for absorption (Horst & Lajolo, 2016; Tsao, 2010). On the other hand, aglycone compounds may be bioavailable in the small intestine, thus readily absorbed by the bloodstream (Bartnik & Facey, 2016; Goodman, 2010). Regarding biological activities, studies have reported that flavonoid aglycones are much more effective than glycosides (Ramanouskaya, Smolnykova, & Grinev, 2009). According to the literature, such biological potential of these compounds may be related to their concentration and the different positions of hydroxyl groups (Casagrande & Darbon, 2001; Ramanouskaya et al., 2009). In a nutshell, aglycones must be more bioavailable than glycosides and potentially more active regarding their biological activities (Iurlina, Saiz, Fritz, & Manrique, 2009). In this regard, paying attention to the different chemical structure patterns of polyphenols and understanding their action mechanisms become of great relevance.**(Dos Santos, Biluca et al. 2021)**

2.2.2.2.1.Deglycosylation of phenolic compounds by hydrolysis and fermentation process: Studies have shown the effects of hydrolysis (acid and alkaline) and fermentation on the phenolic compounds of different food matrices (Leonard, Zhang, Ying, Adhikari, & Fang, 2021; Lukˇsiˇc et al., 2016). In this context, hydrolysis is an efficient way to generate aglycone-rich extracts. This type of extraction method is used to evaluate free phenolic compounds; consequently, some losses of bound phenolic compounds (glycosides) may occur during this process (Tolosa, Rogez, M., & Souza, 2018; Vargas-Leo´n et al., 2018). For instance, 1.0 M HCl diluted in 80% ethanol converted most of the rutin to quercetin within 1 h (Yang et al., 2019). Although the practice of hydrolyzing glycosides into aglycones with HCl before HPLC analysis has been accepted in the last years (Mattila, Astola, & Kumpulainen, 2000), it is crucial to highlight that this method is not suitable for identifying phenolic glycosides that could be present in SBH. Regarding fermentation, Guo et al. (2020) and Wang, Luo, Wu, & Wu (2018) promoted a fermentation process in mulberry and guava leaves, respectively, both with Monascus anka, which is a genus of fungus of natural occurrence in cerumen pots constructed by stingless bees (Paludo et al., 2018). In both studies, the increased amounts of aglycones were associated with fermentation. Besides, enzymatic hydrolysis with complex enzymes (β-glucosidase, xylanase, and hemicellulase) was also conducted after fermentation (Wang, Luo, Wu, Liu, & Wu, 2018), contributing even more to the releasing of aglycones. Both hydrolysis and fermentation aim to evaluate free polyphenols (i.e., aglycones). However, to evaluate bound phenolic compounds (e. g., glycosides), the extraction method should be chosen carefully to avoid deglycosylation. Regarding SBH, enzymatic hydrolysis and fermentation occur naturally during SBH maturation (Michener, 2013). Therefore, a higher concentration of aglycones than glycosides would be expected in SBH. Some peculiar characteristics of SBH (high acidity and high moisture content) (Villas-Boˆas, 2018) and the rich microbiota present in the environment (stingless bees, the colonies, and the botanical source) have a high potential to promote a fermentative process inside the cerumen pots, where SBH is stored (Menezes, Vollet-Neto, Contrera, Venturieri, & Imperatriz-Fonseca, 2013; Neto, 2017; Souza, Alves, & Lopes, 2007; Venturieri, Oliveira, de Vasconcelos, & Mattietto, 2007). Although there is limited information about SBH fermentation, preliminary studies conducted in Brazil by Ital (Food Technology Institute) and the Federal University of Londrina suggested that osmophilic yeasts (naturally present in stingless bees) of Zygosaccharomyces genus are the main microorganisms responsible for the SBH fermentation. In addition, there may be competition between them and other microorganisms, including pathogens, resulting in a safe product for consumption (Villas-Boˆas, 2018). Furthermore, Menezes et al. (2013) believe that SBH undergoes three types of fermentation inside honey pots: carbohydrates are converted into alcohol and CO2, probably by the action of yeasts (Rosa et al., 2003); afterward, under aerobic conditions, bacteria may convert alcohol and O2 into water and acetic acid, being the latter already reported in SBH samples from Malaysia (Shamsudin, Selamat, Sanny, Abd. Razak, et al., 2019). Moreover, acetic fermentation is usually performed by Bacillus strains that are commonly present in SBH (Amin et al., 2020), and sugars may be converted into water and lactic acid since this is one of the main organic acids present in SBH (Shamsudin, Selamat, Sanny, Abd. Razak, et al., 2019). In addition, there are also enzymes responsible for developing other biochemical reactions during SBH production, in which the most investigated are invertase (α-glucosidase) that converts sucrose from nectar into fructose and glucose, being related to honey maturation (Cardona et al., 2019); glucose-oxidase that produces hydrogen peroxide (one of the most important substances regarding antibacterial property, Nogueira-Neto, 1997) and gluconic acid (the main organic acid in SBH, Shamsudin, Selamat, Sanny, Abd. Razak, et al., 2019); diastase (α and β-amylase), that are heat-sensitive enzymes, thus they are correlated to honey quality, (Ahmed et al., 2013); and catalase enzymes that stop hydrogen peroxide production since they eliminate glucose-oxidase (Nogueira-Neto, 1997). There are also many other enzymes responsible for SBH production, e.g., β-galactosidase, esterase lipase (C8), Nacetyl-β-glucosaminidase, acid phosphatase, naphthol AS-BI phosphohydrolase, leucine arylamidase (Costa & Da Cruz-Landim, 2005), and possibly others not reported yet. Briefly, the wide variety of enzymes from different sources (i.e., microorganisms, Gilliam et al., 1990, the hypopharyngeal and salivary glands of bees, Costa & Da Cruz-Landim, 2005, and pollen and nectar, Nogueira-Neto, 1997), naturally present in SBH may act breaking the glycosidic bonds of phenolics during SBH maturation, as proposed by Fig. 3. In this sense, this schematic representation (Fig. 8) was proposed based on studies carried out by De Araújo et al., 2013; Guo et al., 2020; Jim´enez-Lopez, ´ Ruiz-Medina, Ortega-Barrales, & Llorent-Martínez, 2018; Lin et al., 2014; Wang, Luo, Wu, & Wu, 2018. According to the revised literature, even though the microorganism Aspergillus awamori and the enzyme α-Lrhamnoside have not been identified in SBH, they may be potentially present in its microbiota (Foley, Fazio, Jensen, & Hughes, 2014). In this context, the hypothesis of SBH possessing a higher concentration of aglycones than glycosides could make it a product of great biological potential since studies have shown that aglycones present better absorption than glycosides (Gupta, Birhman, Raheja, Sharma, & Kar, 2016; Izumi et al., 2000). However, future studies need to investigate this hypothesis to acquire knowledge regarding the mechanisms of action of polyphenols and their biological potential.**(Dos Santos, Biluca et al. 2021)**

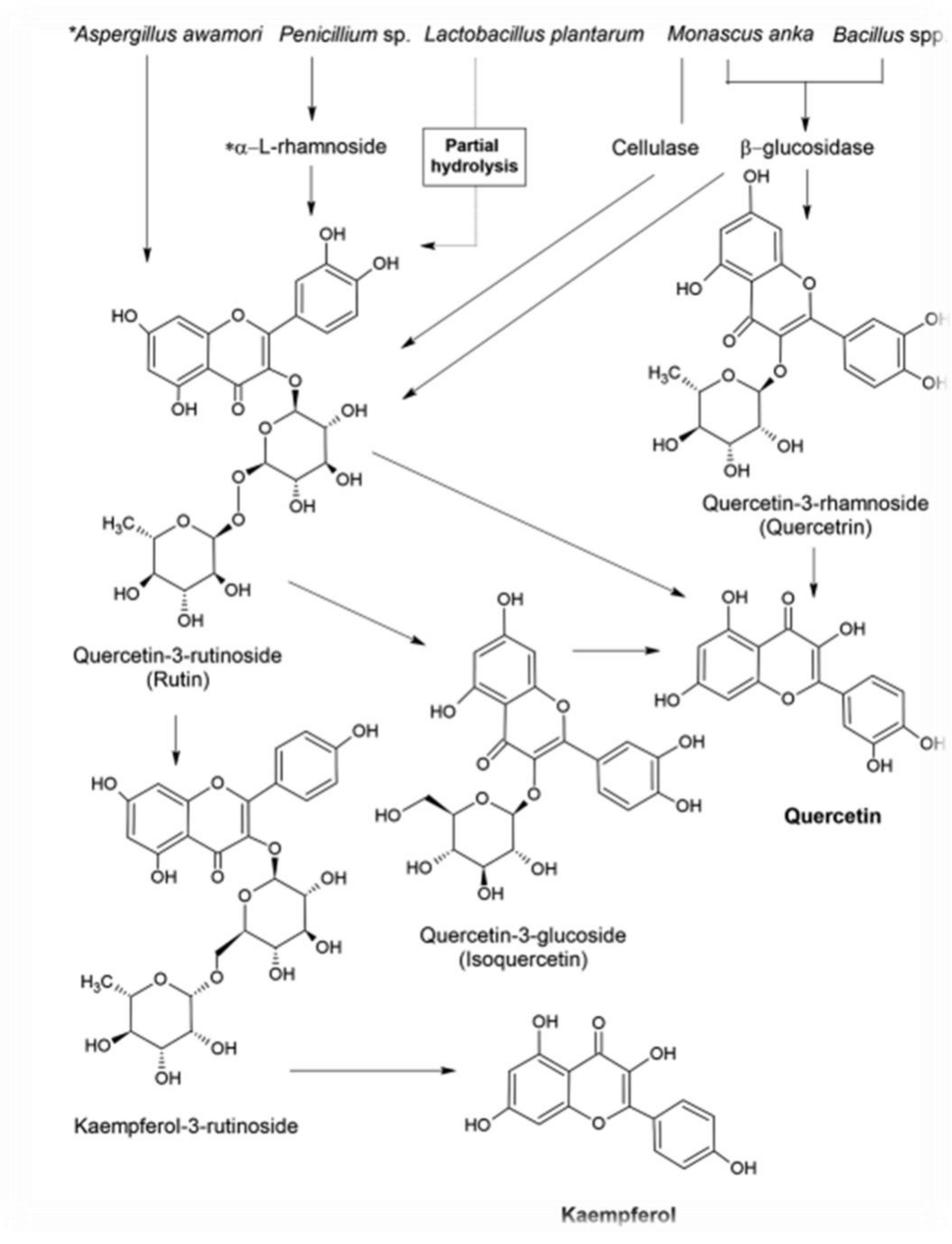


Fig.8. schematic representation of possible flavonoids deglycosylation process in stingless honey.

2.2.2.3.Biological potential of stingless bee honey: In order to elucidate the biological potential and possible health benefits provided by SBH, researchers had begun an extensive investigation into the antioxidant, antimicrobial, and anti-inflammatory activities, which will be treated individually in the following topics. The biological potentials reported so far are at least in part correlated to the phenolic composition of SBH. Moreover, studies have shown that SBH present higher bioactivity than AH (Alvarez-Suarez et al., 2018; Ranneh et al., 2018). Such promising results may be related to the natural fermentation process during honey production in the hive; however, it is still unclear. In this sense, the following topics will present investigations regarding the biological potential of SBH and its possible connection to the phenolic profile.**(Dos Santos, Biluca et al. 2021)**

2.2.3.Pomegranate:

Pomegranate is mentioned three times in The Holy Quraan and as one of the best fruit of choice ever . Pomegranate juice is one of the highly recommended beverages with vitamin C, the juice is extracted from the fruit's sweet red arils pulps and peels. The pomegranate juice is considered a source of phenolic contents **(Fawole and Opara 2022)**. Polyphenolic compounds such as punicalagin and punicalin were isolated from pomegranate juice extracts . Furthermore, the juice has been identified as a source of potassium, phosphorus, calcium, manganese, zinc, and copper .**(Maphetu, Unuofin et al. 2022)**

2.2.3.1. Introduction:

Punica granatum L. is a perishable super fruit grown worldwide. P. granatum plant is characterized as a shrub small tree that is native to the Mediterranean regions.**(Zielińska, Wójcicki et al. 2022)**. In South Africa, the fruit tree is planted as a hedge which attracts many blue birds during the winter and autumn seasons.**(Opara, Fawole et al. 2022)**. P. granatum is an exotic plant in South African soil, given its adaptive behavior, the plant can grow in every region where it is planted. P. granatum is commonly referred to as pomegranate and is a plant of the genus Punica belonging to the family Lythraceae (previously named Punicaceae).**(Maphetu, Unuofin et al. 2022)**. In South Africa, P. granatum is commonly known as "granaat" or "granaatappel" or "bloomgranaat" in Afrikaans language and known as "kgarenate" in Sesotho and commonly referred to as pomegranate in English **(Sun and Shahrajabian 2023)**. Pomegranate is planted across the country and remains one of the loved fruit, which is domestically and commercially available.**(Opara, Fawole et al. 2022)**. The South African pomegranate industry (SAPI) emphasizes that P. granatum is one of the oldest fruit plants which can be used and has been used as a medicinal plant.**(Opara, Fawole et al. 2022)**. The pomegranate plant and its fruit juice possess health benefits, nutritional benefits, therapeutic benefits, and several bioactive compounds.**(Sun and Shahrajabian 2023)** Given the spectrum in which the plant has been documented, the plant is valuable for use of its peels, seeds, seed oils, roots, trunk (barks), wood spout, leaves, flowers, and fruits rinds.**(Opara, Fawole et al. 2022)**. Due to the adaptive nature of the pomegranate, the plant is harvested in various regions and named differently. In Asian countries such as China, Georgia, and Afghanistan diverse number of pomegranates have been reported.**(Sun and Shahrajabian 2023)**. The famous "wonderful" can be found and cultivated in the United States **(Farsi, Kalantar et al. 2023)**, and with emerging cultivators in the Southern hemisphere including South Africa **(Opara, Fawole et al. 2022)**, Peru, Chile, Argentina, and Australia **(Sun and Shahrajabian 2023)**. The pomegranate originated from the ancient Mediterranean areas which have cool winters and warm dry summers climate allowing the plant to grow to its best quality. The pomegranate plant is identified by its growth length, which grows up to 4–5 m long and consists of thorny branches around itself (**Ramos, Darouich et al. 2023)**. Moreover, the plant has flaky bark which contains shinny crumpled petal leaves . Given the characteristics of the plant, the plant is well cultivated and in demand across the globe .**(Maphetu, Unuofin et al. 2022)**. In South Africa, pomegranates are distributed commercially and for home use. Pienaar **(Opara, Fawole et al. 2022)** wrote down that the plant is commercially distributed during the March – July period to the world when the southern hemisphere climate is conducive for pomegranate growing. Moreover, for home use purposes, the plant has been identified as one of the plants to be used for landscaping due to its architectural form and ability to attract bird species by their colorful pinkish flowers and pollen. Pomegranates contain a high amount of bioactive compounds such as phenolics, tannins, anthocyanins, flavonoids, and organic acids and terpenoids .(**Sorrenti, Burò et al. 2023)** .The edible part of the fruit (seeds, peels, and juice) are used for beverages and jams **(Opara, Fawole et al. 2022)**. According to the study by Mphahlele et al. **(Zubia, Babaran et al. 2023)** and Read et al. **(Kumar, Khan et al. 2023)**, pomegranate peels waste can be used as feeds for ruminants. The seeds are used to treat a variety of ailments including cancer, heart diseases, diabetes, and obesity (**Zubia, Babaran et al. 2023)**, and to improve male fertility **(Melgarejo-Sánchez, Nunez-Gomez et al. 2021)**. Other pomegranate use includes cosmetic products production such as anti-dandruff products **(Bhinge, Bhutkar et al. 2021)**. Moreover, the pomegranate plant has been reported to have anti-cancerous **(Pantiora, Balaouras et al. 2023)**, anti-inflammatory **(Pierdomenico, Riccioni et al. 2023)**, anti-ulcer, anti-depressant, diuretic, cardio-protective, antidiarrheal **(Pierdomenico, Riccioni et al. 2023)**, antioxidants, anti-obesity, and anti-diabetic properties **(Mayasankaravalli, Deepika et al. 2020)**. This current review article gathers and presents an update on the ethnomedicinal uses, pharmacological activities, phytochemistry, and molecular mechanisms of Punica granatum L. This knowledge is of paramount importance in the future in drug discovery for the development of novel natural drugs for the treatment and prevention of various ailments.

2.2.3.2. Phytochemicals and chemical structures of P. granatum: The P. granatum contains several phytochemicals. For instance, the bark portion of the plant from Fez was extracted with methanol and revealed the presence of phenolics such as polyphenols, flavonoids, sterols, polyterpenes, with phenolics and flavonoids being the most present chemical compounds with (272.82 ± 32.05 μg/mL) and (387.25 ± 1.75 μg/mL), respectively. Although the bark portion was found to lack saponins and alkaloids phytochemicals . **(Kumar, Khan et al. 2023)**Furthermore, the peel extracted in methanol was found to contain the novel pyrrolizine alkaloids (Punicagranine-1) . Additionally, Adiga et al, reported that the whole pomegranate plant is rich in flavonoids, which can be used to facilitate anti-cancerous cardioprotective activities and enhance memory through cognition rehabilitation. In comparison, the peel still contains the highest chemical compounds of the fruit. Adiga et al. , further investigated the effects of the aqueous peel extract on enhancing cognition which include learning and memory in vitro study, to treat dementia-related disorders. The study concluded that the aqueous peel extract had a significant impact on the test group which improved cognition (exploration, learning, and retention), compared to the control group which resulted in less significant effects. Mayasankaravalli et al. isolated several bioactive compounds of the pomegranate peels using aqueous, ethanol, acetone, chloroform, and petroleum ether. Ethanol and aqueous peel extracts contained more active compounds compared to other extracts. Carbohydrates, tannins, saponin, flavonoids alkaloids, quinones, cardiac glycosides, terpenoids, phenols, coumarins, and steroids were present in the aqueous peel extract. Ethanol peel extract had higher quantities of compounds.The plant contains 17 types of amino acids, minerals, and vitamins C, calcium, iron, phosphorus, retinol, riboflavin, and ferulic acid, with pomegranate bark and roots extracts showing anthelminthic and vermifuge and antiparasitic properties . The pomegranate ethanol peel extract revealed 8 types of proteins extracted from choline chloride urea, ethylene glycol, acetic acid, glucose, sorbitol, citric acid, and sodium acetate urea . Furthermore, punicalin (197.13 ± 86.93 mg/g), punicalagin (54.23 ± 42.23 mg/g), and ellagic acid (25.42 mg/g) were found to be dominant in a peel extract . **(Živković, Šavikin et al. 2021)**In addition, other bioactive compounds have been identified in pomegranate including alkaloids, anthocyanins, tannins, flavonoids, phenolics, proanthocyanidins, sterols, terpenes, xanthonoids, fatty acids, organic acids, lignans, saccharides, and vitamin C. The following chemical structures highlight these phytochemical groups:**(Maphetu, Unuofin et al. 2022)**

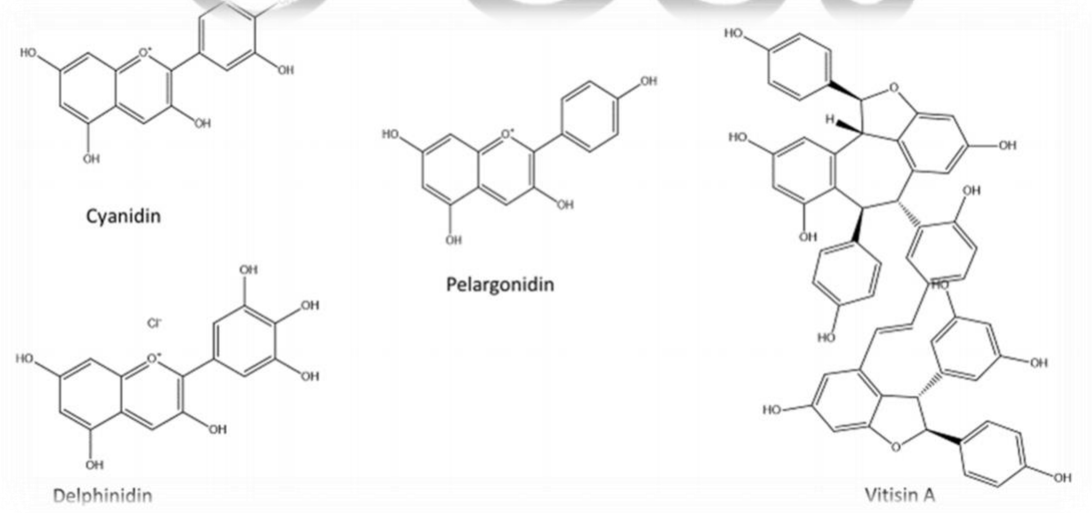
2.2.3.2.1. Alkaloids

Alkaloids such as pelletierine was extracted from P. granatum., reported that the presence of pelletierine is still controversial. However,, it was discovered that pelletierine has anti-cancerous properties in **(Wong, Strandberg et al. 2021)**. The pelletierine derivative compounds found in pomegranate include pseudopelletierine, N-methylpelletierine, isopelletierine, 1-pelletierine, and di-pelletierine . Also, pomegranate alkaloids compounds found include caffeine and pyridium chloride (Figure 9). **(Maphetu, Unuofin et al. 2022)**

Caffeine Pyridium Chloride Pelletierine

fig.9. chemical structures of alkaloid compound isolated from pomegranate

2.2.3.2.2. Anthocyanins: Anthocyanins are important bioactive compounds which give the pomegranate its color though out the ripening process. The most identified anthocyanins compounds include delphinidin, cyanidin, pelargonidin . Moreover, Wang, ozen, ¨ et al. , revealed that vitisin A forms part of the bioactive compounds, (Figure 10). Other identified anthocyanins constituent compounds include cynanidin -3-O-pentoside, pelargonidin-3-O-glucoside, cynanidin-3-O-glucoside, and delphinidin-3-O-glucoside (Figure 10) .**(Maphetu, Unuofin et al. 2022)**



Cyanidin Pelargonidin Delphinidin Vitisin A

Fig.10.chemical structure of anthocyanins/anthocyanidins compounds isolated from pomegranate

2.2.3.2.3. Phenolics: Read et al. **(Read, Deseo et al. 2019)**, identified phenolic compounds such as punicalin, gallic acid, ellagic acid, pyrogallol, (Figure 11) . Additionally, coumaric acid, salycillic acid, vanillic acid, sessamin, caffeic are some of the identified phenolics in the study . Also, phenolic compounds in P. granatum have been found to have inhibitory effects against α-glucosidase activities **(Maphetu, Unuofin et al. 2022).**

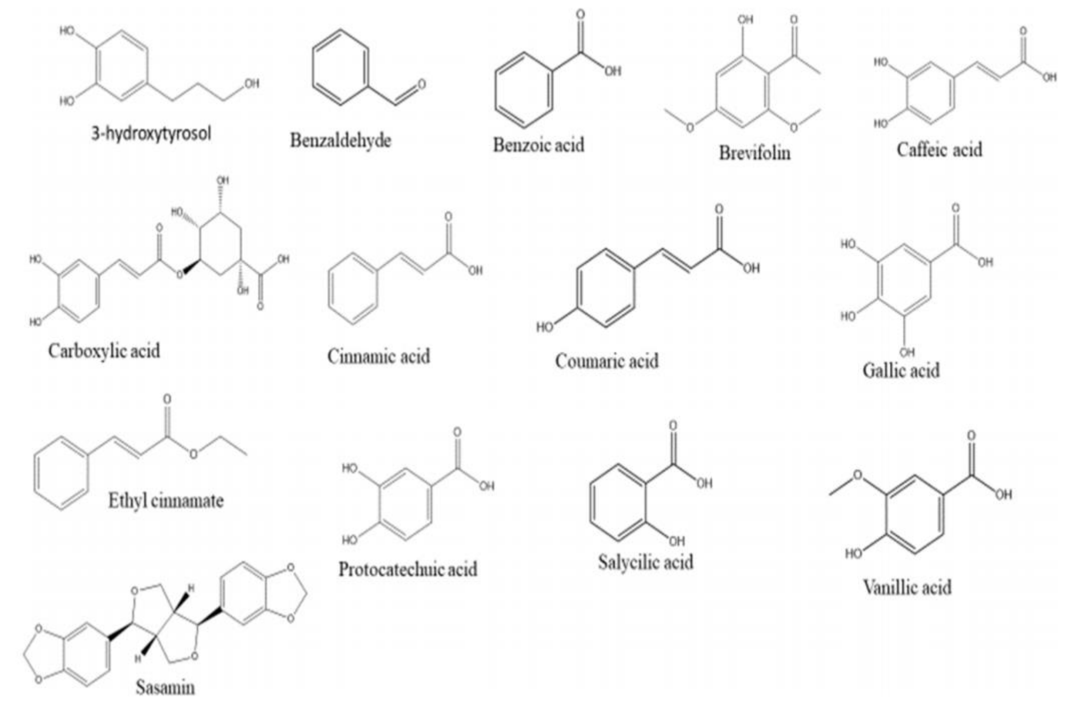


fig.11. chemical structure of phenolic compounds isolated from pomegranate

2.2.3.2.4. Tannins: Pomegranate is a polyphenol-rich fruit that contains tannins from its seeds to its peels . Pomegranate has various pharmacological properties including anti-microbial and anti-viral properties which are direct impacts of tannins bioactive compounds. Additional tannins derivatives found in pomegranate include gallotannins and ellagitannins. Different isolated tannins from pomegranate include 1,2, 3-Tri-O-galloyl-β-4C1-glucose, 2-O-Galloylpunicalin, 3,3′-Di-O-methy lellagic acid, 3,3′,4′-Tri-O-methylellagic acid, castalagin, castalin, casuarinin, corilagin, epicatechin, flavogallonic acid, gallagic acid, gallagyldilacton, granatin A/B, lagerstannin C, pedunculagin, punicacortein A, B, C, and D, punicafolin, punicalagin, punicalin α, and β punicatannin, (Figure 12) **(Maphetu, Unuofin et al. 2022)**.

2.2.3.2.5. Flavonoids: Pomegranates have antimicrobial, antioxidants, anti-atherosclerosis , anti-viral, anti-inflammatory, and anti-cancerous pharmacological activities which are due to the richness of flavonoids bioactive compounds in pomegranates. Flavonoids were identified in the whole fruit, including peels , seeds, leaves, juice , flowers, pericarps, and barks . (Figure 13) illustrates commonly identified P. granatum flavonoids , also identified several common flavonoids including prunin, catechin, chrysin, cyanidin, apigenin, biochanin, glucoside, luteolin, and taxifolin.**(Maphetu, Unuofin et al. 2022**)

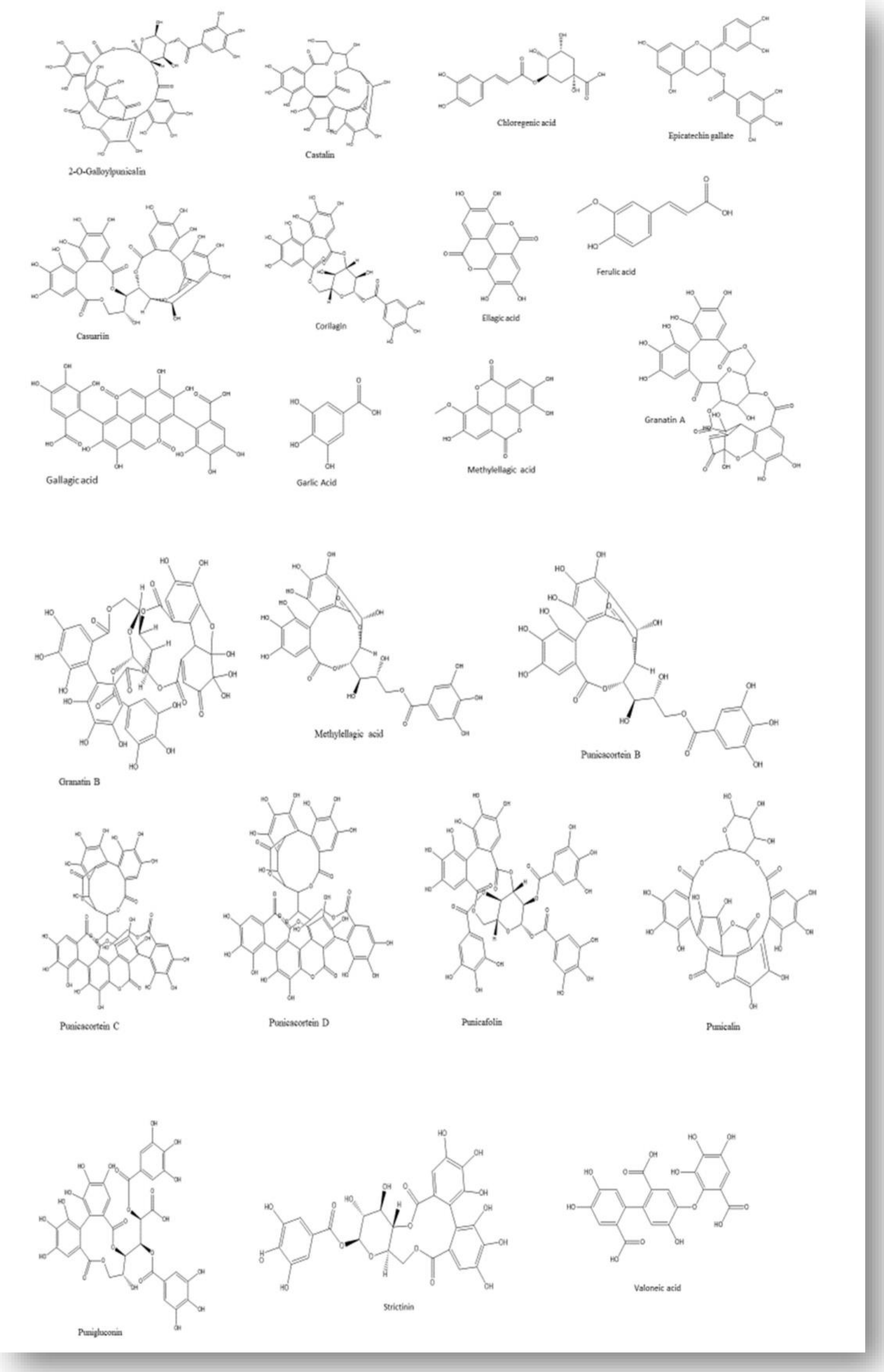


Fig.12. chemical structure of tannins compound isolated from pomegranate.

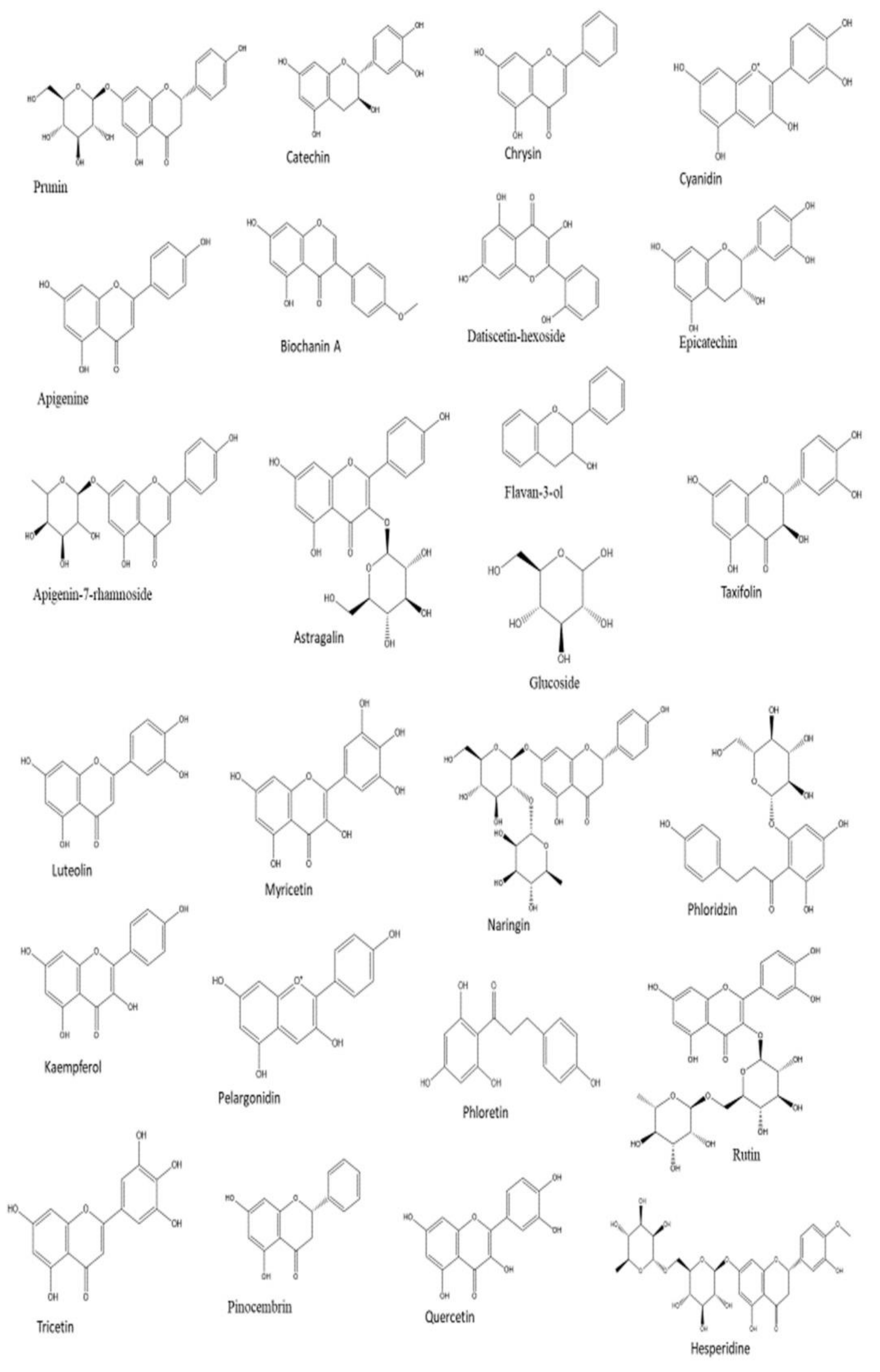


Fig.13.chemical structure of flavonoids isolated from pomegranate.

2.2.3.2.6. Proanthocyanidins: Medicinal plants gained more interest due to the presence of proanthocyanidins, tannins, and flavonoids bioactive compounds and their pharmacological activities . Proanthocyanidins help release catechin, which are essential compounds required to synergize with ascorbic acid to suppress free radicals . In addition, proanthocyanidins compounds identified in pomegranate include procyanidin dimer B2 and B3, arabinose, xylose, galactose, mannose, and rhamnose
(Figure 14) **. (Maphetu, Unuofin et al. 2022)**

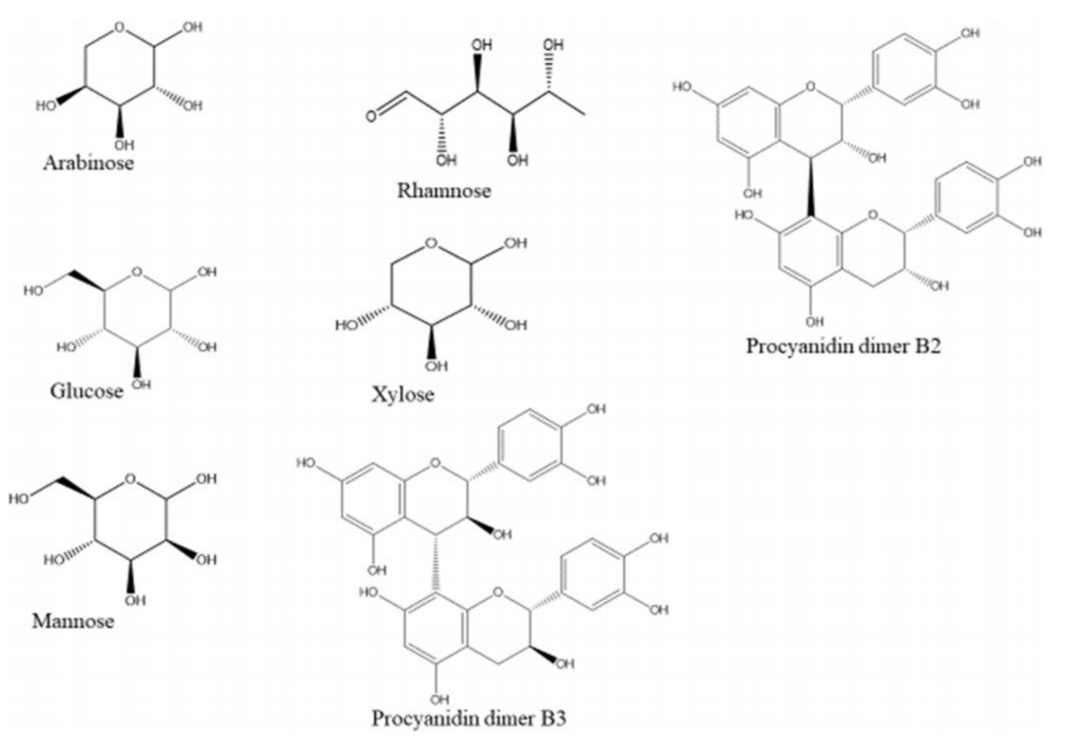


Fig.14. chemical structure of proanthocyanidins isolated from pomegranate.

2.2.3.2.7. Xanthonoids: Xanthonoids are natural polyphenolic compounds that contain several pharmacological effects including anti-oxidants, anti-bacterial, anti-fungal, and anti-viral **(Patil, Agrawal et al. 2021)**. The P. granatum xanthonoid compound identified from the peel is mangiferin, (Figure 15) .

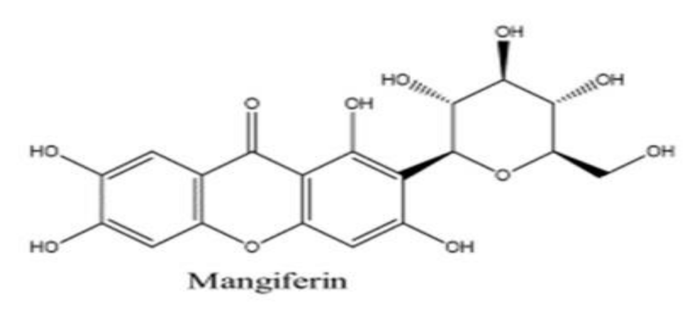


Fig.15.chemical structure of xanthonoids isolated from pomegranate.

2.2.3.2.8. Terpenes and terpenoids: Terpenes and terpenoids are the main bioactive compounds of essential oils and concentrated oils **(Masyita, Sari et al. 2022)**. Terpenes and terpenoids possess various pharmacological benefits such as anticancer, antimicrobial, anti-inflammatory, antioxidant, and antiallergic . Terpenoids (Figure 16) are classified as secondary metabolites produced by medicinal plants to play an essential role in disease resistance . Terpenes constitute various constituents including monoterpenes which are volatile elements , and are found in a small quantity in the pomegranate . Terpenes volatile compounds are represented by alpha (α)-terpenes, alpha-terpineol, and 3-carene, (Figure 17) Also, alcohol, aldehydes, and oxygenated monoterpenes are identified .**(Maphetu, Unuofin et al. 2022)**

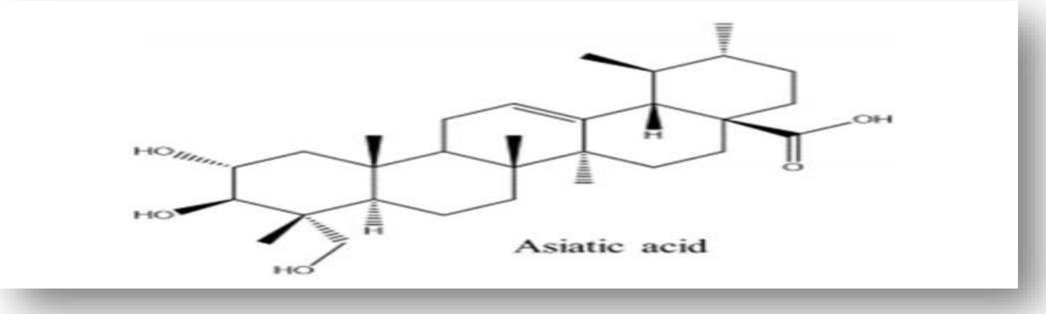


Fig.16. terpenoids compound isolated from pomegranate.

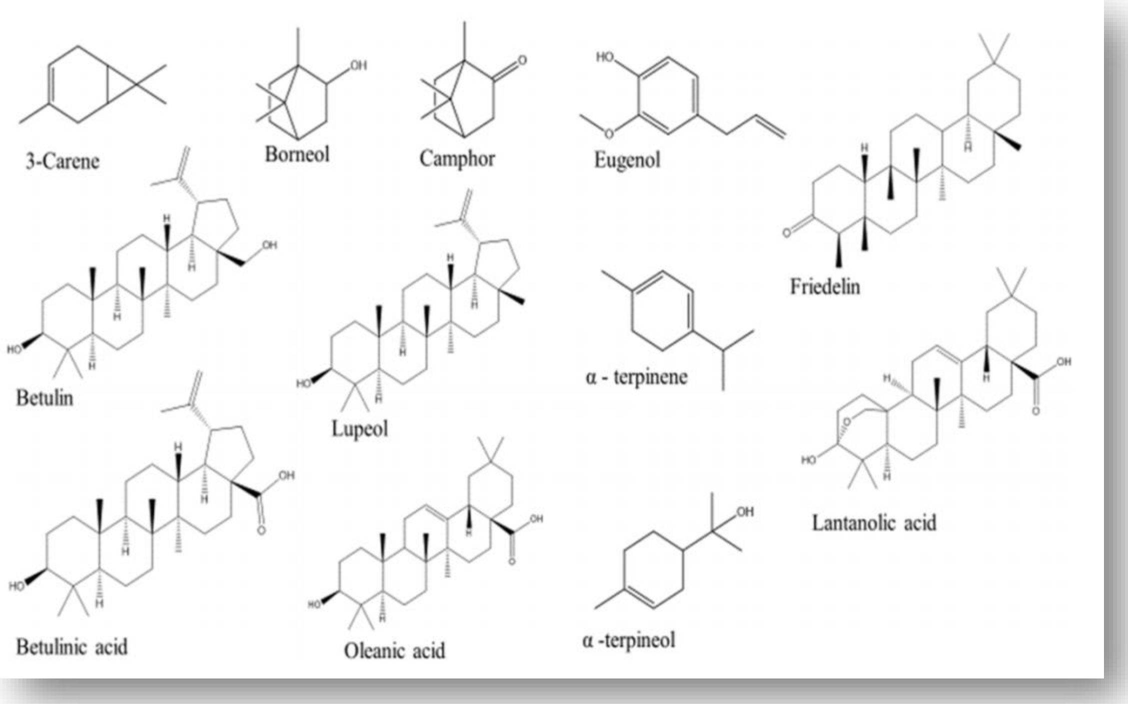


Fig17. Chemical structures of terpenes compound isolated from pomegranate.

2.2.3.2.9. Sterols: Sterols are natural steroids , and are the least present bioactive compounds in pomegranate . Sterols' main function is to reduce cholesterol absorption and low-density lipoprotein cholesterol (LDL-C) in the plasma **(Li, Xin et al. 2022)**. The primary sterol compound indicated in Puneeth and Sharath Chandra is asiatic acid. While Wong et al., identified stigmasterol, sitosterol, and cholesterol, (Figure 15) Sex steroids (estrone, testosterone, and estriol) are present in P. granatum seeds. Similar sterols compounds including daucosterol, sitosteryl-acetate, and campesterol are recognized to be present in pomegranate, (Figure 18) .**(Maphetu, Unuofin et al. 2022)**

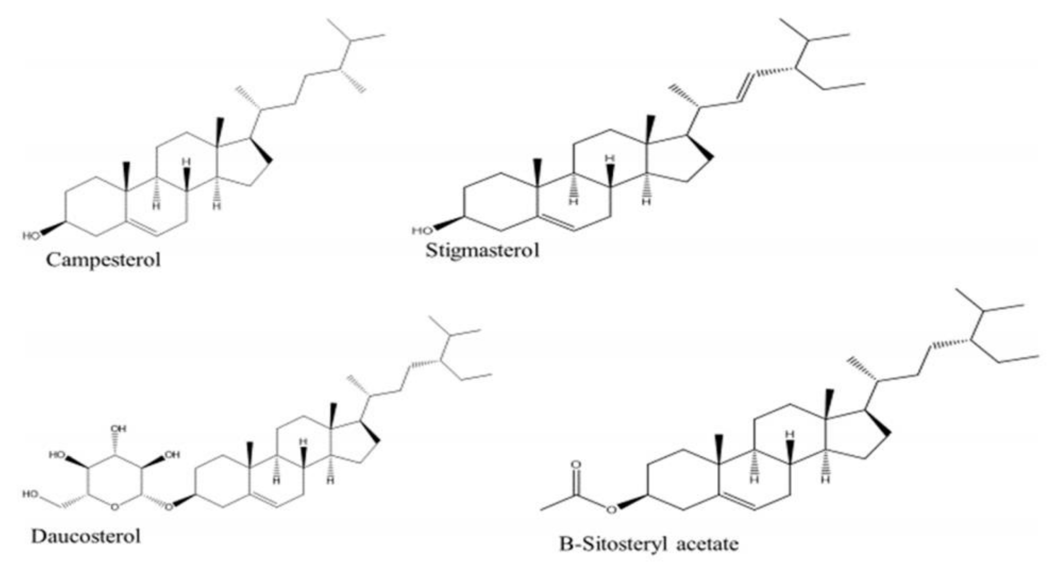


Fig.18. chemical structure of sterol compounds isolated from pomegranate.

2.2.3.2.10. Saccharides: The pomegranate saccharides have been identified to contain health benefits such as enhancing immunomodulatory effects and alleviating hypersensitivity symptoms , and anti-diabetic pharmacological activity . Sucrose, fructose, glucose, and maltose (Figure 19), are the main saccharides compounds found in the pomegranate . **(Maphetu, Unuofin et al. 2022)**

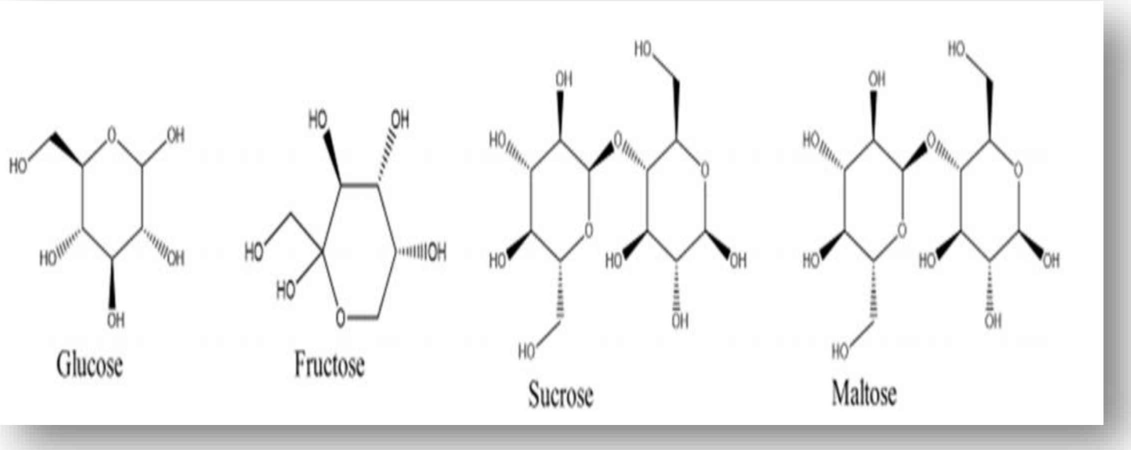


Fig.19. chemical structure of saccharides compound isolated from pomegranate.

2.2.3.2.11. Lignans: Lignans are secondary metabolites which protect plants from pathogens **(Rodríguez-García, Sánchez-Quesada et al. 2019)**. They have been mentioned to possess health benefits such as defending against cardiovascular diseases, anti-oxidants, anti-tumor, and anti-inflammatory activity . From the plant juice, Fernandes et al. highlighted 4 major lignans, namely pinoresinol, secoisolariciresinol, syringaresinol, and cyclolariciserol, (Figure 20) While its indicated that there are several lignans present in P. granatum seeds and whole fruit including matairesinol, and medioresinol (Figure 20). Moreover, conidendrin, isohydroxymatairesinol, isolariciresinol, phylligenin, secoisolariciresinol, pomegralignan, punicatannin C are some of the lignans identified in P. granatum (Figure 20) .**(Maphetu, Unuofin et al. 2022)**

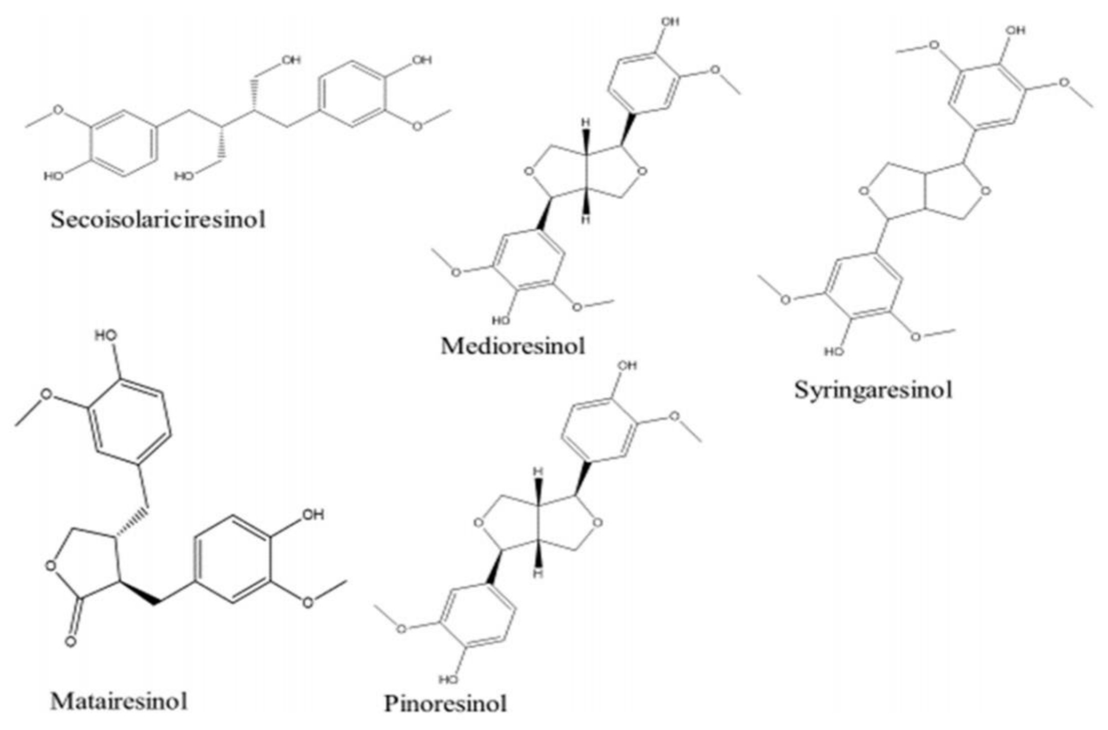


Fig.20. chemical structure of lignans compound isolated from pomegranate.

2.2.3.2.12. Fatty acids and organic acids: P. granatum consists of 83.6% of saturated fatty acids and 16.3% of unsaturated fatty acids. The unsaturated fatty acids form the P. granatum seed components **(Momeni and Asadi-Gharneh 2021)**. Essential oils including fatty acids and organic acids have been documented to possess various pharmacological effects including anti-microbial, anti-oxidant, insecticide, anti-helminthic, and antinociceptive activity . While, volatile compounds and organic oils were identified to be present in a pomegranate such as punic acid, heneicosenoic acid, nonadecanic acid, steriac acid, palmitic acid, oleic acid, linolenic acid, linoleic acid, octoic acid, coumestrol amongst others were identified, (Figure 21) .**(Maphetu, Unuofin et al. 2022)**

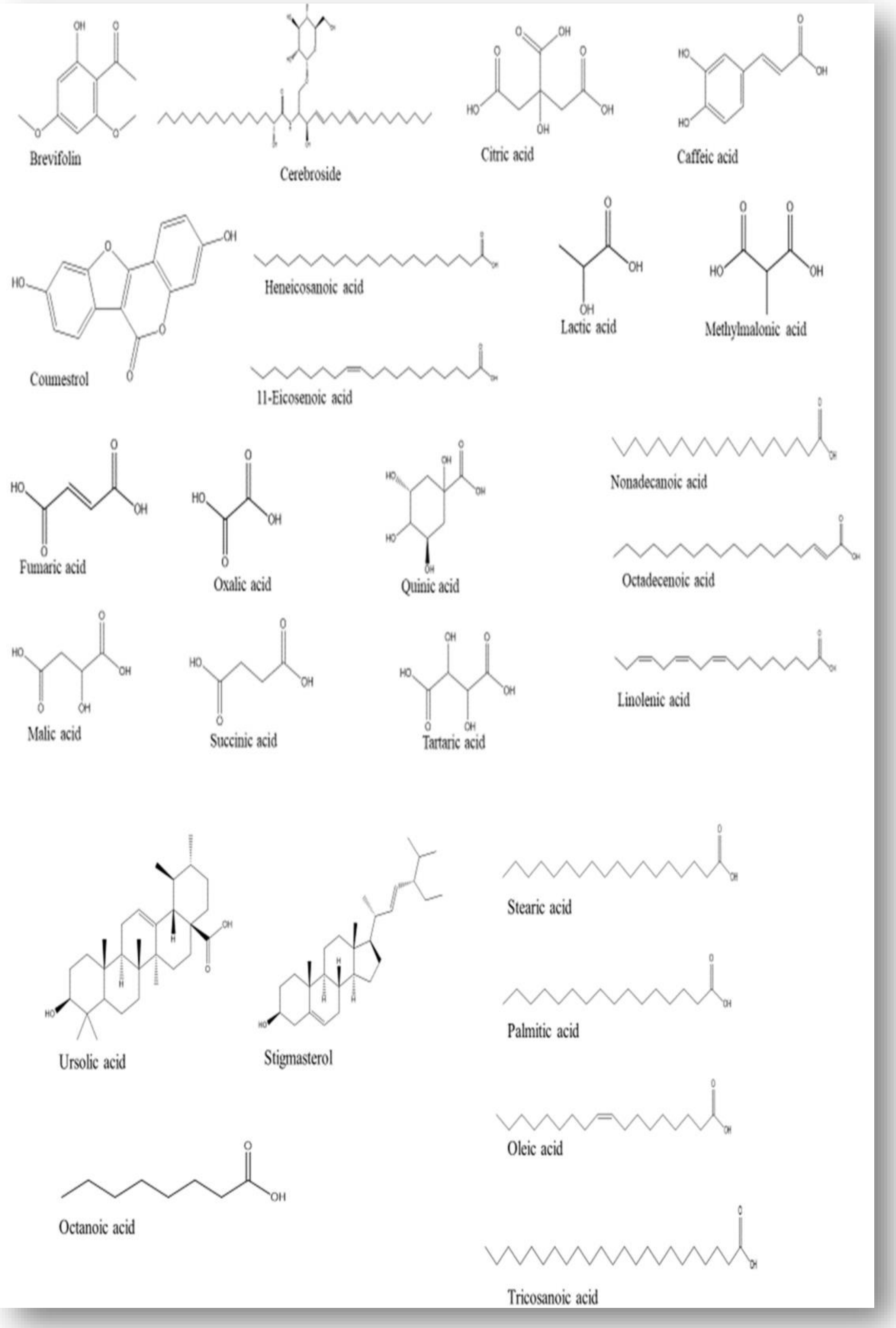


Fig.21. chemical structure of fatty acids and organic acid compounds isolated from pomegranate.

2.2.3.2.13. Vitamin C: vitamin C is found in the pomegranate juice, (Figure 22). Vitamin C is essential in providing nutritional and therapeutic effects . Moreover, consumption of pomegranate juice is associated with significant improvement in reducing fatigue and improving quality of life .**(Esposito, Santarcangelo et al. 2022)** Owing to the numerous cultivars of pomegranate, the bioactive components presence/absence in specific tissues of a particular cultivar may differ in contents, types, and proportions of constituents due to variation in climatic conditions where the cultivar is grown. Bioactive molecules are derived from the interaction between plants and their environment .**(Maphetu, Unuofin et al. 2022)**

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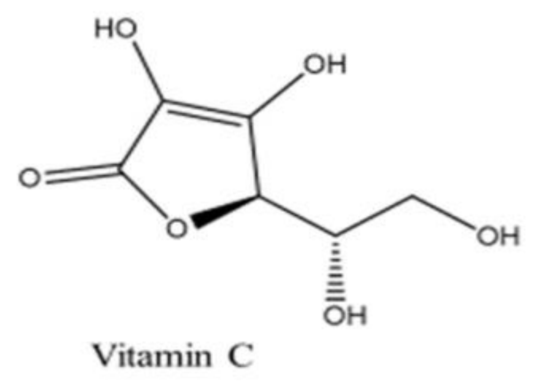


Fig.22. chemical structure of vitamin c compounds isolated from pomegranate.

2.2.4.Grapes/berries: grapes menthioned eleven time in the holly Quraan , that's why its one of the best fruits ever , used as fruit , sweetner as raisins /currant , vingar and fresh juice . Grape (*Vitis vinifera L.*) is one of the most typical fruit of the Mediterranean diet, characterised by high polyphenols content with marked antioxidant and anti-inflammatory activities (Goszcz *et al.*, 2017). By using transcriptional profiling techniques, it has become increasingly clear that polyphenols can influence the expression of genes. Many of these genes are key elements of cell signalling cascades (Spencer 2009; Fraga and Oteiza 2011) and regulatory non-coding RNAs (ncRNAs) (Budisan *et al.*, 2017).**(Milella, Gasparro et al. 2020) ,** also berries resembles grapes in their feautures and the main active conistituent (resveratrol) , Natural polyphenols are divided into phenolic acids, flavonoids, stilbenes, and lignans (Tresserra-Rimbau et al., 2018). p-Coumaric, caffeic, ferulic and synaptic acids are the principal phenolic acids available in human nutritional food. Quercetin, myricetin and catechin are the main flavonoids found in food, whereas resveratrol (RV) is the most studied stilbene structure. Polyphenols are responsible for several health benefits of consuming fresh fruits and vegetables and are the attractive focus to face health challenges in several illnesses (Fernandes et al., 2017a; Sarubbo et al., 2017). Among many polyphenolic compounds, here we focus on RV, which is found in common dietary sources
such as grapes, berries, peanuts.**(Grinan-Ferre, Bellver-Sanchis et al. 2021)**

2.2.4.1. Resveratrol : RV (3,5,4′-trihydroxystilbene) is a polyphenol present in black grapes and its derivatives.However, its primary dietary sources include also blackberries, peanuts, and peanut products. Currently, RV has gained extensive attention due to its therapeutic potential. Numerous health effects have been related to its intake, including antioxidant, antiinflammation, neuroprotective, anti-cancer, and anti-ageing activity (Baur and Sinclair, 2006; Malhotra et al., 2015; Jardim et al., 2018; Cosín-Tomas ` et al., 2019). A meta-analysis of randomised controlled trials suggests that RV may be therapeutic for humans (Marx et al., 2018). Until now, scientific research had shown that RV could prevent or slow the progression of a wide variety of illnesses (Fernandes et al., 2017a). In addition to neurodegenerative diseases, RV can prevent cardiovascular diseases, including cancer, some hepatic (e.g. cholestasis) (Farghali et al., 2009; Wu et al., 2005; Ara et al., 2005) and ischemic injuries, insulin resistance, fat accumulation and inflammation associated with obesity, improvement of cognitive decline (Jeon et al., 2012) as well as enhance stress resistance (Palomera-Avalos ´ et al., 2017) and extend the lifespan from yeast to vertebrates (Porquet et al., 2014).**(Grinan-Ferre, Bellver-Sanchis et al. 2021)**

2.2.4.1.1. Mechanism of action of Resveratrol: RV is an effective drug which was named as a “promiscuous molecule” because of seems to act on many different molecular pathways and binding partners (Britton et al., 2015). Nevertheless, this variety of pathways might also explain the diverse range of effects in which RV appears to be beneficial for health, ageing and neurodegenerative diseases. The following sections contain a summary of the RV mechanisms to explain its actions (Fig. 23).**(Grinan-Ferre, Bellver-Sanchis et al. 2021)**

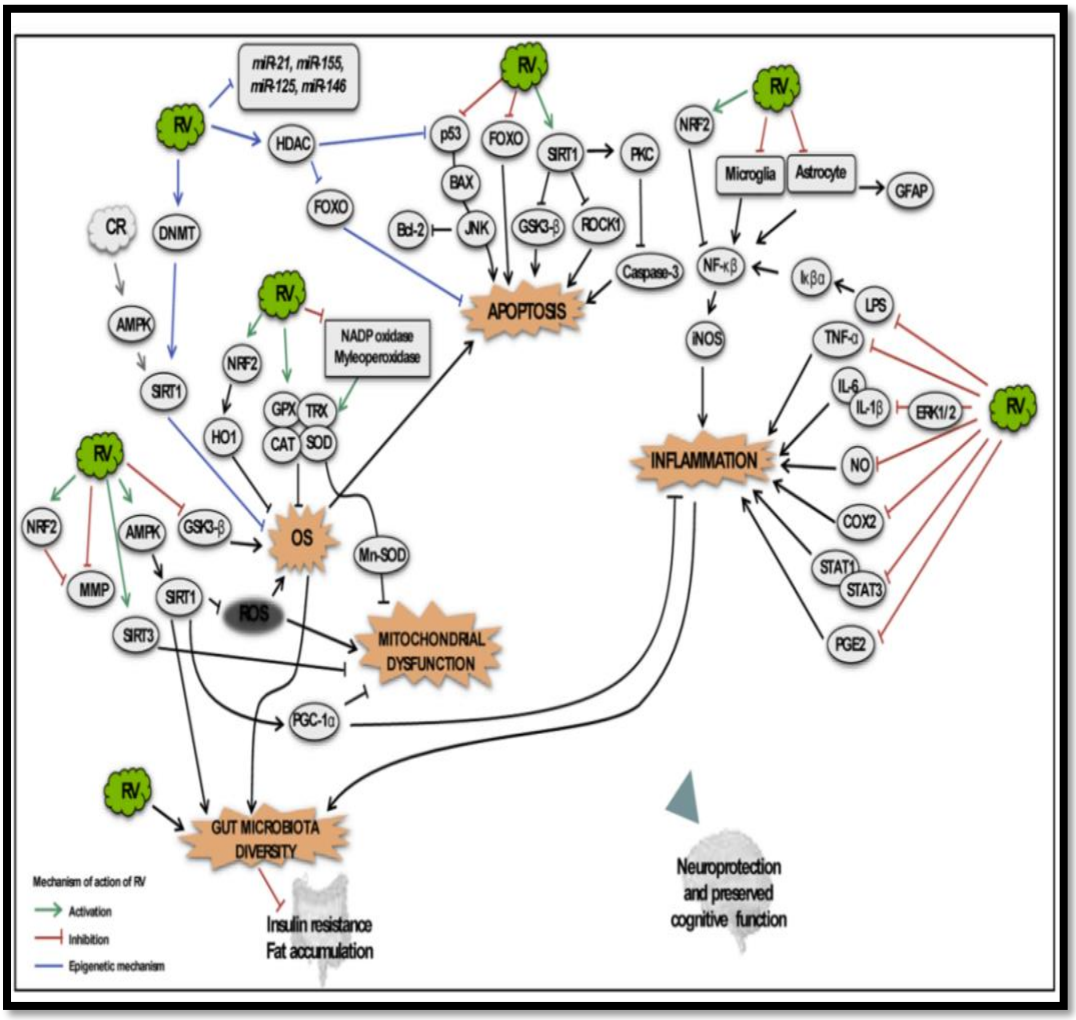


Fig.23. scheme of putative mechanisms of action of RV on different process (epigenetics , OS , mitochondrial dysfunction , inflammation , apoptosis , and gut microbiota) that mediate neuroprotection and preserve the cogntitive function.

2.2.5.date: it's the best fruit ever where it's mentioned seventeen time in the holly Quraan & and it was the best food for prophet Mohammed peace and god prayer's upon him . Date palm is one of the oldest fruit trees on Earth and has been closely associated with human life in the Middle East since ancient times, including Saudi Arabia, which is the parent country of date palm, the second largest producer of date fruit in the world and the ranks of developed countries in the cultivation and production of dates of all kinds. Date fruit is used in a variety of industrial applications. Dates are an excellent source of nutrients and antioxidants such as phenolics and carotenoids, essential fatty acids, and minerals, all of which play a vital role in human health maintenance and can thus be employed as functional foods and nutraceuticals, Dates are an excellent source of nutrients and antioxidants.**(Alhuzali, Jibrin et al. 2023)**

2.2.5.1.Introduction : The date palm (Phoenix dactylifera L) is the most important crop of the Gulf region in the Middle East (AlAbdoulhadi et al., 2011). There is a difference between historians in determining the original homeland of the date palm, as opinions suggested that it belongs to the Arab Gulf region, as it is the largest palm region in the world, and then it was transferred to Iraq about four thousand years BC(Ali, 2010). More than 2,000 different types of dates are grown around the world (Tang et al., 2013). The date palm (Phoenix dactylifera L.) is a common tree in Saudi Arabia, especially in desert locations. It is important for food production as well as food security. Arab countries produced 75 percent of global date production (about 5,096.99 tons) (Elfeky & Elfaki, 2019). According to (Shaikh et al., 2019) the Kingdom of Saudi Arabia is one of the top 10 dates producing countries in the world.**(Alhuzali, Jibrin et al. 2023)**, Ajwa dates (Phoenix dactylifera L.; family Arecaceae) are considered interesting nutraceuticals, as their fruits are edible and nutritious, being good sources of vitamins (A, B 1, B 2, and B3), minerals (Mg, Mn, Ca, K, and Na) carbohydrates, flavonoid glycosides, flavanols, dietary fibers, steroids (cholesterol, stigmasterol, campesterol and α-sitosterol) and fatty acids (Palmitolieic acid, oleic, linoleic and linolenic acid); in addition to their medicinal value owing to the presence of a wide range of polyphenols and bioactive phytochemicals . In recent years, there has been a lot of interest in the numerous health-promoting characteristics of date fruits, which has led to a lot of in-vitro and in-vivo pharmacological research, as well as the identification and quantification of several classes of phytochemicals.**(Abdelghffar, Obaid et al. 2022)**

2.2.5.2. The Nutritional Value of Dates: The date palm's fruit is high in nutrients and is mentioned multiple times in the Holy Quran. The date is recommended in Islamic and traditional medicine for health and disease prevention since it contains several micronutrients in addition to being a good energy source (Mousavi et al., 2014). kimri, khalal, rutab, and tamer are the four stages of ripening of date fruits (Ashraf & Hamidi-Esfahani, 2011). The chemical composition of date fruits changes depending on the stage of maturity, cultivar, growing environment, post-harvest conditions, and a variety of other factors. The chemical composition of the date fruit also influences its nutritional and therapeutic properties (Tang et al., 2013). Carbohydrates, which include reducing sugars like glucose and fructose as well as non-reducing sugars like sucrose, and small amounts of polysaccharides like cellulose and starch, are the major chemical constituents of dates (Aljaloud et al., 2020). Dried dates have a higher sucrose content than soft dates. Soft dates contain reducing sugars, except for a few varieties that contain sucrose (Eltayeb et al., 1999; Tafti & Fooladi, 2006). Dates are a high source of energy because they contain 70% carbohydrates, with 100 grams of the pulp containing around 314 calories(Baliga et al., 2011). Dates contain between 1% and 7% protein, which includes essential amino acids required for human metabolic function. Date proteins, contain twenty-three (23) different amino acids, some of which are not found in common fruits like oranges, apples, and bananas. The amino acids lysine, histidine, arginine, aspartic acid, threonine, glutamic acid, serine, proline, glycine, alanine, cystine, valine, methionine, isoleucine, leucine, tyrosine, and phenylalanine are found in most date cultivars (Ayad et al., 2020). Dates have a low-fat content. Fresh dates (kimri stage) have about 0.14 g fat per 100 g, while dried dates have about 0.38 g per 100 g (tamer stage). Lipids are mostly concentrated in the skin and are more important for protecting the fruit than for contributing to the date's nutritional value. Dates contain both saturated and unsaturated fatty acids. Saturated fatty acids include capric, lauric, myristic, palmitic, stearic, margaric, arachidic, heneicosanoic, behenic, and tricosanoic acids. Unsaturated fatty acids include palmitoleic, oleic, linoleic, and linolenic acids (Ibrahim et al., 2021). Dates contain dietary fiber, which may contribute significantly to raising their nutritional value (Maqsood et al., 2020). The total dietary fiber content of date fruits has been estimated to be between 6.5 and 11.5%. (up to 90 percent of which is insoluble and 10 percent of soluble dietary fiber) (AlShwyeh, 2019). Dates have a total dietary fiber level of 6.26 to 8.44 g/100g, with 84 % to 94 % insoluble fiber (Ishurd et al., 2002). A daily intake of 100 g of dates delivers around 50% to 100% of the recommended daily fiber intake (Aljaloud et al., 2020). Dates are rich in many nutrients, with dried dates containing 15 minerals that are beneficial as a dietary supplement for an example magnesium, manganese, phosphorus, iron, calcium, potassium, sodium, and zinc. Depending on the mineral, the percentage of each mineral in dried dates varies (Ibrahim et al., 2021). Each mineral's percentage in dried dates varies from 0.1 to 916 mg/100g of date flesh (Aljaloud et al., 2020; Khan et al., 2008). Dates flesh contains a high percentage of potassium, as it is the predominant microelement in them (Ayad et al., 2020). They also contain low levels of sodium and high concentrations of iron (Gnanamangai et al., 2019). Dates contain a wide range of vitamins such as vitamin A, B1, B2, B3, B5, and vitamin C. Dates contain vitamin A, which possesses antioxidant properties (Gnanamangai et al., 2019). Furthermore, because vitamins are depleted during the drying process, fresh dates have higher vitamin concentrations than dried dates (Hamad et al., 2015; Hassan et al., 2017). Dates are a rich source of antioxidants. Among them, especially carotenoids (beta-carotene, lycopene, lutein, zeaxanthin, and neoxanthin), phenols; Cinnamic acids and their derivatives, flavonoid glycosides, flavones, flavonols, flavoxanthin, anthocyanins. On the other hand, the concentration of these phytochemicals in dates diminishes as they continue to progress into the ripening stage (M. Al-Farsi et al., 2005; Ghnimi et al., 2017). The phenolic content of fresh and dried dates is 193.7 mg/100g and 239.5 mg/100g, respectively (Nasir et al., 2015).**(Alhuzali, Jibrin et al. 2023)**

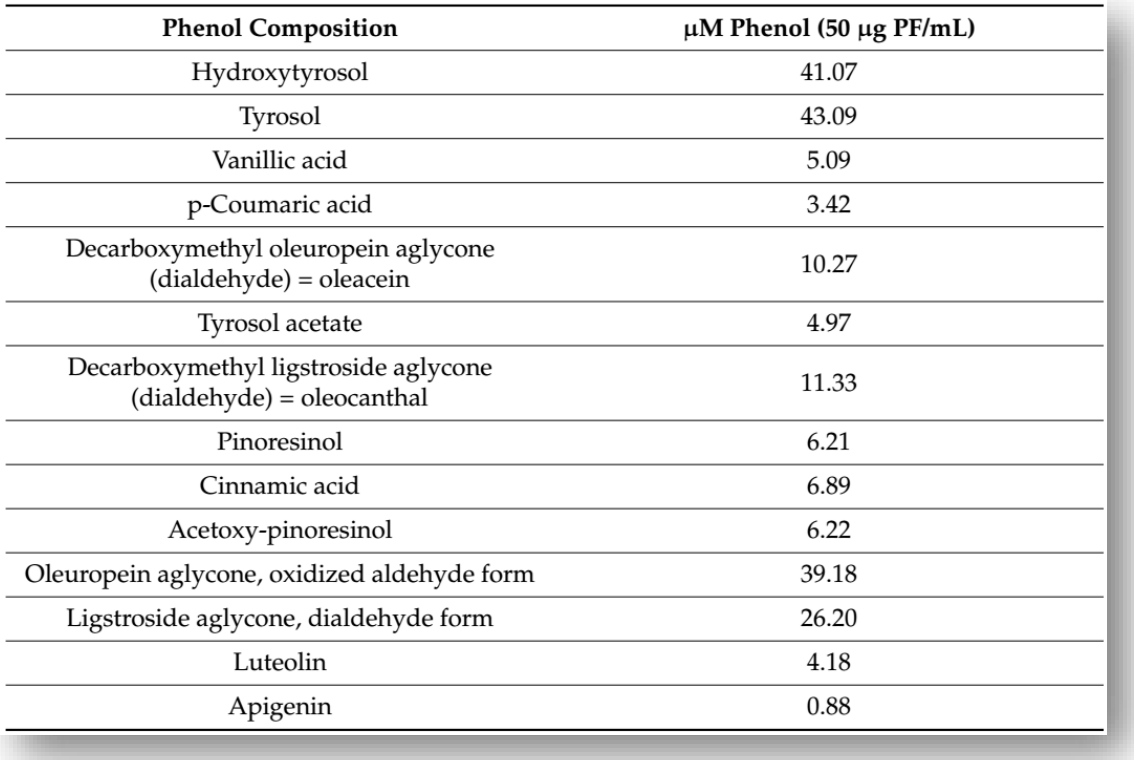
2.2.5.3. Antioxidant Activities: Dates contain diverse therapeutic benefits and biological activities, as well as a high nutritional value, and have been used as a natural cure to treat a variety of noncommunicable illnesses and disorders. Dates compositional study reveals that they have a high antioxidant potential due to their capacity to scavenge free radicals. The primary antioxidants contained in dates include carotenoids, polyphenols, and tannins. These antioxidants impede neuroprotection by functioning as a signal of antioxidant enzymes in the defense process (Pujari et al., 2014). Natural antioxidants have a variety of health advantages, including cancer prevention, protection against microorganisms and chronic inflammation, a lower risk of heart disease, and antimutagenic characteristics (Neeser & Bruce German, 2004). Due to their high concentration of related phytochemicals such as carotenoids, phenolics, tocopherols, flavonoids, and ascorbic acid, dates are vital for improving the intake of natural antioxidants in the human daily diet (Younas et al., 2020). Furthermore, the antioxidant potential of dates differs depending on cultivar, data type, and provenance. Moreover, the antioxidant content of dates varies depending on the region (Idowu et al., 2020). As a result, it is necessary to consider these variables when choosing date fruit as a nutraceutical.**(Alhuzali, Jibrin et al. 2023)**

2.2.6.olive oil : It’s the stain or food dressing as prescribed in the Holy Quraan in the 7th time while other six times it's menthioned by its name olive and best tree is that in tour sini where Allah talks to prophet mosa peace and good prayer's upon him . VOO is known to be a significant bioactive food with a variety of advantageous qualities, and it may be useful in the treatment of various immune-inflammatory illnesses. On top of the fatty acid composition, where oleic acid as a major compound is considered an important contributor to these effects, VOO has other biological minor components that also account for its beneficial activities. The effect of the phenols from VOO on neutrophils, a key cell type in the immune response, was investigated in order to unravel the mechanisms behind the response. Results showed similar effects mediated by both total PF and isolated HTyr in $A\beta_{1-42}$-activated human neutrophils, suggesting that HTyr plays a predominant role in the antioxidant and anti-inflammatory effects of the PF and strengthening the current knowledge concerning the main biological properties attributed to HTyr. Nevertheless, other bioactive substances found in the PF (e.g., tyrosol, pinoresinol, or oleocanthal, among others) may also contribute to PF's beneficial effects. In fact, earlier studies have referred to these small polyphenols in olive oil as a type of natural substance with anti-inflammatory and antioxidant capabilities. Considering that $A\beta_{1-42}$ is an early trigger in the pathogenesis of AD, leading to synaptic and cognitive impairments, these results show the beneficial effect of phenols in managing the inflammation associated with neuronal diseases, slowing down the development of the process.**(Rivero-Pino, Grao-Cruces et al. 2023)**

2.2.6.1. Introduction: Virgin olive oil (VOO) is the major source of fatty acids in the traditional Mediterranean diet, and its ingestion is associated with a reduced risk of chronic degenerative diseases, including cardiovascular pathologies, immune-inflammatory disorders, and cancer . The positive effects of VOO have been historically attributed to the extraordinary oleic acid content, but it is also largely recognized that the minor components like thosepresent in the phenolic fraction (PF) may be of biological relevance . In fact, the high concentration of phenolic compounds in the PF from VOO has been reported to be a relevant player in the beneficial effects associated with the Mediterranean diet . Some of these phenolic compounds can exert one or more bioactivities, including anti-inflammatory, antioxidant, antimicrobial, antiproliferative, antiarrhythmic, and vasodilatory effects, as well as the capacity to regulate relevant cellular signaling pathways . The Mediterranean diet, characterized by better cardiovascular health due to VOO, is a food model highly recognized by the scientific community and the World Health Organization.Inflammation is a physiopathological phenomenon involved in the genesis of numerous diseases as a response of the immune system to injurious stimuli such as tissue injury,infection, or toxicants . During physiological inflammation, with a primary role in theclearance of extracellular pathogens, neutrophils and monocytes are recruited from the circulation to sites of inflammation, infiltrated into the affected tissues, and then these cells produce oxidants, complement components, Fc receptors, prostaglandins, cytokines, and chemokines that cooperate to achieve healing and to restore homeostasis . Upon identifying cellular injuries, immune cells like microglia, astrocytes, and activated T cells can cause neuroinflammation. Alzheimer's disease (AD) and other neurodegenerative disorders can arise as a result of a persistent neuroinflammation. In this regard, beta-amyloid (Aβ1-42) is an early trigger in the development of AD, leading to synaptic and cognitive deficiency. As the relationship between VOO and an anti-inflammatory response has been shown , it is relevant to unravel the contribution of the PF to these beneficial effects in human neutrophils. This information is key in order to clarify the possible positive impact of phenols during inflammation management and to better understand the complex mechanisms of neuroinflammation and how it is affected by the intake of VOO. The aim of this study was to evaluate whether the PF and its most abundant compound, hydroxytyrosol (HTyr), modulate the activation mediated by Aβ1-42 in human neutrophils, in order to unravel the mechanisms behind the beneficial effects of VOO. For this purpose, the Aβ1-42-induced expression of pro-inflammatory genes and surface markers and the release of pro-inflammatory cytokines in freshly isolated neutrophils from healthy volunteers exposed to the phenols were evaluated.**(Rivero-Pino, Grao-Cruces et al. 2023)**

2.2.6.2.Characterization of the Phenolic Fraction: The composition of PF is detailed in Table 4. The main components found in the phenol fraction were the aldehyde form of oleuropein aglycone and the dialdehyde formof ligstroside aglycone, followed by HTyr and tyrosol, representing around 67% of the total PF. These results are in line with previous reports aiming to characterize the phenolic fraction of VOO . Phenolic compounds are accumulated during fruit ripening, and both agronomic (i.e., cultivars or environmental factors) and processing factors (e.g., malaxation time) have an impact on their biosynthesis and biotransformation factors . For instance, the content of HTyr has been reported to range from 0.28 to 7.57 mg/kg in olive oil in an evaluation of 80 different cultivars . Thus, the content of HTyr in the test item is relatively high. The antioxidant and anti-inflammatory properties of olive phenols were recently reviewed, highlighting the relevance of HTyr .**(Rivero-Pino, Grao-Cruces et al. 2023)**

Table 4. Main composition of PF from VOO using COI/T20/29doc.



Phenol Composition	µM Phenol (50 µg PF/mL)
Hydroxytyrosol	41.07
Tyrosol	43.09
Vanillic acid	5.09
p-Coumaric acid	3.42
Decarboxymethyl oleuropein aglycone (dialdehyde) = oleacein	10.27
Tyrosol acetate	4.97
Decarboxymethyl ligstroside aglycone (dialdehyde) = oleocanthal	11.33
Pinoresinol	6.21
Cinnamic acid	6.89
Acetoxy-pinoresinol	6.22
Oleuropein aglycone, oxidized aldehyde form	39.18
Ligstroside aglycone, dialdehyde form	26.20
Luteolin	4.18
Apigenin	0.88

2.2.6.3. Effect of PF and HTyr on Neutrophil Viability: Cell survival was determined with MTT assay, and the viability at all doses assessed was >95% (data not shown). It was observed that PF up to 50 µg/mL and HTyr at 41 µM (equivalent concentration of HTyr found in PF at 50 µg/mL) for 6 h had no adverse effects on neutrophil viability. Considering these results, the rest of the assays were carried out at concentrations of 25 and 50 µg/mL.**(Rivero-Pino, Grao-Cruces et al. 2023)**

2.2.6.4.mechanism of neuroprotective & antioxidant action of VOO:

2.2.6.4.1.Regulation of Myeloperoxidase, Neutrophil Elastase, and Cyclooxygenase-2 Gene Expression: Gene expression following exposure to the PF and pure HTyr was evaluated in the Aβ1-42-activated neutrophils. Aβ1-42-treated neutrophils up-regulated myeloperoxidase (MPO), neutrophil elastase (NE), and cyclooxygenase-2 (COX-2) gene expression compared with untreated neutrophils (Figure 24). PF at both concentrations of 25 and 50 µg/mL, and HTyr at 41 µM, interfered with the enhanced transcriptional activity of MPO, NE, and COX-2 genes in Aβ1-42-treated neutrophils. In the case of PF, the response was observed in a dose-dependent manner. MPO is a local modulator of tissue injury and the subsequent inflammation related to many diseases, which is mostly expressed in neutrophils . In the case of MPO gene expression, the PF led to a decrease lower than the basal levels (control), whereas the HTyr decreased to a lesser extent, indicating that the effects are due to the contribution of different compounds, rather than HTyr being the main contributor. NE, which can be passively liberated or actively produced, has been correlated with the development of several inflammatory diseases , whereas cyclooxygenase-2 (COX-2) expression by the neutrophils results in PGE2 synthesis, which may account for alterations in tissue homeostasis. The regulation of NE seems to be more affected by other phenols present in the fraction rather than HTyr, compared with the other markers evaluated, since at 25 µg/mL the decrease, though significant, is not very relevant. The highest decrease is observed with the PF at 50 µg/mL where the levels are comparable to the control; thus, the increased concentration of phenols might be contributing to this effect. The pattern of gene expression found for COX-2 is similar to the other markers but the difference among samples is not very pronounced, suggesting in this case that HTyr is highly contributing to the regulation of COX-2.**(Rivero-Pino, Grao-Cruces et al. 2023)** .

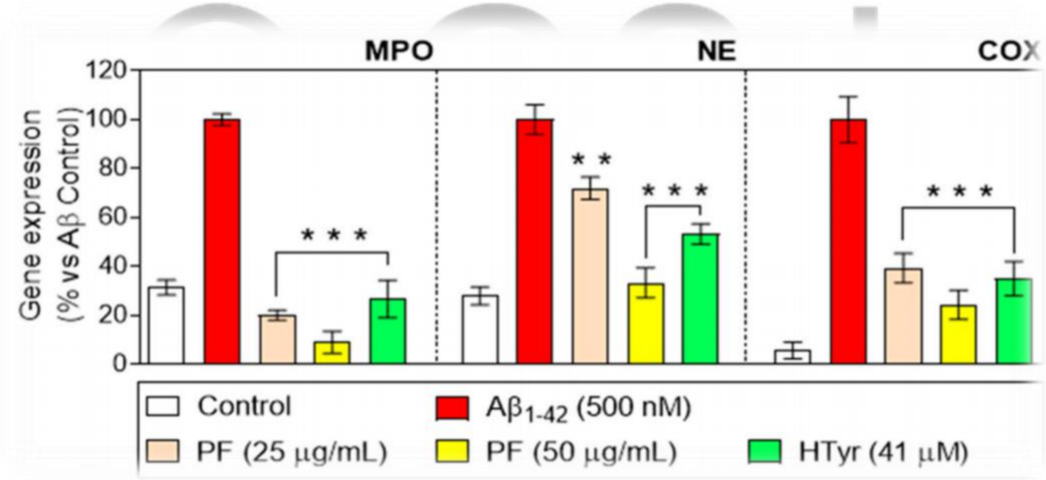


Fig.24. Relative gene expression of myeloperoxidase (MPO), neutrophil elastase (NE), and cyclooxygenase-2 (COX-2) in primary human neutrophils stimulated with Aβ1-42 (500 nM), after treatment with the PF from VOO (25 and 50 µg/mL) or hydroxytyrosol (HTyr, 41 µM) for 6 h. Values are means of the three independent experiments in triplicate, with their standard errors represented by vertical bars (** $p < 0.01$; *** $p < 0.001$ vs. Aβ1-42-treated cells).

2.2.6.4.2. Regulation of Metalloproteinases and Peroxisome Proliferator-Activated Receptor-γ Gene Expression: Metalloproteinases (MMPs) modulate the events of immune cell development, which are considered relevant for persistent inflammatory response . Therefore, we investigated the influence of PF and HTyr on the gene expression of three major MMPs (MMP-1, MMP-3, and MMP-9). As peroxisome proliferator–activated receptor (PPAR)-γ agonists have been reported to inhibit MMPs and pro-inflammatory cytokines , whether the PF and HTyr can affect PPAR-γ gene expression in Aβ1-42-treated human neutrophils was also investigated. Aβ1-42-treated neutrophils up-regulated MMP gene expression compared with untreated neutrophils. As shown in Figure 25A, the incubation with PF for 6 h produced a significant down-regulation of all MMPs gene expression in Aβ1-42-treated human neutrophils. As can be observed, the effects of olive oil phenols on the expression of MMP could be considered highly biologically relevant, as it counteracts the effect, leading to even lower values of expression compared with the control for MMP-1, whereas the effect on MMP-3 and MMP-9 is a partial decrease. The effect of HTyr is very relevant for MMP-3, whereas in the case of MMP-9, results suggest that the effects are due to the different phenols contained as a whole, rather than because of HTyr exclusively. These findings were further endorsed by a significant up-regulation of PPAR-γ gene expression in Aβ1-42-treated human neutrophils following the incubation with 50 μg/mL of PF and 41 μM of HTyr ($p < 0.05$; $p < 0.001$ vs. Aβ1-42-control, respectively, Figure 25B).**(Rivero-Pino, Grao-Cruces et al. 2023)**

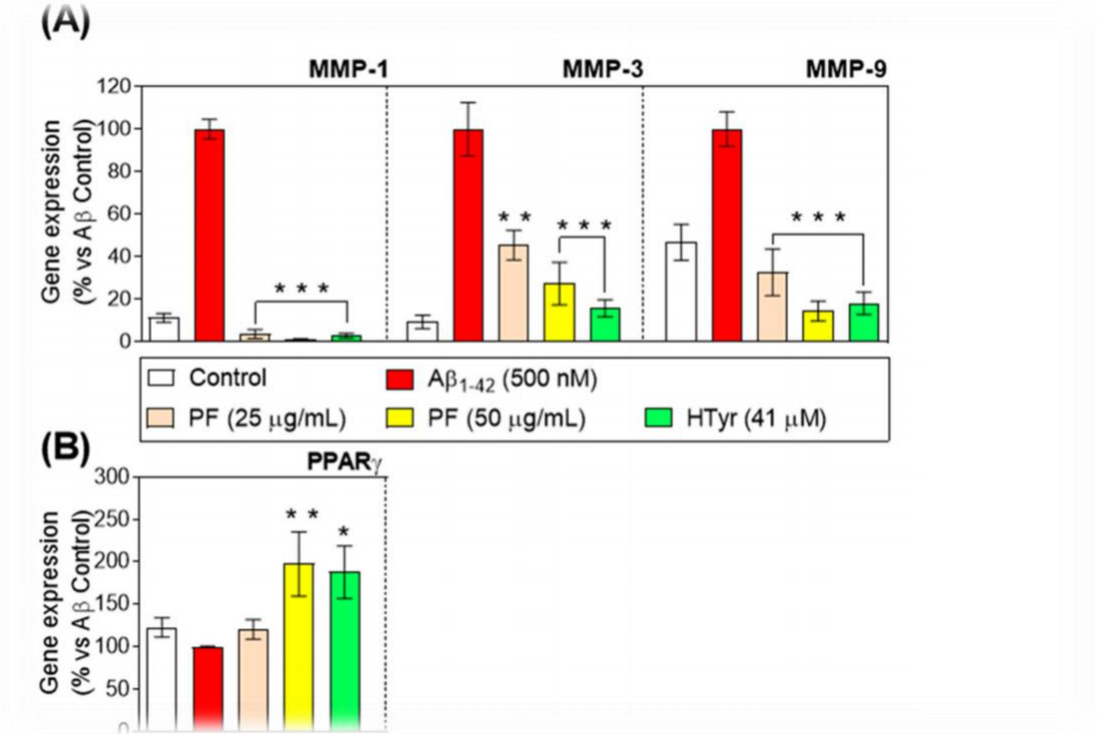


Fig.25. Relative gene expression of (A) MMP-1, MMP-3, and MMP-9 and (B) PPAR-γ in Aβ1-42-stimulated primary human neutrophils treated with the PF from VOO (25 and 50 μg/mL) or hydroxytyrosol (HTyr, 41 μM) for 6 h. Values are means of the three independent experiments in triplicate, with their standard errors represented by vertical bars (* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$vs. Aβ1-42-treated cells)

2.2.6.4.3.Down-Regulation of Toll-like Receptor 4 and Pro-Inflammatory Cytokine Gene Expression and Secretion: The stimulation of toll-like receptor (TLR) 4 by Aβ1-42 causes the release of vital immunoregulatory and pro-inflammatory cytokines, both of which are necessary to effectivelyactivate the innate immune response. In this study, an up-regulation of the TLR4 geneexpression in Aβ1-42-treated human neutrophils was reported, but this was counteracted by the treatment with PF and HTyr for 6 h ($p < 0.001$ vs. Aβ1-42-control, Figure 26A). Furthermore, the PF and HTyr significantly decreased the gene expression and productionof the pro-inflammatory cytokines TNF-α, IL-1β, IL-6, and IFN-γ at all doses after 6 h($p < 0.001$ vs. Aβ1-42-control, Figure 26B). The regulation of TLR4 is suggested to be due tothe HTyr, as it was observed that the decrease was more pronounced when the exposure was performed with the isolated compound. This behavior was different for the rest of the markers in Figure 26 . For instance, the gene expression of TFN-α and IL-6 is significantly different from the Aβ1-42-treated neutrophils and lower than the decrease effect caused by HTyr. This suggests that the other phenols

(Table 4) in the test item are responsible for this counteracting effect. For the other parameters evaluated (IL-1β and IFN-γ) the pattern is similar, where the contribution seems to be balanced among the different phenols, since the HTyr is exerting the same effect as the PF.

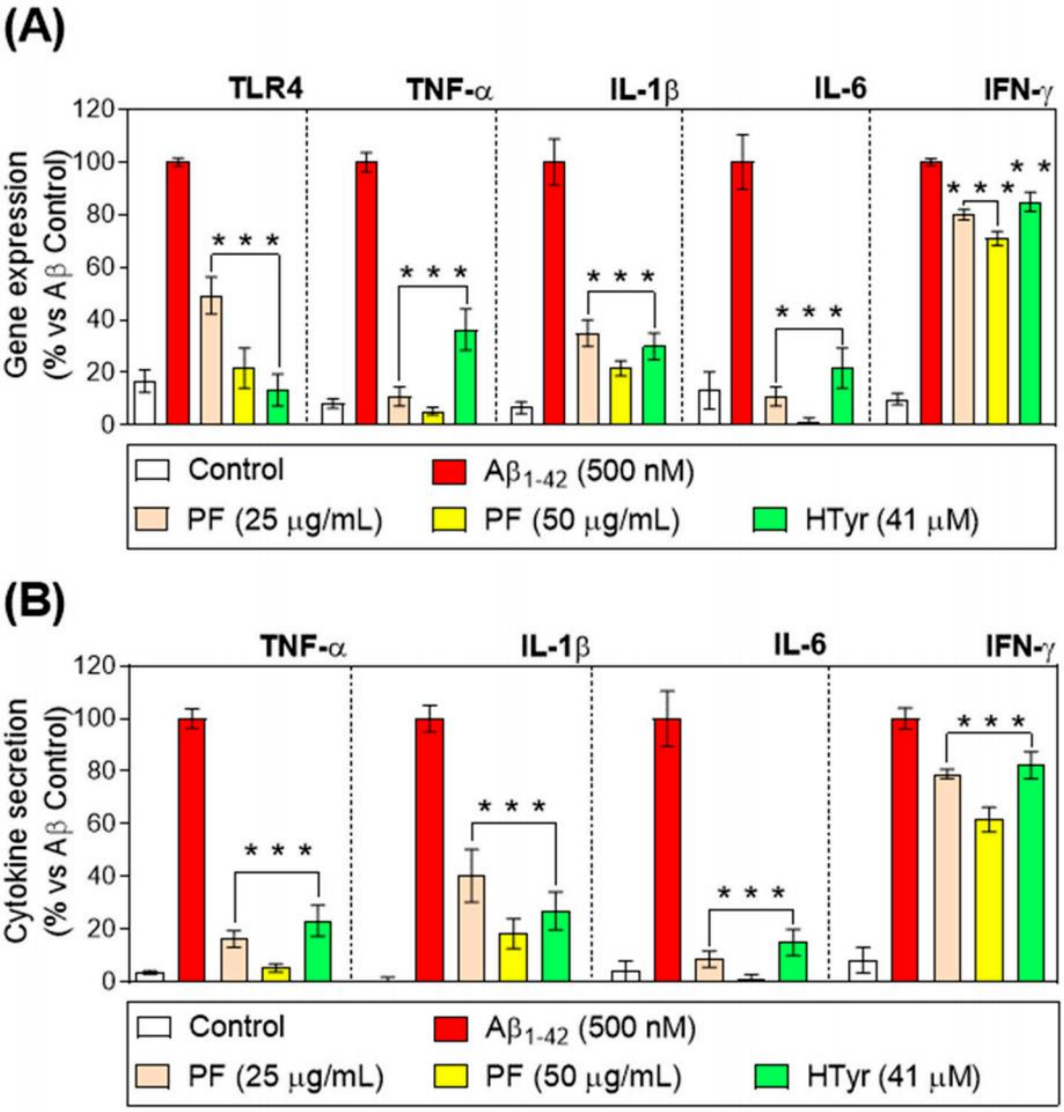


Fig.26. A) Relative gene expression of TLR-4, tumor necrosis factor (TNF)-α, interleukin (IL)-1β ,IL-6, and interferon (IFN)-γ. (B) Cytokine expression of TNF-α, IL-1β, IL-6, and IFN-γ after the treatment of Aβ1-42-stimulated primary human neutrophils with the PF from VOO (25 and 50 μg/mL) or hydroxytyrosol (HTyr, 41 μM) for 6 h. Values are means of the three independent experiments in triplicate, with their standard errors represented by vertical bars (** $p < 0.01$; *** $p < 0.001$ vs. Aβ1-42-treated cells).

IL-8 was described to be one of the first chemokines triggering neutrophils after secretion by stimulated monocytes . Aβ1-42-treated neutrophils up-regulated IL-8 gene expression and secretion compared with untreated neutrophils (Figure 27). In this study, the treatment of Aβ1-42-stimulated human neutrophils with the PF and HTyr for 6 h at concentrations up to 50 μg/mL (PF) and at 41 μM (HTyr) resulted in a decrease in the IL-8 gene expression and production by neutrophils. Furthermore, the PF at the highest concentration inhibited IL-8 release in a more significant manner than HTyr at 41 μM ($p < 0.01$; $p < 0.001$ vs. Aβ1-42-control, Figure 27). **(Rivero-Pino, Grao-Cruces et al. 2023)**

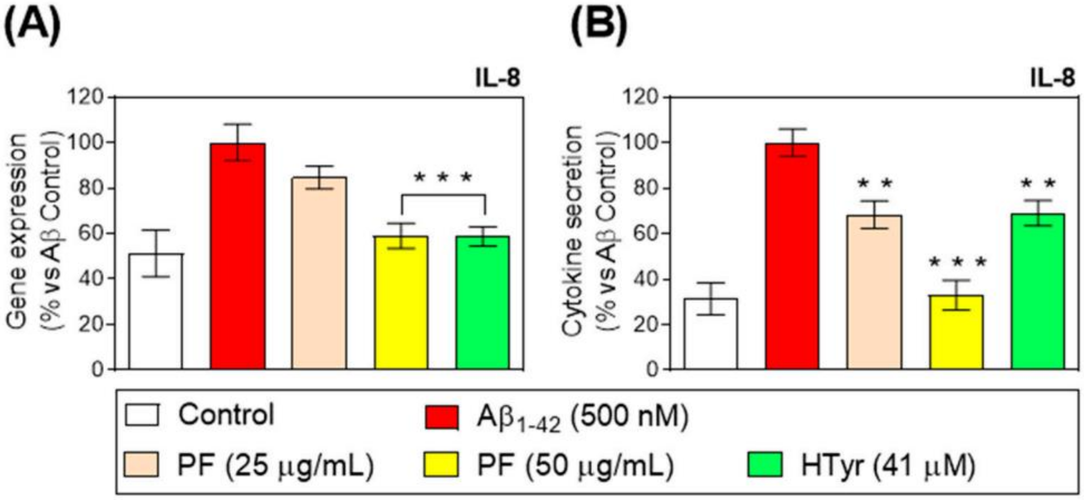


Fig.27.(A) Relative gene expression and (B) release of IL-8 in Aβ1-42-stimulated primary humanneutrophils after treatment with the PF from VOO (25 and 50 μg/mL) or hydroxytyrosol (HTyr,41 μM) for 6 h. Values are means of the three independent experiments in triplicate, with theirstandard errors represented by vertical bars (** $p < 0.01$; *** $p < 0.001$ vs. Aβ1-42-treated cells).

2.2.6.4.4.Olive Oil Phenols Prevent Activation of Human Neutrophils: The neutrophil population in peripheral blood can be discriminated with flow cytometry based on their forward- and side-scatter characteristics. After testing several combinations of antibodies, the best results were obtained by gating the CD16b and CD62L population. When cells were gated, we analyzed them according to their CD16b+ and CD62L- expression. The CD16b + CD62L- population was subjected to other activation markers analysis such as CXCR1 and CD63 (Figure 28). As expected, we found a higher content of activated neutrophils in Aβ1-42 -treated cells ($p < 0.001$ vs. Aβ1-42-control, Figure 28. Interestingly, we observed a significant decrease after the treatment with HTyr 41 μM compared with PF (50 μg/mL), which does not differ from the control, supporting the evidence that HTyr is one of the main contributors of the bioactivity described for phenols of olive oil. **(Rivero-Pino, Grao-Cruces et al. 2023).**

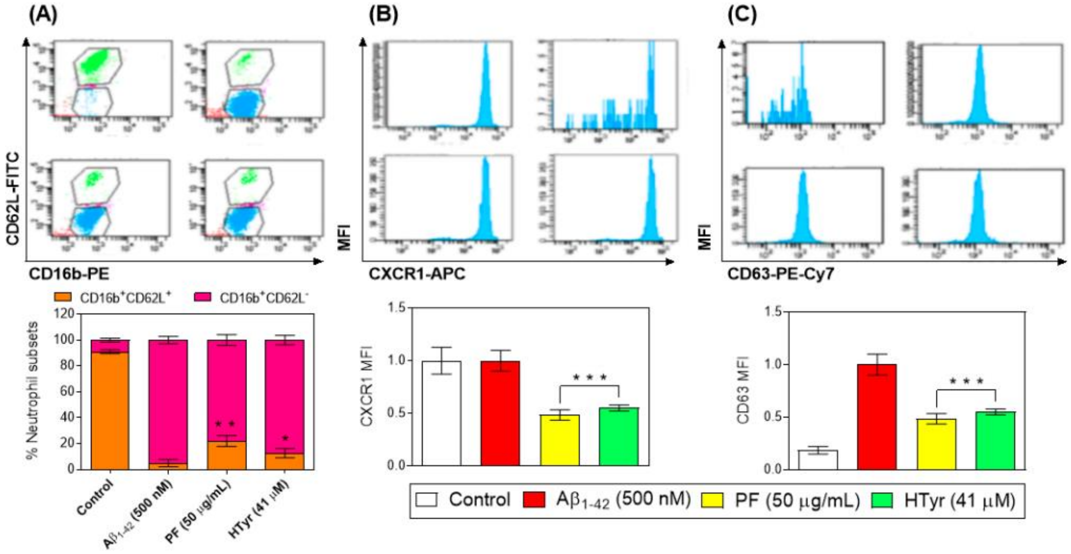


Fig.28. Membrane expression of (A) CD16b, (B) CXCR1, and (C) CD63 in Aβ1-42-stimulated primary human neutrophils treated with the PF from VOO (25 and 50 μg/mL) or hydroxytyrosol (HTyr, 41 μM) for 6 h. Values are means of the three independent experiments in triplicate, with their standard errors represented by vertical bars (* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$ vs. Aβ1-42-treated cells).

2.2.7.Figs: Fig (Ficus carica) is one of the most abundant fruits in the Mediterranean diet that promote human health owing to its bioactive compounds such as polyphenols, carotenoids, vitamins, organic acids, triterpenoids, phytosterols, and fatty acids. Flavonoids, including anthocyanins, flavonols, flavanols and flavones, and phenolic acids and coumarins, are the main polyphenolic compounds present in figs. The levels of bioactive compounds in figs depend on the variety, cultivation, environmental conditions, and processing parameters. Dark-colored fruits contain higher bioactive compound concentrations than figs with light-colored skin. Therefore, the skins of fig fruit should not be discarded as they contain several health-promoting nutrients. Accumulation of polyphenols in fig fruits increases during fruit ripening, whereas the levels of carotenoids reduce as the fruits mature. Drying process results in the reduction of some bioactive compounds, especially anthocyanins and carotenoids, as well as vitamins. On the other hand, the content of specific bioactive compounds such as organic acids is reported to enhance in dried figs. Overall, both fresh and dried figs are good sources of bioactive compounds that possess health-promoting properties.

2.2.7.1. Introduction: The common fig (Ficus carica L.), belonging to the Moraceae family, is one of the most abundant fruits in the Mediterranean diet, promoting health by preventingpathophysiological conditions related to chronic diseases (Kamiloglu & Capanoglu, 2013). Traditionally, Ficus carica has been used to treat disorders linked with the endocrine system (e.g., diabetes), respiratory system (e.g., asthma, cough, and liver diseases), gastrointestinal tract (e.g., vomiting and ulcer), and reproductive system (e.g., menstruation pain), as well as infectious diseases (e.g., scabies, gonorrhea, and skin disease) (Badgujar et al., 2014). These health-promoting effects of figs are associated with the presence of bioactive compounds. The fig cultivation originated in the East Mediterranean region, which was later expanded into the West Mediterranean area (Teruel-Andreu et al., 2021). Today, with an annual production of 310 thousand tons, Türkiye is the world's leading fig producing country, accounting for approximately 25% of the world's total production. Other major fig producing countries include Egypt, Morocco, Iran, Algeria, and Spain. Therefore, the Mediterranean basin and the Near East remain crucial for fig production. Although not listed among the top fig-producing countries, Australia and Netherlands are reported to be the largest exporters of this crop, with a combined value of over US$30 million in 2019 (FAOSTAT, 2021). The peel color of fig fruits ranges from green to dark purple. Although figs are often consumed after removing the peels, they can also be consumed together with the peel (Solomon et al., 2006). Fresh figs have a short post-harvest life ranging between a week to 10 days. However, the combination of a cooled and carbon dioxide-enriched environment enhances the shelf life of the fruit by up to a month. Figs are also often consumed as dried fruits that can be stored for 6–8 months, ensuring proper preservation (Slatnar et al., 2011; Veberic et al., 2008). Some other processed fig products include jam, marmalade, or paste utilized in various bakery products (Saif et al., 2020). Phytochemical studies on figs and their processed products revealed the presence of several bioactive compounds, including polyphenols, carotenoids, vitamins, organic acids, triterpenoids, phytosterols, and fatty acids. The concentration of these bioactive compounds is highly dependent on the fig variety, cultivation technique, environmental conditions, and processing parameters, among others. In this chapter, we provided an overview of the findings in the literature on the bioactive compounds of figs. The levels of polyphenols, carotenoids, vitamins, organic acids, triterpenoids, phytosterols, and fatty acids in figs were discussed in detail, along with the parameters that influence the levels of these compounds.**(Kamiloglu and Akgun 2023)**

2.2.7.2.Phytochemistry & Polyphenols of figs: Polyphenols are secondary plant metabolites that possess antioxidant, antimicrobial, antiviral, and anti-inflammatory properties. According to epidemiological studies and related meta-analyses, long-term intake of diets rich in plant polyphenols protects against the development of chronic diseases such as cardiovascular diseases, diabetes, certain types of cancers, and neurodegenerative diseases. Polyphenols are classified into different groups based on the number of phenol rings they include and the structural components (Ignat et al., 2011; Pandey & Rizvi, 2009). According to the findings in the literature, fig fruits are rich sources of polyphenols. However, the two most well-known sources of polyphenols, red wine and tea, contain lower levels of polyphenols than figs (Mawa et al., 2013; Vallejo et al., 2012). The major polyphenol groups present in fig fruits include flavonoids, phenolic acids, and coumarins (Figure 29), which are discussed in detail in the following sections.**(Kamiloglu and Akgun 2023)**

Bioactive Compounds of Fig (Ficus carica)

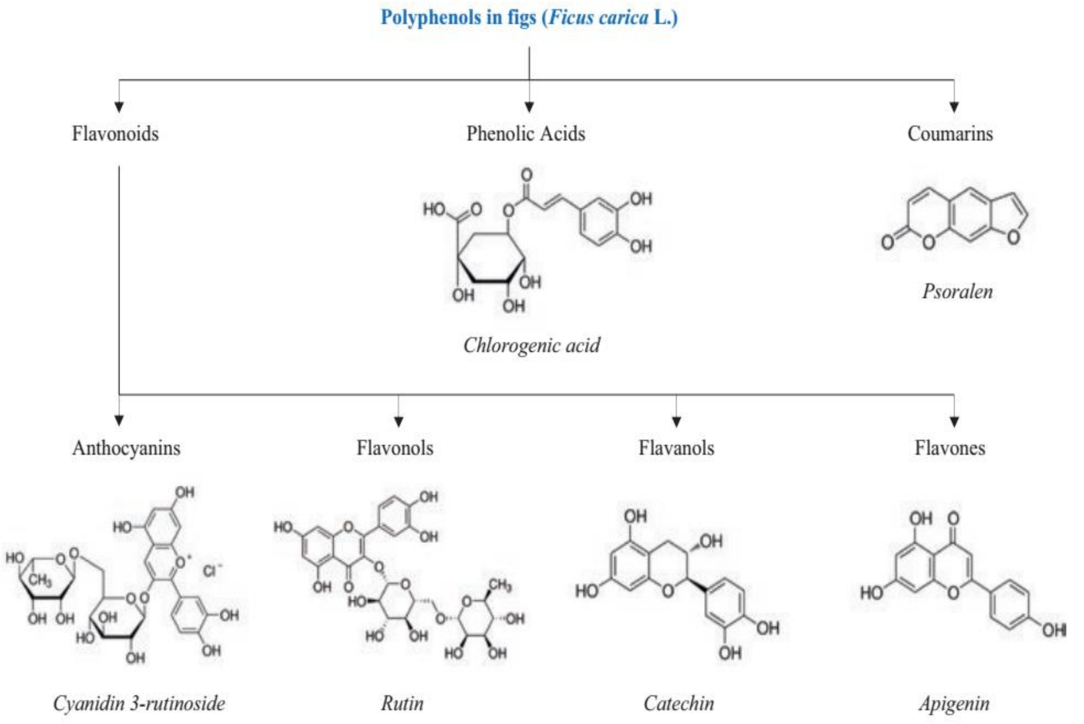


Fig.29.Major classes of polyphenols in figs(Ficus carica L.)

2.2.8.Ginger: a well in the paradise called salsabila spring pumping ginger for mixing with delicious juices of the heaven that's why its suitable for mixing with food and drinks

2.2.8.1.Introduction: Ginger (Zingiber officinale) is a member of the Zingiberaceae plant family, native to Southeast Asia. For centuries, ginger has been consumed in different ways by Asia's indigenous peoples, mainly in China and India, both as spice and sweetener in the local cuisine and as herbal medicine for treating many diseases. Specifically, in the traditional Chinese, Indian, and Ayurvedic medicine, ginger is believed to have therapeutic effects. It is used as a remedy for cough relief due to its expectorant action to loosen and expel phlegm. Ginger is also used for pain alleviation, treatment of nausea, vomiting, and poisoning and for facilitating digestion . Currently, it is known that ginger has antioxidant, antiinflammatory, and antitumor properties and its effectiveness in the prophylaxis and treatment of gastrointestinal, cardiovascular, respiratory, and neurological diseases has been demonstrated by several research studies . Rhizome is the edible part of the plant. The nutraceutical value of ginger is attributed to the bioactive compounds contained in the rhizome, such as gingerols (GNs), shogaols (SGs), paradols, and zingiberene . Volatile phenolic compounds, mainly 6-GN, as well as 4-, 8-, 10-, and 12-GNs, found in fresh ginger rhizome give ginger its pungent fragrance and unique aroma. These compounds are sensitive to pH and temperature changes, and gingerols are rapidly converted to their corresponding 6-, 8-, and 10-SGs during processes that require extreme heat such as drying and roasting. Extracts derived from rhizomes and processing methods may vary widely on chemical composition and associated properties, with dried ginger as a key player in antioxidant activity. Dry ginger powder is also known as Sonth in Hindi, Sonti in Telugu, Soonth in Gujarati, Suntha in Marathi, and Shunti in Kannada. The major phenolic compounds in ginger are mainly gingerols, the active constituent of fresh ginger. The other major polyphenols are abundant in active phytochemicals such as shogaols, paradols, zerumbone, zingerone, gingerols, and 1-dehydro-gingerdione. Shogaols can be derived from ginger with heat treatment or long-term storage. Paradols can form shogaols after hydrogenation. Besides these, ginger raw fiber is also involved in polysaccharides, lipids, and organic acids. Ginger active compounds are critically implicated in different biological activities such as anti-inflammatory, antitumor, antimicrobial, and antioxidant activities (Figure 30) . Therefore, dried ginger rhizome represents the major source of 6-SG which is the most prominent dehydration product (Figure 31). Recent studies have demonstrated that 6-SG has superior biological actions as compared to 6-GN with no associated side effects.**(Ozkur, Benlier et al. 2022)**

2.2.8.2. Ginger and Healthy Ageing: Active and healthy ageing is defined as the maintenance of one's ability to perform activities of daily living without being affected by cognitive and functional impairment and chronic illnesses . Mounting evidence suggests that ginger can promote healthy ageing, reduce morbidity, and prolong healthy lifespan . For over three decades, studies have reported that the antioxidant, anti-inflammatory, antimicrobial, antitumor, and antihypercholesterolemic features of the bioactive compounds found in ginger account for its aforementioned health benefits (Figure 31). It is believed that ginger can also protect, prevent, and even treat many diseases related to ageing by modulating molecular targets involved in their pathogenesis .**(Ozkur, Benlier et al. 2022)**

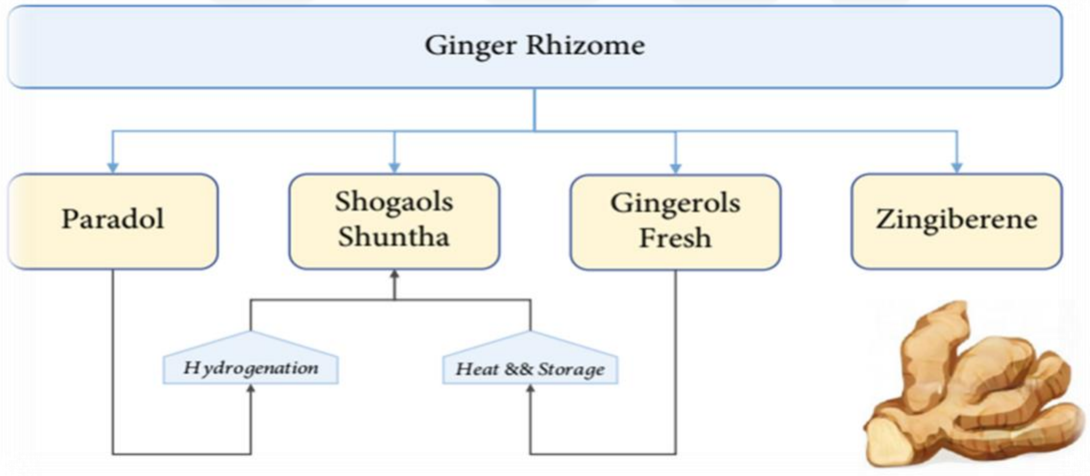


Fig.31. Ginger rhizome active compounds.

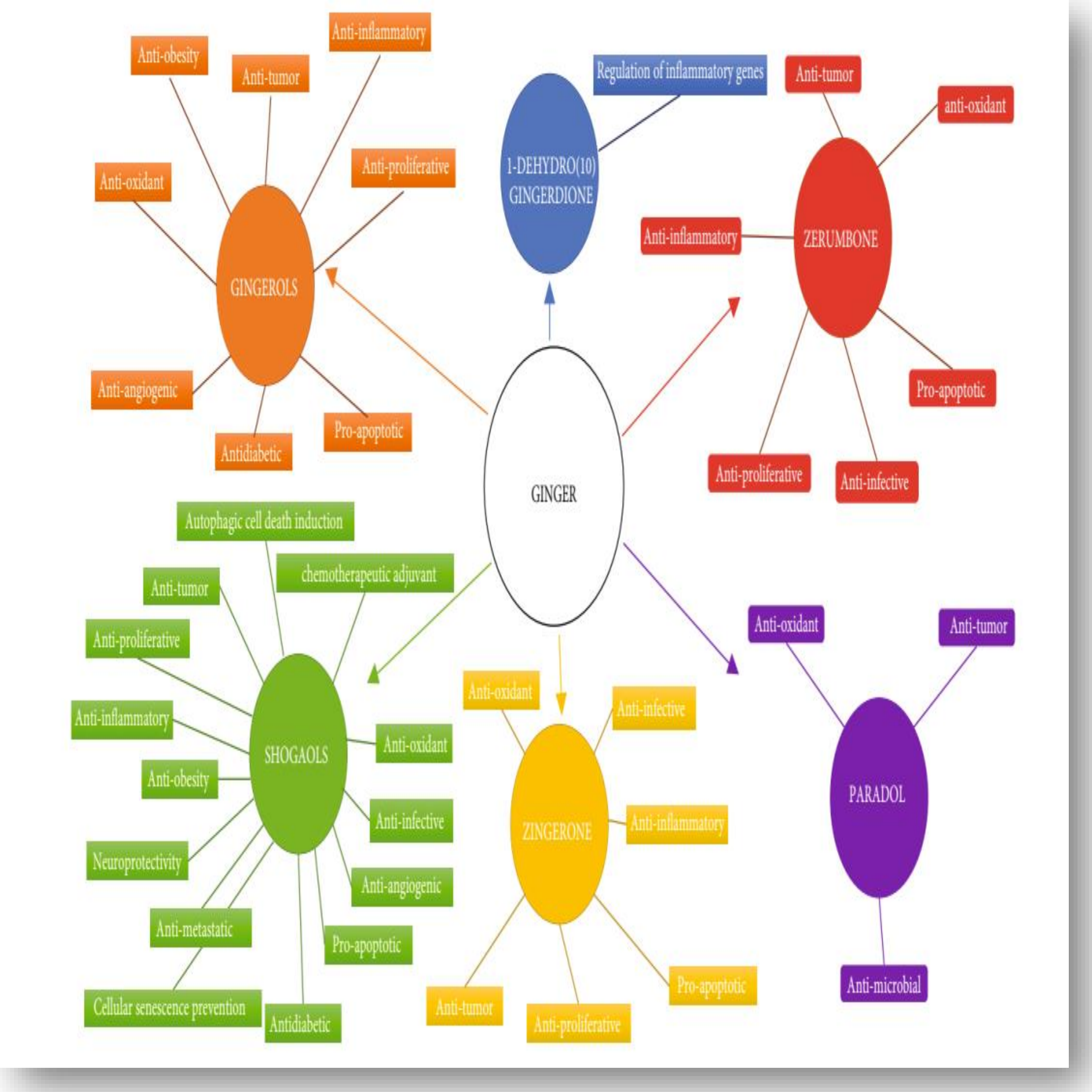


Fig.30. Figure 1: Illustration of the wide range of the health effects of ginger. A great range of those natural products' beneficial effects for the human organism have been verified and investigated at a molecular and mechanistic basis. Emphasis is given in this review on the antioxidant, anti-inflammatory, and anticarcinogenic properties of ginger.

2.2.8.3.Active constituents & other effects: Ginger rhizomes contain carbohydrates (50–70 %), lipids (3–8 %), terpenes, and phenolic compounds. Terpene components of ginger include zingiberene, β-bisabolene, α-farnesene, β-sesquiphellandrene, and α-curcumene, while its phenolic compounds are gingerol, paradols, and shogaol . In addition, ginger contains other constituents such as flavonoids, vitamin C, Mg, Ca, Fe, which are used to treat many ailments, including pain, indigestion, stomach aches, diarrhea, nausea, colds, coughs, congestion, rheumatoid, arthritis, sprains, muscle aches, sore throats, nausea, constipation, indigestion, fever, infectious diseases, and helminthiasis and nausea . It has anti-inflammatory, anti -hyperglycemic, and anti-tumor effects, as well as anti-pyretic, anti-apoptotic, anti-platelet, antioxidant, anti-diabetic, analgesic, cardiotonic, and cytotoxic properties .**(Elebiyo, Olori et al. 2022)**

2.2.9.Vinegar: prophet Mohammed peace and god prayer's Upon him said the best Idam is vinegar which means the best thing you can add for flavoring food specially balsamic tybe. Vinegar has been used as a flavoring agent world-wide and is very popular in Asian countries. Shanxi province in northern China is well known for its vinegar production and consumption. Compared toother regions in China, approximately 30–50 times more vinegar is consumed in Shanxi. Our epidemiological survey of nephrolithiasis prevalence raised the possibility that daily intake of vinegar contributes to a lesser risk of nephrolithiasis likely due to regulation of urinary excretion of citrate and calcium as reported here.The principal bioactive component of vinegar is acetic acid, which is a short-chain fatty acid (SCFA). SCFAs in vivo are principally derived from fermentable nondigestible substrates including acetic, butyric, and propionic acids . Acetate has been reported to be readily absorbed in the intestines, transported into the blood stream, and easily incorporated in tissues . Several studies reported that treatment with SCFAs, especially acetate, reduced kidney damage in different kidney injury animal models . In this study, we found for the first time that vinegar inhibits CaOx kidney stone formation likely through regulating urinary excretion of citrate and calcium in humans as well as in the animal model. This anti-CaOx stone formation effect of vinegar at least derives from acetic acid in vinegar as acetic acid alone can mimic the effect of vinegar in the rat model in suppressing CaOx crystal formation. In addition, inhibition of miRNAs that were found to be mediating the effect of acetate in tissue cultured cells can block the effect of vinegar in vivo while miRNAs themselves can fully mimic the protection of vinegar in the rat model. Thus although vinegar contains many components that might influence its efficacy of suppressing kidney stone, a principal molecule must be the acetic acid itself. Acetate does so likely through epigenetic regulation of histone acetylation in addition to its potential binding to G-protein membrane receptors (GPR41 and GPR43) . Consistent with a previous finding that acetate can function as an epigenetic metabolite to promote cancer cell survival under hypoxic stress , we found that acetate could in-fluence urinary citrate and calcium excretion to inhibit renal CaOx crystals formation. It does so likely through regulating histone acetylation at H3K9 and H3K27 with a consequent activation of transcription of miR-130a-3p, miR-148b-3p and miR-374b-5p, which in turn can suppress the expression of NADC1 and CLDN14, two key regulators of renal citrate and calcium excretion (Figure 32).**(Zhu, Liu et al. 2019)**

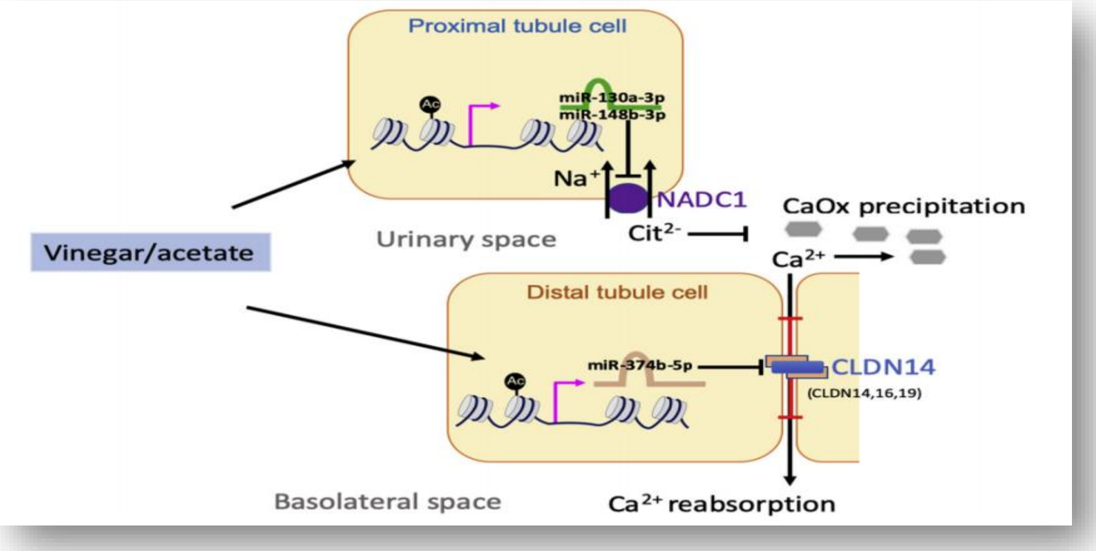


Fig.32. . A scheme of vinegar effect. The scheme summarizes the pathway described: vinegar or acetate enhances the H3K9 or/and H3K27 acetylation levels at miR-130a, miR-148b, miR-374b promoter regions, which downregulate Nadc1 and Cldn14 expression, and increase urinary citrate excretion while decrease calcium excretion to suppress CaOx crystal formations.

2.3 Fasting according to the noble Prophet's sonnah: fasting is a good deed by which a person draws closer to his lord and it's one of the characteristics of angels which purify the soul and give self power and patience against any thing, relief binge eating /diseases and eases the odds and it leads to heaven where the next stage of the Immortal life. Prophet Mohammed god prayr's and peace upon him said that fasing gives health and complete this system and chosed the best suitable days for fasting which are Monday and Thursday from each week and 13th,14th,15th days of each Arabian month . Significant improvements were observed in HDL levels and liver function tests, which can be attributed to the loss of body weight. Improvement in liver function tests may be related to the changes in cytokines and alteration in sleep patterns. Ramadan-like fasting, along with the nutritional education prior to fasting, may be beneficial and effective in the spiritual and overall well-being. **(Urooj, Kotebagilu et al. 2020)**, Evidence is accumulating that eating in a 6-hour period and fasting for 18 hours can trigger a metabolic switch from glucose-based to ketone-based energy, with increased stress resistance, increased longevity, and a decreased incidence of diseases, including cancer and obesity.**(De Cabo and Mattson 2019)**, fasting induce significant changes in genes expressionand only small changes in proteins involved in iron metabolism in human leukocytes.Observed decrease in genes involved in iron storage and export and increase in thoseresponsible for iron import into a cell resemble those data when only iron deficiency wasapplied. Conversely, we did not observe significant changes in proteins like ferritin H, Land ferroportin after 8 d of fasting what has been shown in iron deficiency state inducede.g., by iron chelator.**(Borkowska, Tomczyk et al. 2021)**

3.Nutrivigillence& food questionnaire:

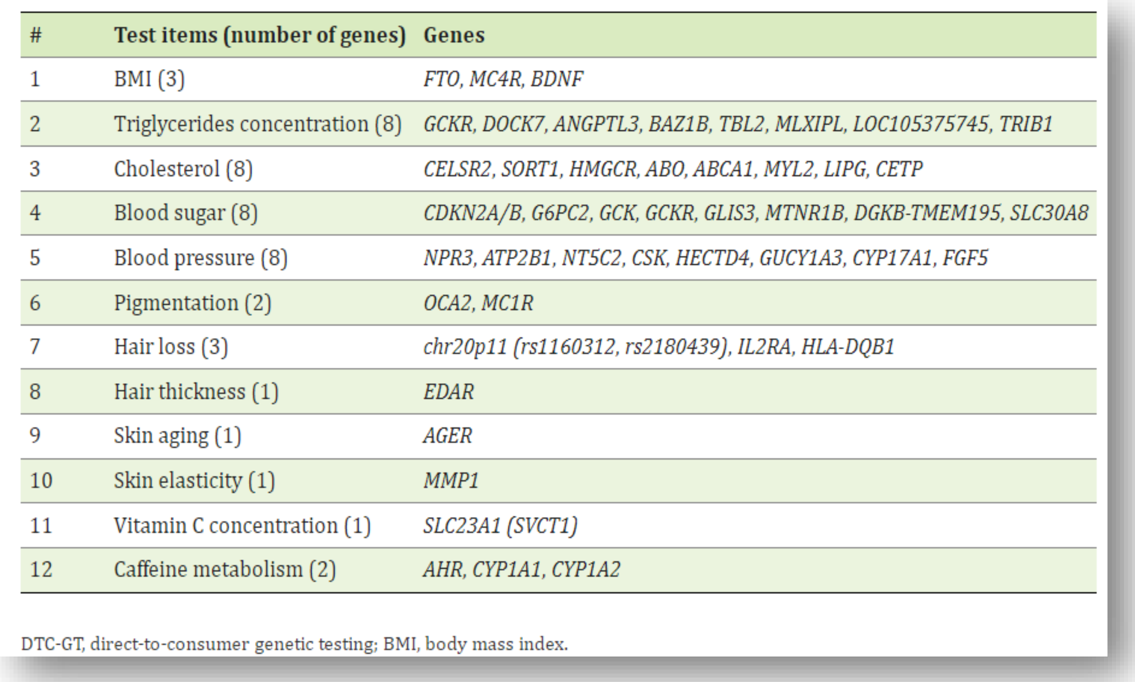
3.1.nutrivigillence: for development of nutritional and natural treatment of disease program .Whereas various organisations already handle adverse event reports of non-registered health-enhancing products case-by-case, improved governance of vigilance could support protecting consumers from unsafe products in the Netherlands. However, this explorative study also shows that the priority for a full vigilance system dedicated to all commodities is questioned by interviewees, and practical limitations may affect effectiveness of a vigilance system for non-registered products. Like France and Italy, who address specific categories of nonregistered products, adverse event reports could be prioritised to higher-risk products. The first steps for systematically organising vigilance in the Netherlands have been taken by appointing Lareb for receiving adverse reports of non-registered health-enhancing products, along with additional intentions described by the Minister of Health to improve food supplement safety.**(De Boer, Geboers et al. 2022)**

3.2.food questionnaire: Important to develop the GAHD food system and for best nutritional education results . like this study which concluded that The Food and Nutrition Literacy Questionnaire (FNLQ-SC) developed here had good reliability, and it can potentially be a useful instrument for assessing food and nutrition literacy.**(Liu, Su et al. 2021)**

4.Genetic testing: Nutrigenomics is an exciting field bridging the gap between genetic testing and nutrition. With a plethora of fad diets around, it's challenging to figure out which dietary advice is best for you as an individual. Nutrigenomics eases that overwhelm by providing a genetic assessment that can help tailor a diet just for you, taking the guesswork out of the equation. With nutrigenomic testing and an individualized nutrition plan, you will have the tools you need for optimal personal health.**(Christie and ND 2023)**. Several studies that evaluated gene-diet interactions have revealed that the associations between genotype differences and responses to nutrients and dietary factors are robust for some genes. This suggests that genetic testing can be implemented in clinical nutrition, thus providing dietitians with crucial insights on genetic susceptibility and allowing them to provide personalized counseling and meal planning based on this genetic information. Nevertheless, more studies on gene-diet interactions are needed to accumulate comprehensive scientific evidence and promote the use of DTC-GT in the field of personalized clinical nutrition.**(Lee and Han 2021)**. According to the Notice Notification 2016-9 of the Ministry of Health and Welfare, which was enacted on June 30, 2016, DTC-GT was allowed to provide information regarding 12 items represented by 46 genes, including blood sugar, blood pressure, hair loss, and vitamin C metabolism (Table 5) . The Genetic Committee under the National Bioethics Review Committee reviewed scientific evidence that sufficiently verified and expanded the available test items from 11 to 56 in total (Table 6). The number of genetic test items was limited to 56 items, but the types of genes and SNPs for each item could be selected autonomously by the company . The second DTC-GT service certification was conducted from March 2020 to February 2021. Through this initiative, the genetic test items that could be directly evaluated by genetic testing institutions other than medical institutions were expanded from 56 to up to 70 items (Table 6), and 8 recognized genetic testing institutions (Labgenomics, Macrogen, TeragenEtex, DNAlink, Medizen Humancare, Geninus, SCLHealthcare, and NGeneBio) were allowed to test up to 70 gene items .**(Lee and Han 2021)**

Table 5

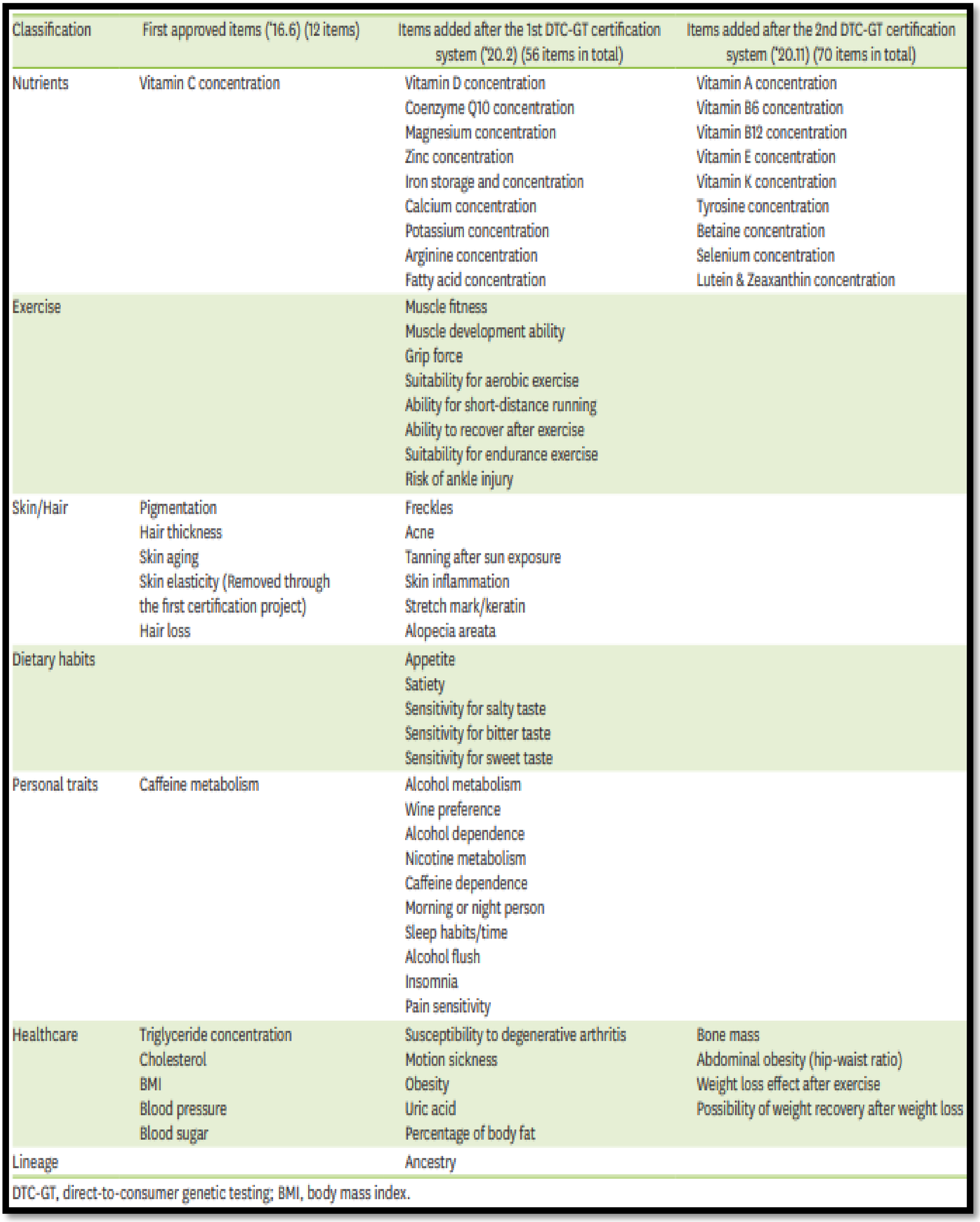
Genetic test items that for DTC-GT in 2016 (12 test items and 46 genes)



#	Test items (number of genes)	Genes
1	BMI (3)	*FTO, MC4R, BDNF*
2	Triglycerides concentration (8)	*GCKR, DOCK7, ANGPTL3, BAZ1B, TBL2, MLXIPL, LOC105375745, TRIB1*
3	Cholesterol (8)	*CELSR2, SORT1, HMGCR, ABO, ABCA1, MYL2, LIPG, CETP*
4	Blood sugar (8)	*CDKN2A/B, G6PC2, GCK, GCKR, GLIS3, MTNR1B, DGKB-TMEM195, SLC30A8*
5	Blood pressure (8)	*NPR3, ATP2B1, NT5C2, CSK, HECTD4, GUCY1A3, CYP17A1, FGF5*
6	Pigmentation (2)	*OCA2, MC1R*
7	Hair loss (3)	*chr20p11 (rs1160312, rs2180439), IL2RA, HLA-DQB1*
8	Hair thickness (1)	*EDAR*
9	Skin aging (1)	*AGER*
10	Skin elasticity (1)	*MMP1*
11	Vitamin C concentration (1)	*SLC23A1 (SVCT1)*
12	Caffeine metabolism (2)	*AHR, CYP1A1, CYP1A2*

DTC-GT, direct-to-consumer genetic testing; BMI, body mass index.

Table 6. Genetic test items allowed for DTC-GT that added after the 1st and 2nd DTC-GT certification systems

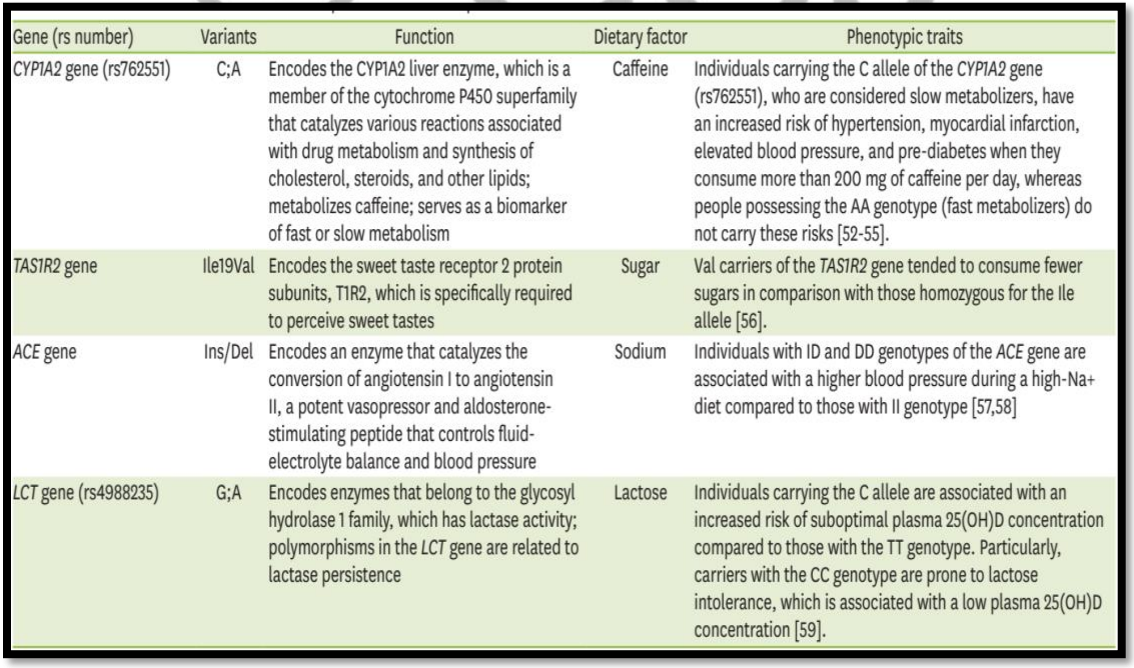


Classification	First approved items ('16.6) (12 items)	Items added after the 1st DTC-GT certification system ('20.2) (56 items in total)	Items added after the 2nd DTC-GT certification system ('20.11) (70 items in total)
Nutrients	Vitamin C concentration	Vitamin D concentration Coenzyme Q10 concentration Magnesium concentration Zinc concentration Iron storage and concentration Calcium concentration Potassium concentration Arginine concentration Fatty acid concentration	Vitamin A concentration Vitamin B6 concentration Vitamin B12 concentration Vitamin E concentration Vitamin K concentration Tyrosine concentration Betaine concentration Selenium concentration Lutein & Zeaxanthin concentration
Exercise		Muscle fitness Muscle development ability Grip force Suitability for aerobic exercise Ability for short-distance running Ability to recover after exercise Suitability for endurance exercise Risk of ankle injury	
Skin/Hair	Pigmentation Hair thickness Skin aging Skin elasticity (Removed through the first certification project) Hair loss	Freckles Acne Tanning after sun exposure Skin inflammation Stretch mark/keratin Alopecia areata	
Dietary habits		Appetite Satiety Sensitivity for salty taste Sensitivity for bitter taste Sensitivity for sweet taste	
Personal traits	Caffeine metabolism	Alcohol metabolism Wine preference Alcohol dependence Nicotine metabolism Caffeine dependence Morning or night person Sleep habits/time Alcohol flush Insomnia Pain sensitivity	
Healthcare	Triglyceride concentration Cholesterol BMI Blood pressure Blood sugar	Susceptibility to degenerative arthritis Motion sickness Obesity Uric acid Percentage of body fat	Bone mass Abdominal obesity (hip-waist ratio) Weight loss effect after exercise Possibility of weight recovery after weight loss
Lineage		Ancestry	

DTC-GT, direct-to-consumer genetic testing; BMI, body mass index.

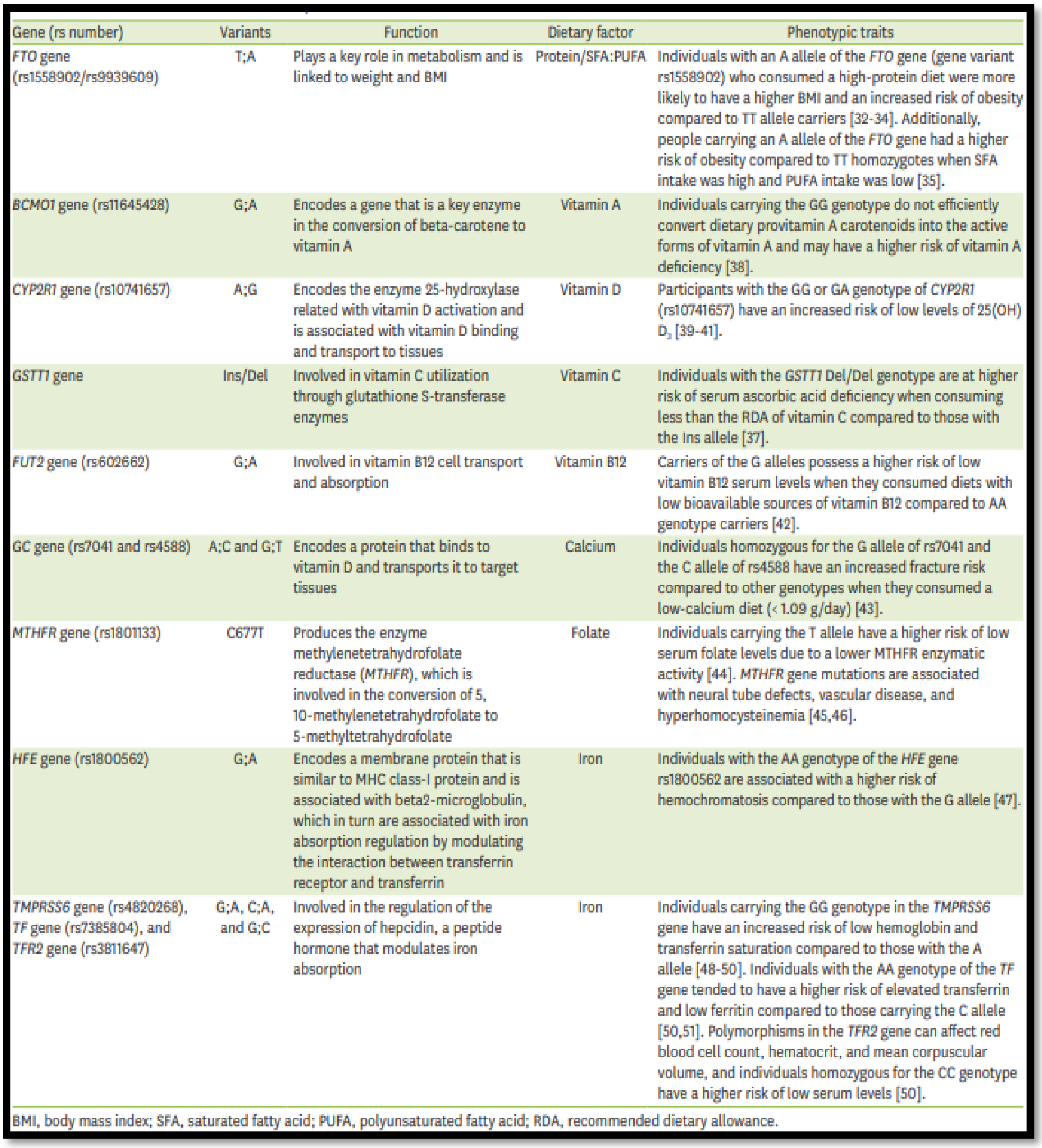
4.1. APPLICATION OF DTC-GT FOR CLINICAL NUTRITION: Genetic variations associated with nutrient intake responses or dietary factors Nutrigenetics is defined as the study of the differential response to specific nutrients based on genetic variations . Several genes and alleles have been found to affect the absorption, utilization, and intake of nutrients or dietary components . Table 7 summarizes genetic variations that are known to affect the response to various macronutrients, vitamins, and minerals. The FTO gene is known to play an important role in metabolism and is linked to body weight and body mass index (BMI) . Some nutrients such as protein, saturated fatty acids (SFAs), and polyunsaturated fatty acids (PUFAs) may also alleviate genetic predispositions associated with a higher BMI and body weight . The A allele of the FTO gene (gene variant rs9939609) has been linked to an increased risk of obesity and higher BMI when individuals consume high-protein diets compared to individuals exhibiting the TT genotype . Further, people with the A allele of the FTO gene had a higher obesity risk compared to the TT homozygotes when saturated fatty acid intake was high and polyunsaturated fatty acid intake was low . Moreover, the GSTT1 gene polymorphism is a well-known genetic variation associated with serum vitamin C levels. The GSTT1 gene is involved in the utilization of vitamin C via the glutathione S-transferase enzyme . Individuals with the GSTT1 Del/Del genotype are at increased risk of vitamin C deficiency when they consume less than the recommended dietary allowance (RDA) of vitamin C, whereas those with the Ins allele do not exhibit these risks . Table 8 summarizes genetic variations known to impact the response to food components. Caffeine is the active compound in coffee, one of the most widely consumed beverages worldwide. This compound has been investigated in numerous studies to elucidate its effect on the association between CYP1A2 gene variants and phenotypic traits. Individuals with the C allele of the GYP1A2 gene (gene variant rs762551) are considered slow metabolizers and tend to have an increased risk of hypertension, myocardial infarction, and elevated blood pressure when they consume more than 200 mg of caffeine per day, whereas AA homozygotes do not have these risks .**(Lee and Han 2021)**

Table 8. Genetic variations associated with responses to food components



Gene (rs number)	Variants	Function	Dietary factor	Phenotypic traits
CYP1A2 gene (rs762551)	C;A	Encodes the CYP1A2 liver enzyme, which is a member of the cytochrome P450 superfamily that catalyzes various reactions associated with drug metabolism and synthesis of cholesterol, steroids, and other lipids; metabolizes caffeine; serves as a biomarker of fast or slow metabolism	Caffeine	Individuals carrying the C allele of the *CYP1A2* gene (rs762551), who are considered slow metabolizers, have an increased risk of hypertension, myocardial infarction, elevated blood pressure, and pre-diabetes when they consume more than 200 mg of caffeine per day, whereas people possessing the AA genotype (fast metabolizers) do not carry these risks [52-55].
TAS1R2 gene	Ile19Val	Encodes the sweet taste receptor 2 protein subunits, T1R2, which is specifically required to perceive sweet tastes	Sugar	Val carriers of the *TAS1R2* gene tended to consume fewer sugars in comparison with those homozygous for the Ile allele [56].
ACE gene	Ins/Del	Encodes an enzyme that catalyzes the conversion of angiotensin I to angiotensin II, a potent vasopressor and aldosterone-stimulating peptide that controls fluid-electrolyte balance and blood pressure	Sodium	Individuals with ID and DD genotypes of the *ACE* gene are associated with a higher blood pressure during a high-Na+ diet compared to those with II genotype [57,58]
LCT gene (rs4988235)	G;A	Encodes enzymes that belong to the glycosyl hydrolase 1 family, which has lactase activity; polymorphisms in the *LCT* gene are related to lactase persistence	Lactose	Individuals carrying the C allele are associated with an increased risk of suboptimal plasma 25(OH)D concentration compared to those with the TT genotype. Particularly, carriers with the CC genotype are prone to lactose intolerance, which is associated with a low plasma 25(OH)D concentration [59].

Table 7. Genetic variations associated with responses to nutrient intake



Gene (rs number)	Variants	Function	Dietary factor	Phenotypic traits
FTO gene (rs1558902/rs9939609)	T;A	Plays a key role in metabolism and is linked to weight and BMI	Protein/SFA:PUFA	Individuals with an A allele of the *FTO* gene (gene variant rs1558902) who consumed a high-protein diet were more likely to have a higher BMI and an increased risk of obesity compared to TT allele carriers [32-34]. Additionally, people carrying an A allele of the *FTO* gene had a higher risk of obesity compared to TT homozygotes when SFA intake was high and PUFA intake was low [35].
BCMO1 gene (rs11645428)	G;A	Encodes a gene that is a key enzyme in the conversion of beta-carotene to vitamin A	Vitamin A	Individuals carrying the GG genotype do not efficiently convert dietary provitamin A carotenoids into the active forms of vitamin A and may have a higher risk of vitamin A deficiency [38].
CYP2R1 gene (rs10741657)	A;G	Encodes the enzyme 25-hydroxylase related with vitamin D activation and is associated with vitamin D binding and transport to tissues	Vitamin D	Participants with the GG or GA genotype of *CYP2R1* (rs10741657) have an increased risk of low levels of 25(OH) D_3 [39-41].
GSTT1 gene	Ins/Del	Involved in vitamin C utilization through glutathione S-transferase enzymes	Vitamin C	Individuals with the *GSTT1* Del/Del genotype are at higher risk of serum ascorbic acid deficiency when consuming less than the RDA of vitamin C compared to those with the Ins allele [37].
FUT2 gene (rs602662)	G;A	Involved in vitamin B12 cell transport and absorption	Vitamin B12	Carriers of the G alleles possess a higher risk of low vitamin B12 serum levels when they consumed diets with low bioavailable sources of vitamin B12 compared to AA genotype carriers [42].
GC gene (rs7041 and rs4588)	A;C and G;T	Encodes a protein that binds to vitamin D and transports it to target tissues	Calcium	Individuals homozygous for the G allele of rs7041 and the C allele of rs4588 have an increased fracture risk compared to other genotypes when they consumed a low-calcium diet (< 1.09 g/day) [43].
MTHFR gene (rs1801133)	C677T	Produces the enzyme methylenetetrahydrofolate reductase (*MTHFR*), which is involved in the conversion of 5, 10-methylenetetrahydrofolate to 5-methyltetrahydrofolate	Folate	Individuals carrying the T allele have a higher risk of low serum folate levels due to a lower MTHFR enzymatic activity [44]. *MTHFR* gene mutations are associated with neural tube defects, vascular disease, and hyperhomocysteinemia [45,46].
HFE gene (rs1800562)	G;A	Encodes a membrane protein that is similar to MHC class-I protein and is associated with beta2-microglobulin, which in turn are associated with iron absorption regulation by modulating the interaction between transferrin receptor and transferrin	Iron	Individuals with the AA genotype of the *HFE* gene rs1800562 are associated with a higher risk of hemochromatosis compared to those with the G allele [47].
TMPRSS6 gene (rs4820268), *TF* gene (rs7385804), and *TFR2* gene (rs3811647)	G;A, C;A, and G;C	Involved in the regulation of the expression of hepcidin, a peptide hormone that modulates iron absorption	Iron	Individuals carrying the GG genotype in the *TMPRSS6* gene have an increased risk of low hemoglobin and transferrin saturation compared to those with the A allele [48-50]. Individuals with the AA genotype of the *TF* gene tended to have a higher risk of elevated transferrin and low ferritin compared to those carrying the C allele [50,51]. Polymorphisms in the *TFR2* gene can affect red blood cell count, hematocrit, and mean corpuscular volume, and individuals homozygous for the CC genotype have a higher risk of low serum levels [50].

BMI, body mass index; SFA, saturated fatty acid; PUFA, polyunsaturated fatty acid; RDA, recommended dietary allowance.

4.2. Significance of DTC-GT in clinical nutrition: DTC-GT can motivate consumers to participate more actively in overall health management and may play an important role in the implementation of personalized clinical nutrition . Clinical dietitians can use DTC-GT to provide nutritional counseling and meal planning based on the genetic background of their patients. This information can provide the clinician with important insights regarding the individual's genetic susceptibilities and dietary factors that can increase the risk of disease.

Nevertheless, extensive research on gene-diet interactions is still required. Further, to avoid misuse and protect the public, nutrigenetic advice should be grounded in clear evidence based on a cautious and valid assessment resulting from the outcomes of many nutrigenetic studies . Additionally, dietitians and healthcare professionals should be qualified and skilled in this rapidly evolving field **.(Lee and Han 2021)**

5.herbal and natural products for treatment of genetic /nutritional diseases:

The need to establish the green pharmacy and making the firist line of treatment in the traditional medicine and treatment with medicinal herbs and functional food , like the successful Chinese experience in this regard which results in longitivity and preservation of human genes and protection against chemical and hazardous mutations. Phenolic compounds are one of the most important types of compounds with an important role in growth and reproduction, providing protection against pathogens and predators, and they could be the main determinant of antioxidant potential of foods. Phenolics are a heterogeneous collection of compounds generated as secondary metabolites in plants. Phenolic compounds are aromatic or aliphatic compounds with at least one aromatic ring to which one or more OH groups are connected. They are subdivided into different groups depending on the number of phenolic rings that they possess and the structural elements joined to them. They are naturally occurring compounds present in several foods such as cereals, fruits, vegetables, and beverages. Polyphenols can also be found in dried legumes and chocolate. The distribution of phenolic compounds in plant tissues and cells change considerably according to the type of chemical compound. They also contribute towards the color and sensory characteristics of fruits and vegetables. Different classes of phenolic compounds in plants are simple phenolics, benzoquinones, hydroxybenzoic acids, acetophenones, phenylacetic acids, hydroxycinnamic acids, phenylpropanoids, naphthoquinones, xanthones, stilbenes, anthraquinones, flavonoids, isoflavonoids, lignans, neolignans, biflavonoids, lignins, and condensed tannins. Hydroxybenzoic acids are gallic acid and Protocatechuic acid. Hydroxycinnamic acids are *p*-coumaric acid, caffeic acid, ferulic acid, sinapic acid, and other components such as coumarins (umbelliferone, esculetin, scopoletin, resveratrol, piceatannol, pterostilbene), curcuminoids (curcumin, demethoxycurcumin, bisdemethoxycurcumin), condensed tannins or proanthocyanidins (procyanidin B1), and lignan (sesamin). From a human physiological viewpoint, phenolic compounds are important in defense responses such as antioxidant, anti-aging, antiproliferative, and anti-inflammatory. High phenolic activity in many species could prove to be beneficial towards human health if included as part of food designs for a healthy diet. Flavonoids are the largest group of natural phenolic compounds, and, based on the differences in the pyran ring, flavonoids can be divided into flavones, isoflavones, flavanonols, flavonols, flavanones, flavan-3-ols, and anthocyanidins. They can be subdivided into different subgroups on the basis of the carbon of the C ring on which the B ring is attached and the degree of unsaturation and oxidation of the C ring. Flavonoids in which the B ring is linked in position 3 of the C ring are called isoflavones. Those in which the B ring is linked in position 4 are called neoflavonoids, while those in which the B ring is linked in position 2 can be further subdivided into several subgroups on the basis of the structural characteristics of the C ring. The most prominent health benefits of phenolic compounds are antioxidant activity, anti-inflammatory properties, antifungal activity, antimicrobial activity, antibacterial properties, anti-coronavirus activities, neuroprotective potential, appropriate for skin health, suitable for wound healing, and anticancer activities. Flavonoids, a group of natural substances with variable phenolic structure, are found in vegetables, fruits, grains, bark, stems, roots, flowers, wine, and tea. Flavonoids are considered as an important constituent in different pharmaceutical, medicinal, nutraceutical, and cosmetic applications. They belong to a class of low-molecular-weight phenolic compounds that are extensively distributed in the plant kingdom. Future research is needed to determine the pharmaceutical benefits of phenolic and flavonoid compounds of medicinal plants, especially traditional Chinese medicinal plants, and to gain a better understanding of these chemical compounds in medicinal plants and herbs. It is also important to increase analytic techniques to allow the collection of more data on excretion and absorption. **(Sun and Shahrajabian 2023).** In the following are successful treatment researches on that field.

5.1.pomegranate: Oral PFE administration decreased COX-2 and iNOS expression.

The PFE suppressed NF-kB activation, nuclear translocation, and phosphorylation of NF-kB at Ser by the I kappa B kinase complex (IKK α, β, γ). It prevented dissociation of NF-kB from I kappa B alpha (IkBα) through the suppression of phosphorylation, degradation of IkBα, and

IKK activation. In addition, the authors revealed that consumption of PFE inhibited phosphorylation of MAPK pathways, the ERK, the JNK, and the p38 . Interestingly, PFE treatment was also found to suppress human lung carcinoma A549 cells growth by inhibiting MAPK proteins phosphorylation, P13K, Akt phosphorylation, and NF-kB activation *(Figure 33)* . Therefore, pomegranate can be used as a natural chemopreventive and chemotherapeutic in combating cancer. However, further studies are vital to confirm their safety and efficacy.**(Maphetu, Unuofin et al. 2022) ,** . Gene expression analysis results revealed that treating HK-2 infected cells with PPE (0.04 mg/mL) downregulated the expression of ACE2 and transmembrane protease, serine 2 (TMPRSS2) genes that aid the virus to infect the host cells. Besides, PPE (80%), PC (50%), and EA (10%) suppressed 3CL protease enzymatic activity responsible for SARS-COV2 replication, see (Figure 34). The authors concluded that PPE and its polyphenols are promising inhibitors to hinder SARS-CoV-2/ACE2 binding interaction, and hence virus infection and replication. However, further in vivo studies are needed to determine its safety and effectiveness **.(Maphetu, Unuofin et al. 2022)** , . Administration of PGF polyphenols extract (50–100 mg/kg) for about a month enhanced insulin sensitivity, attenuated FBG levels, TG, TC, HDL-C, and free fatty acids (FFA). PGF improved liver glycogen content, and antioxidant status (CAT, SOD, GPx), and reduced MDA levels. PGF mechanism of action is through the activation of the phosphorylation of insulin receptor substrate 1 (IRS-1), Akt, and glycogen synthase kinase 3 beta (GSK-3β) expression, thus leading to an increase in insulin sensitivity, see (Figure 35). Another mode of action, PGF improves insulin sensitivity by inhibiting the endoplasmic reticulum (ER) stress signaling pathway (Figure 35). ER stress stimulates the activation of unfolded protein response (UPR), inositol-requiring enzyme 1 (IRE1), IRE1α, then the transformation of transcription factor X-box binding protein 1 (XBP1), leading to phosphorylation of IRS-1, and ultimately insulin resistance . A study by Wu and Tian **(Pantiora, Balaouras et al. 2023)**, explored the anti-obesity and -diabetic activities of PGF active compounds on α-glucosidase, α-amylase, and lipase (Figure 35). PGF isolated compounds including tricetin 4′− 0-β—glucopyranoside, tricetin, luteolin, ellagic acid, granatin B, gallic acid, punicalagin, apigenin, and luteolin-4′− 0-glucoside. Their results showed that all compounds had inhibitory activity against α-glucosidase, α-amylase, and lipase. However, tricetin and ellagic acid were highly effective, both had more powerful inhibitory activity on α-glucosidase than acarbose the anti-diabetic drug. It is postulated that the hydroxyl groups found in the chemical structures of compounds may be responsible for the inhibitory activity . Another study evaluated the activity of pomegranate (juice, seeds, flowers, and peels) on rat intestinal α-glucosidase and porcine pancreatic α-amylase. The methanol extract of PGF displayed a stronger inhibitory effect on both enzymes, while PPE only on α-glucosidase among others. In addition, pomegranate polyphenols such as ellagic acid and gallic acid both inhibited α-glucosidase . In addition, a study by Huang et al. , examined the antidiabetic effect of PGF and its mechanism of action on glucose metabolism. Daily intake of methanol extract of pomegranate flower (500 mg/kg) suppressed an increase in glucose levels in Zucker diabetic fatty (ZDF) rats. PGF enhanced glucose metabolism and insulin sensitization by increasing the expression of cardiac PPARγ mRNA, and glucose transporter-4 (GLUT-4) levels in ZDF rats. PGF stimulated the activity of lipoprotein in human TPH-1-differentiated macrophage cells. Also, their results revealed that the antidiabetic activity of PGF extract is caused by the presence of gallic acid .**(Maphetu, Unuofin et al. 2022)** , Hepatic or liver fibrosis is a condition depicted by the overproduction of transforming growth factor β (TGF-β), which brings about excessive accumulation of extracellular matrix proteins such as collagen and fibrinogen **(Kohlhepp, Liu et al. 2023)**. Nuclear factor erythroid2-related factor 2 (Nrf2) and nuclear factor kappa B (NF-kB) transcription factors play important roles in antioxidant and inflammatory responses, and they are also implicated in the development of liver fibrosis . Another study , examined the antifibrogenic activity of pomegranate juice (PGJ) against diethylnitrosamine (DEN)-induced hepatic fibrosis in mammalian (rats) model of liver fibrosis. DEN injection attenuated enzymatic antioxidant activities such as superoxide dismutase (SOD) and catalase (CAT), and glutathione-S-transferase (GST) by increasing the production of harmful reactive oxygen species (ROS). DEN impaired liver function by inducing excessive inflammation via increasing inflammatory responses and COX-2 expression levels. The study revealed that treatment with PGJ improved the activities of SOD, CAT, and GST, and reduced the elevated levels of malondialdehydes (MDA) via regulation of NF-kB and Nrf2 signaling pathways. Also, PGJ decreased the activities of inflammatory cytokines (such as TNFα, and IL-6), chemokines, adhesion molecules, and COX-2 expression in the liver by downregulating the NF-kB signaling pathway. The present study **by (Zapata, Castro-Sepulveda et al. 2023)**, investigated the ameliorative effect of pomegranate peel extract (PPE) on carbon tetrachloride (CCl4)-induced hepatic fibrosis in a rat model. The results demonstrated that the use of PPE restored antioxidant status by attenuating the concentration of MDA and increased the activity of glutathione peroxidase (GSH-Px) via activation of Nrf2. PPE decreased the expression levels of smooth muscle alpha-actin (α-SMA), collagen 1 alpha 2 (COL1A2), and transforming growth factor-beta (TGF-β) proteins in liver tissues by suppressing phosphorylation of p38 mitogen-activated protein (MAPK),(Figure 36) illustrates the process. The authors further explored whether the co administration of PPE and Nrf2 inhibitors can alter the expression of p38 MAPK. Their results demonstrated that Nrf2 inhibitors did not modify the expression of p38 MAPK. Thus, the study has postulated that Nrf2 is downstream signaling in the p38 MAPK pathway .

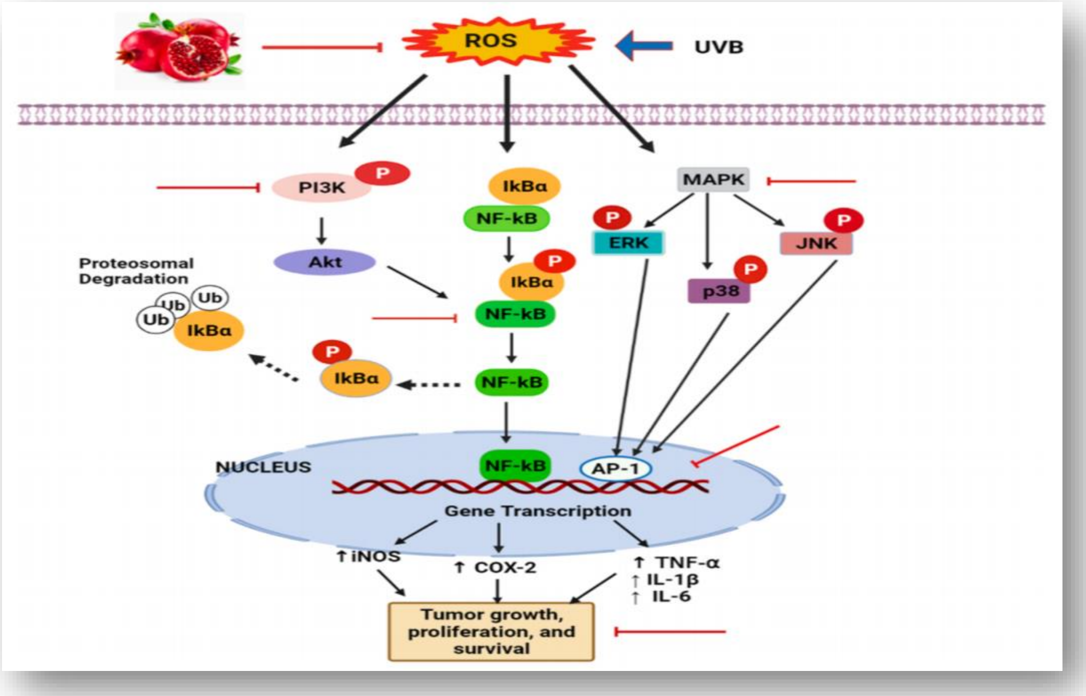


Fig. 33. Anticancer molecular pathways of pomegranate. Abbreviations: NF-kB – nuclear factor kappa B; IkBα – I Kappa B kinase alpha; MAPK - mitogen-activated protein kinase; ERK -extracellular signal-regulated kinase; JNK – Jun N-terminal kinases; AP-1 – activator protein 1; PI3K phosphoinositide 3-kinase; Akt - protein kinase B; iNOS - inducible nitric oxide; COX-2 - cyclooxygenase 2; TNF-α – tumor necrosis factor-alpha; IL-1β – interleukin 1 beta; IL-6 – interleukin 6; ROS – reactive oxygen species; UVB - ultraviolet B; P – phosphorylation; Ub – ubiquitination. The figure was created using BioRender.com by the authors..

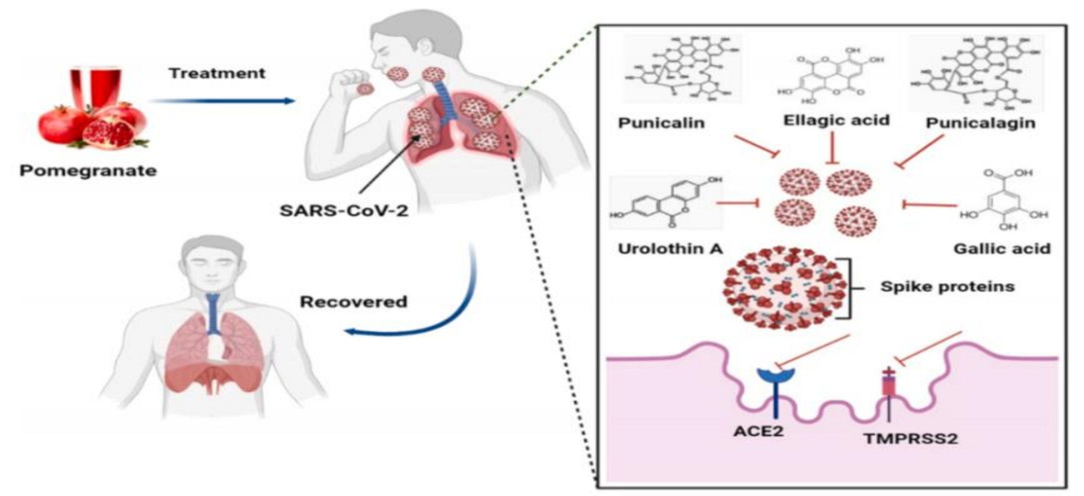


Fig. 34. . Potential mechanism of pomegranate and phytochemicals inhibiting SARS-CoV-2 and ACE2 interaction. Abbreviations: SARS-CoV-2 – severe acute respiratory syndrome coronavirus; ACE2 - angiotensin-converting enzyme 2; TMPRSS2 - transmembrane protease, serine 2. The figure was created using BioRender.com by the authors.

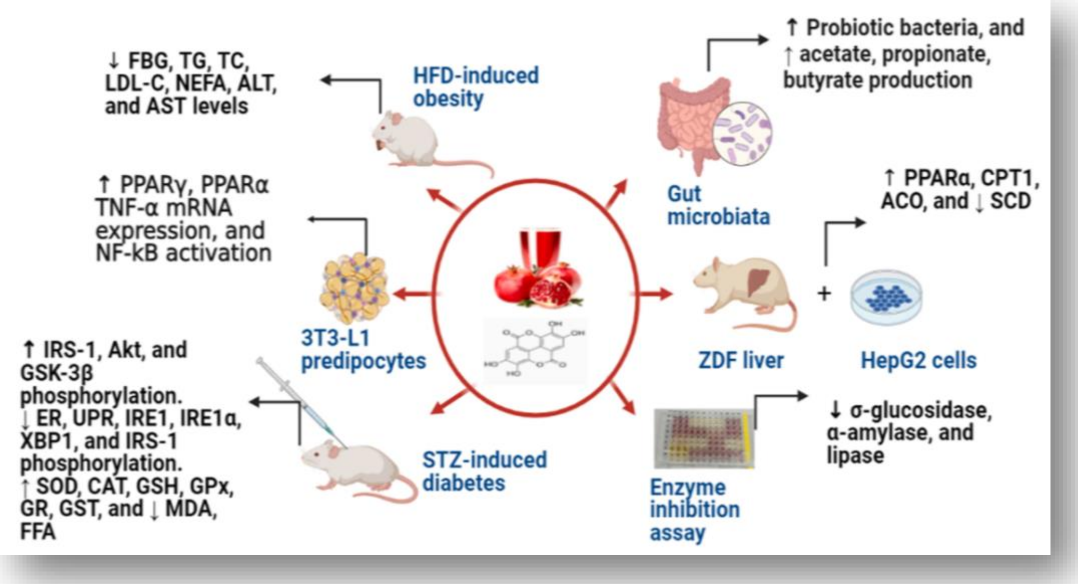


Fig. 35. . Summarized mechanisms of pomegranate and bioactive compounds ameliorate obesity, diabetes, and gut microbiota. Abbreviations: PPARγ – peroxisome proliferator-activated transcriptional factor-alpha; TNF-α tumor necrosis factor; mRNA – messenger ribonucleic acid; NF-kB – nuclear factor kappa B; FBG – fasting blood glucose; TG- triglyceride; TC - total cholesterol; LDL-C - low-density lipoprotein cholesterol; NEFA - non-esterified fatty acid; ALT – alanine transaminase; AST – aspartate transaminase; IRS-1 - insulin receptor substrate 1; Akt – protein kinase B; GSK-3β – glycogen synthase kinase 3 beta; ER - endoplasmic reticulum; UPR - unfolded protein response; IRE1 - inositol-requiring enzyme 1; IRE1α - inositol-requiring enzyme 1 alpha; XBP1 - -box binding protein 1; SOD -superoxide dismutase; CAT – catalase; GSH – glutathione; glutathione peroxidase; GR – glutathione reductase; GST – glutathione S-transferase; MDA – malondialdehyde; FFA - free fatty acids; HFD - high-fat diet; STZ -streptozotocin; CPT1 - carnitine palmitoyltransferase-1; ACO - acyl-CoA oxidase; ZDF – Zucker diabetic fatty. The figure was created using BioRender.com by the authors.

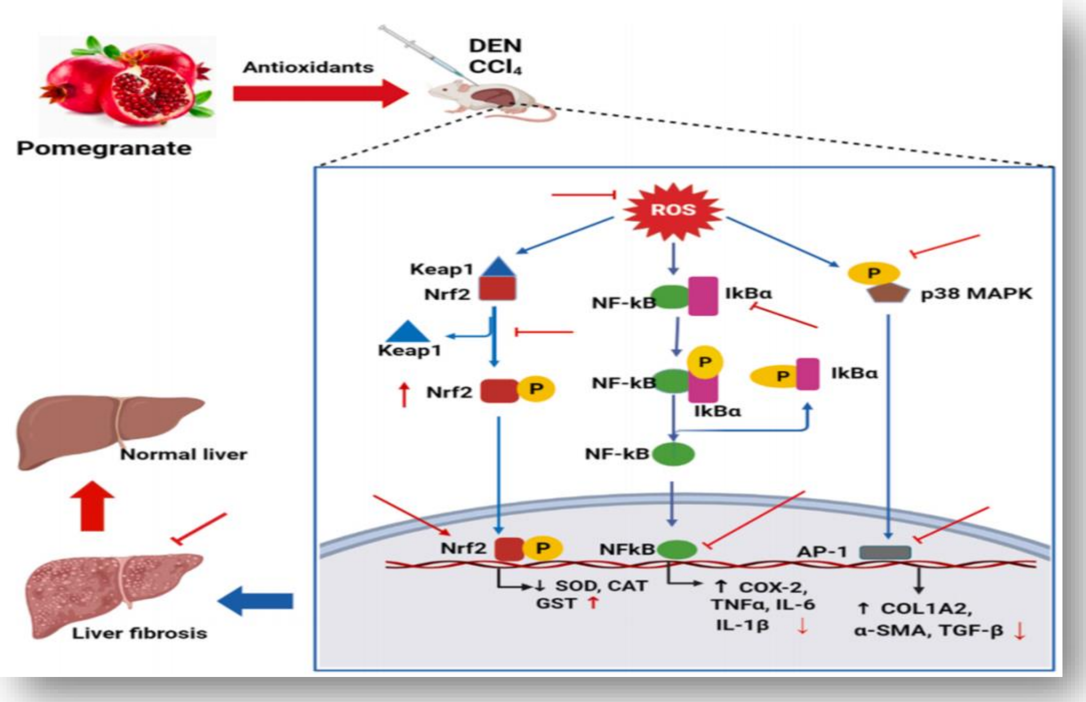


Fig. 36. Molecular mechanism of pomegranate inducing hepatic anti-fibrotic effect. Abbreviations: NF-kB – nuclear factor kappa B, IkBα – I kappa B kinase alpha; COX-2 – cyclooxygenase-2; nuclear factor-erythroid factor 2-related factor 2 (Nrf2); P38 MAPK - mitogen-activated protein kinase; AP-1 – activator protein 1; COL1A2 – collagen 1 alpha 2; α-SMA – smooth muscle alpha-actin; TGF-β – transforming growth factor-beta; Keap1 – kelch-like ECH-associated protein 1; SOD – superoxide dismutase; CAT – catalase; GST - glutathione S-transferase, P - phosphorylation; ROS – reactive oxygen species; DEN – diethylnitrosamine; carbon tetrachloride.

5.2.ginger: a rhizome of a monocotyledonous perennial herb commonly called ginger. Ginger is widely distributed across the tropics of America, Africa, Asia, and Australia, and has been used as a spice for over 2000 years. It has also been traditionally used for its anti-diabetic, analgesic, antipyretic, antiviral, anticancer, and anti-inflammatory effects. It is often prescribed as an effective therapy for the traditional treatment of gastrointestinal and respiratory disorders owing to its antiseptic and antioxidant properties. In 2017, the Food and Drug Administration (FDA) designated ginger essential oil and natural ginger extract as generally safe for human consumption.**(Elebiyo, Olori et al. 2022)**

5.3.AJwa dates Fruit(ADF): Ajwa dates fruits (ADF) value as a natural antioxidant fruit. We observed that ADF reduce oxidative stress in CPinduced nephrotoxicity by downregulating Nox4 expression and inactivating H2O2, NO, MPO, MCP-1, and caspases pathways as well as upregulating Nrf2 expression and synthesis of significant antioxidant molecules like GSH, SOD, and CAT, which reduces kidney injury. Also, these data show that ADF can attenuate CP-induced anemia, leucopenia, oxidative stress, lipid peroxidation, apoptosis, and pro-inflammatory cytokine release. The presence of bioactive substances in ADF may explain their preventive capabilities. These findings imply that consuming Ajwa dates fruits could help people receiving chemotherapy.**(Abdelghffar, Obaid et al. 2022)** , The harmful effects of Cisplatin treatment on antioxidant defense system were considerably reduced after (Ajwa dates)ADFE administration, showing that ADFE has reno-protective prophylactic tool to alleviate the chemotherapy-induced damage through its antioxidant mechanisms (Figure 37).**(Abdelghffar, Obaid et al. 2022)**

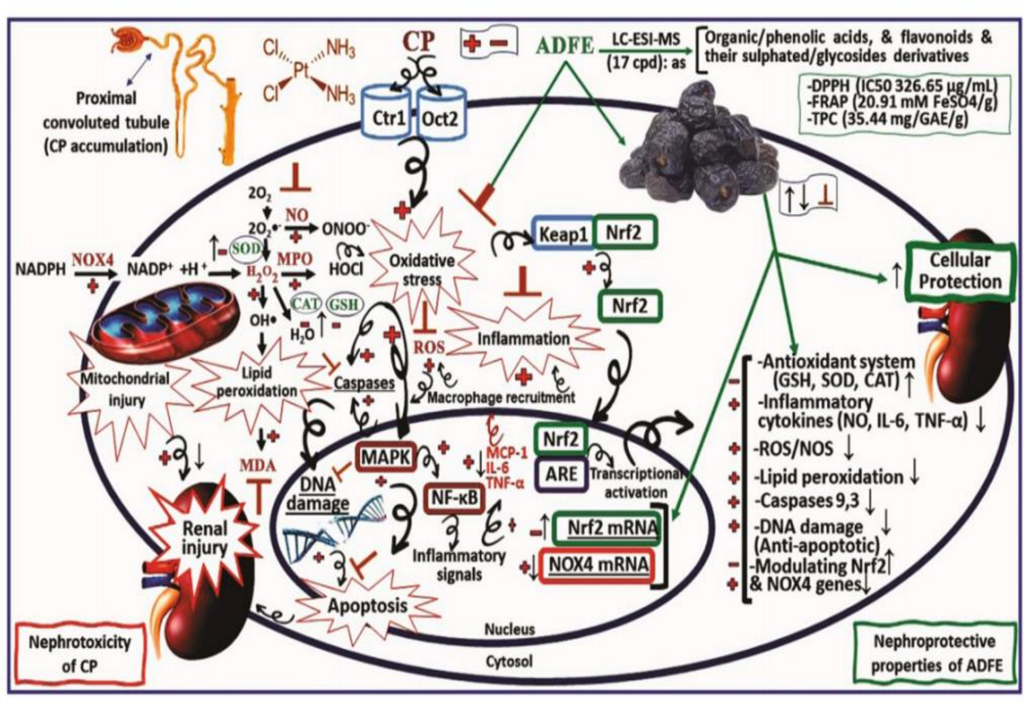


Fig.37. Schematic diagram representing the nephroprotective activity of ADF (Phoenix dactylifera) via activating Nrf2, augmenting the antioxidant system, inhibiting NOX4 pathway, alleviating oxidative stress, attenuating lipid peroxidation, mitigating inflammation and modulating apoptosis induced by CP. ADFE: Ajwa dates fruits extract, ARE: antioxidant-response element, IL-6: Interleukin-6; CAT: catalase, CP: cisplatin, Ctr1: copper transporter 1 receptor, DPPH: 2,2-diphenylpicrylhydrazyl, FRAP: Fluorescence recovery after photobleaching, GAE: gallic acid equivalent, GSH: reduced glutathione, Keap1: Kelch-like ECH-associated protein 1, MAPK: mitogen-activated protein kinase, MCP-1: Monocyte chemoattractant-1, MDA: malondialdehyde, MPO: Myeloperoxidase, NADPH: Nicotinamide adenine dinucleotide phosphate hydrogen, NF-KB: Nuclear factor kappa B, NOX4: NADPH oxidase-4, Nrf2: nuclear factor erythroid 2–related factor 2, O2-: superoxide, OCT2: organic anion transporter 2 receptor, SOD: superoxide dismutase, TNF-α: tumor necrosis factor alpha, TPC: Total phenolic content. The þ and ↑ indicates activation/ induction of CP and ADFE, respectively, and — and ↓ (or ⊥) indicates inhibition/blockade of CP and ADFE, respectively.**(Abdelghffar, Obaid et al. 2022)**

5.4. Grapes & berries(Resveritrol):

The functional analysis of differentially expressed genes revealed significant changes in processes critical for organismal and cell wellbeing such as inflammation and immunity, thrombosis, DNA and protein repair, autophagy and mitochondrial biogenesis. From our analysis of lncRNAs down-regulated in our study, we observed that many of them are over-expressed in many types of tumours, chronic diseases due to the persistency of inflammation and metabolic syndromes such as obesity. Altogether, these findings provide exciting clues for the crucial role of ncRNAs in grape intake's long-term effects on a series of biological processes. These lncRNAs would deserve to be further investigated for potential applications in the care of chronic diseases and cancer and their prevention.**(Milella, Gasparro et al. 2020)**

5.4.1.Resveratrol in AD(Alzheimer Disease): anti-amyloidogenic and anti-tauopathy effects AD is the main cause of dementia and is characterized by progressive cognitive and memory deficits. The pathological hallmarks of AD include the accumulation and deposition of Aβ in the senile plaques, and hyperphosphorylation Tau (p-Tau) protein, a microtubule assembly protein formation of neurofibrillary tangles (Grill and Cummings, 2010). OS plays a crucial role in the aetiology of AD (Tonnies ¨ and Trushina, 2017), as described above. Likewise, neuronal death (Ehrnhoefer et al., 2011) and synaptic abnormalities (Kashyap et al., 2019) also exhibit essential roles in AD. Furthermore, one of the molecular changes of ageing that might contribute to the development of AD is the deficiency in cellular control mechanisms that degrade aberrant proteins (Vilchez et al., 2014). The ubiquitin-proteasome system (UPS) is the primary proteolytic mechanism to aberrant clearance proteins, including

Aβ and p-Tau (Ciechanover and Kwon, 2015; Xin et al., 2018). In this way, functional alterations of UPS and its molecular components indicate impairment of the proteasome function in AD brain (Keller et al., 2000; Tseng et al., 2008; Gadhave et al., 2016) and represent a clear link with the ageing process. RV upregulates proteasome activity in AD models, suggesting a recovery of the UPS functionality (Corpas et al., 2019). Therefore, the activation of proteolysis systems by RV may be critical in both prevention and therapy against AD and neurodegenerative diseases characterized by the accumulation of aberrant proteins. RV is involved in the maintenance of quality control of proteins mediated by UPS, mainly by SIRT1 pathway activation (Corpas et al., 2017; Tomita et al., 2015). This polyphenol promotes Aβ clearance and a decrease in its production through stimulation of proteasomal proteolysis, as shown in cell lines expressing APP695 (Marambaud et al., 2005) and in a C. elegans model of AD (Regitz et al., 2016). It has been shown that when RV was incubated with Aβ can decrease the length and the number of fibrils (Ge et al., 2012) and Aβ plaques (Porquet et al., 2014). RV may decrease Aβ generation by favouring the non-amyloidogenic pathway of Aβ Precursor Protein (APP) degradation (Kelsey et al., 2010; Porquet et al., 2013). In this context, RV reduces the amyloidogenic pathway and increases the amyloid-degrading enzyme Neprilysin (NEP) levels in AD mouse models (Corpas et al., 2019)). Thus, RV reduces the activity of β-secretase (BACE) through the activation of SIRT1 (Porquet et al., 2014; Jeon et al., 2007). Likewise, a study, using neuronal and non-neuronal cells and mice models, showed that the anti-amyloidogenic activity of RV is also mediated by AMPK (Porquet et al., 2013; Vingtdeux et al., 2010), which then maintains mitochondrial integrity by regulating normal autophagy (Wu et al., 2011). Furthermore, RV administration reduces p-Tau levels in AD models, which occur mainly through the deacetylation of the tau protein by SIRT1 (Min et al., 2010), favouring p-Tau degradation by the proteasome-mediated pathway (Tan et al., 2008). Besides, other studies also showed the potential of RV attenuating Tau levels in rats (Patil et al., 2013) by the upregulation of BAG family molecular chaperone regulator 2 (BAG2) levels and inhibiting the hyperphosphorylation and aggregation of Tau (Pasinetti et al., 2015; He and Yan, 2013) by the inhibition of GSK-3β and Ca2+/calmodulin-dependent protein kinase II (CaMKII), and the activation of Protein phosphatase 2 (PP2A) (He and Yan, 2013; Schweiger et al., 2017). Interestingly, RV induces normalization of Heat Shock Protein (Hsp) 70 and the ubiquitinated proteins in agreement with SIRT1 regulation (Westerheide et al., 2009) (Figure 38).**(Grinan-Ferre, Bellver-Sanchis et al. 2021)**

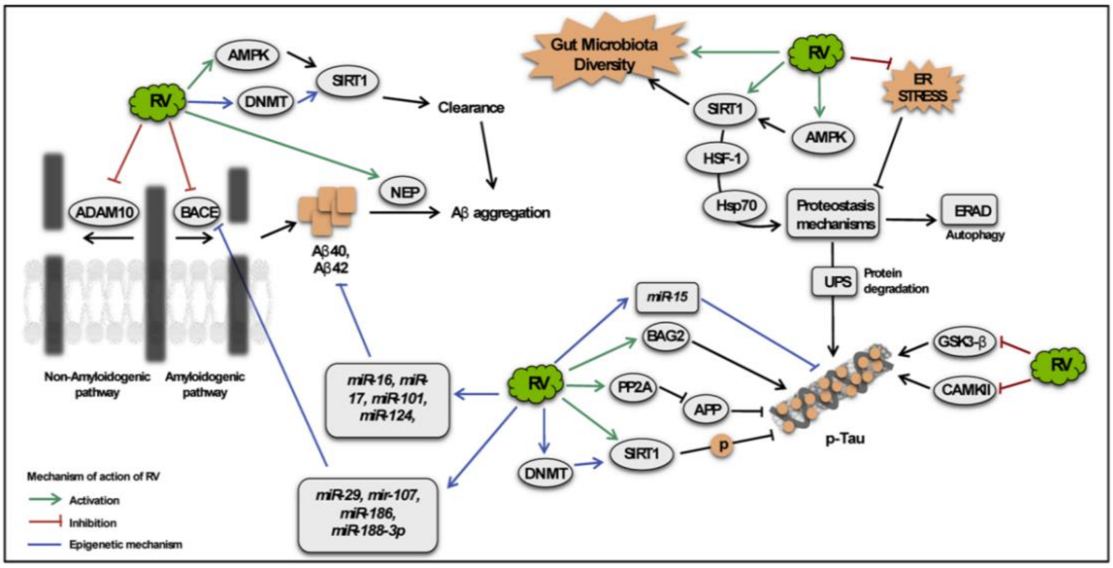


Fig.38. scheme of the specific molecular and cellular mechanisms , including epigenetics , that are activated or inhibited by RV and are implicate in neuropathological hallmarks AD modification.

5.5.spirulina algae: *Spirulina platensis* and/or *Dunaliella* sp. powder to improve their protein, fat and ash content. Batista et al., (2019) formulated wheat crackers products with different microalgae species such *Spirulina platensis*, *Chlorella vulgaris*, *Tetraselmis* sp. and *Phaeodactylon* sp. and observed that, by adding a 6 % of Spirulina and Chlorella extracts, the protein content was significantly higher than in control crackers. In addition to the high protein and essential amino acid content, some algae species may contain uncommon bioactive molecules, as the sulfonic acid derivatives taurine (Tau), its precursor hypotaurine (HypTau) and the homologue homotaurine (HTau), which may contribute to modulate several diseases and can provide protection against free radicals and heavy metals (Colovic, Vasic, Djuric, & Krstic, 2018).Tau (2-aminoethanosulfonic acid), a conditionally essential amino acid for humans and essential for animals, is gaining attention for its several implications in human diseases. For instance, Zanto, Hennigan, Östberg, Clapp, & Gazzaley (2011) identified Tau as a preventive factor for coronary heart disease. Tau has recently been pointed out as a promising new therapeutic agent in the treatment of diseases affecting the muscles, the central nervous and the cardiovascular systems as well as against cancer and other metabolic disorders such diabetes type 2 (Gossai and Lau-cam, 2009, Schaffer and Kim, 2018). Hatab et al., (2019) found that Tau showed potent antitumor activities to control hepatocellular carcinoma. Tau was also demonstrated to play a protective function in different neurodegenerative models for Parkinson's, Alzheimer's and Huntington's diseases (Jakaria et al., 2019).**(Terriente-Palacios and Castellari 2022)** , spirulina can indeed inhibit the change in immune cells and strengthen the eosinophils and basophils. Therefore, the spirulina supplement was beneficial to the stabilization of the ratio of leukocytes, monocytes, eosinophils, and basophils in elite university athletes. Furthermore, spirulina has a positive effect on rapid-onset allergies and responses to parasites or pathogenic bacterium, aiding in the improvement of immune regulation.**(Zhang, Zhang et al. 2022)**

5.6.Mushrooms: mushrooms and their bioactive components offer significant neuroprotection and play a vital role in inhibiting NDs' initiation and progression. Mushrooms can also be used as supplements in the prevention of NDs. Polysaccharides, polysaccharopeptide, β-glucans, and several polyphenolic compounds are the major secondary metabolites widely used to treat NDs. Mushrooms also balance the redox and energy homeostasis and alleviate the causes of the progression of these diseases [163]. Mushrooms posses potent therapeutic activity in AD through neuroinflammatory pathways . Further studies are needed to isolate and characterize novel bioactive components in different mushrooms. Maximum studies have been performed in AD and PD. Therefore, mushrooms' neuroprotective activity should be tested significantly in other neurodegenerative diseases such as HD, MS, and ALS. Clinical studies on humans regarding mushroom and its bioactive components will be needed to prove their efficiency. From drug designing analysis, some studies quantifying the mushroom compounds and other natural bioactive compounds have effective computational binding affinities against NDs multi-drug targets. However, the chemical compounds from edible mushrooms will serve more finding opportunities to invent novel lead structures for clinical chemistry.**(Rai, Mishra et al. 2021)**

5.6.1. Coriolus versicolor (Cv): Polysaccharopeptide derived from Coriolus versicolor (Cv) offers an immunomodulatory activity to treat several diseases . Hericium erinaceus (HE) and its derived polysaccharide can modulate the redox condition that has been used to treat several diseases [80]. In AD, HE effectively modulates the redox state and enhances the endogenous LXA4 expression . Therefore, HE shows a therapeutic compound in the AD treatment through the LXA4 signaling pathway. Like HE, Cv can also treat AD by balancing the redox state and influences the expression of LXA4 (Figure 39). Cv offers neuroprotective activity in the rat model of AD by modulating LXA4 signaling pathways and balancing the redox homeostasis in the rat model of AD. Therefore, Cv might be used shortly to treat AD in an innovative way . HE and Cv are also edible and might be supplemented to the AD, taking as a neuroprotective strategy.**(Rai, Mishra et al. 2021)**

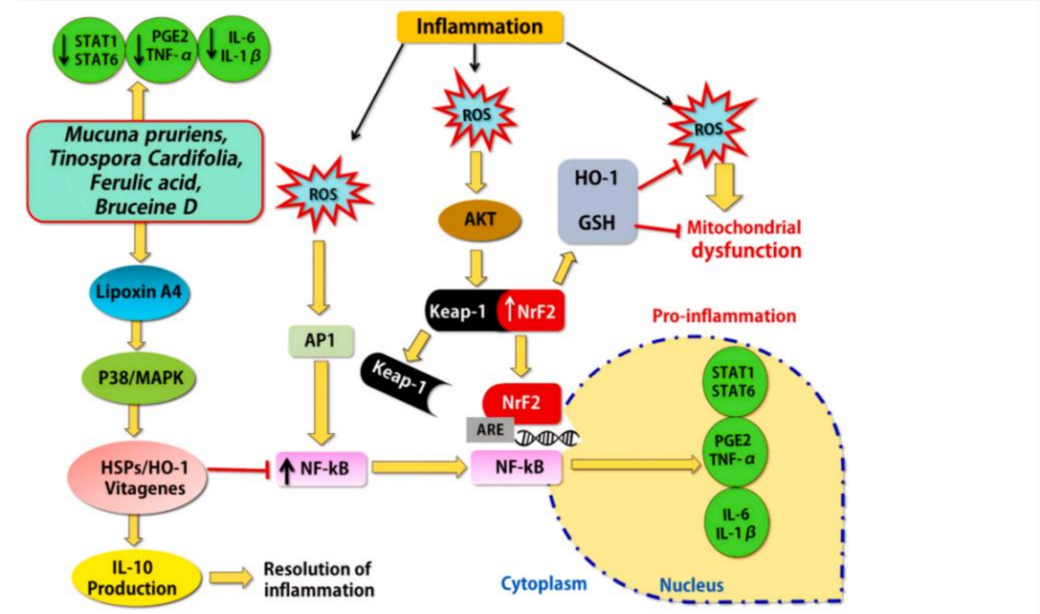
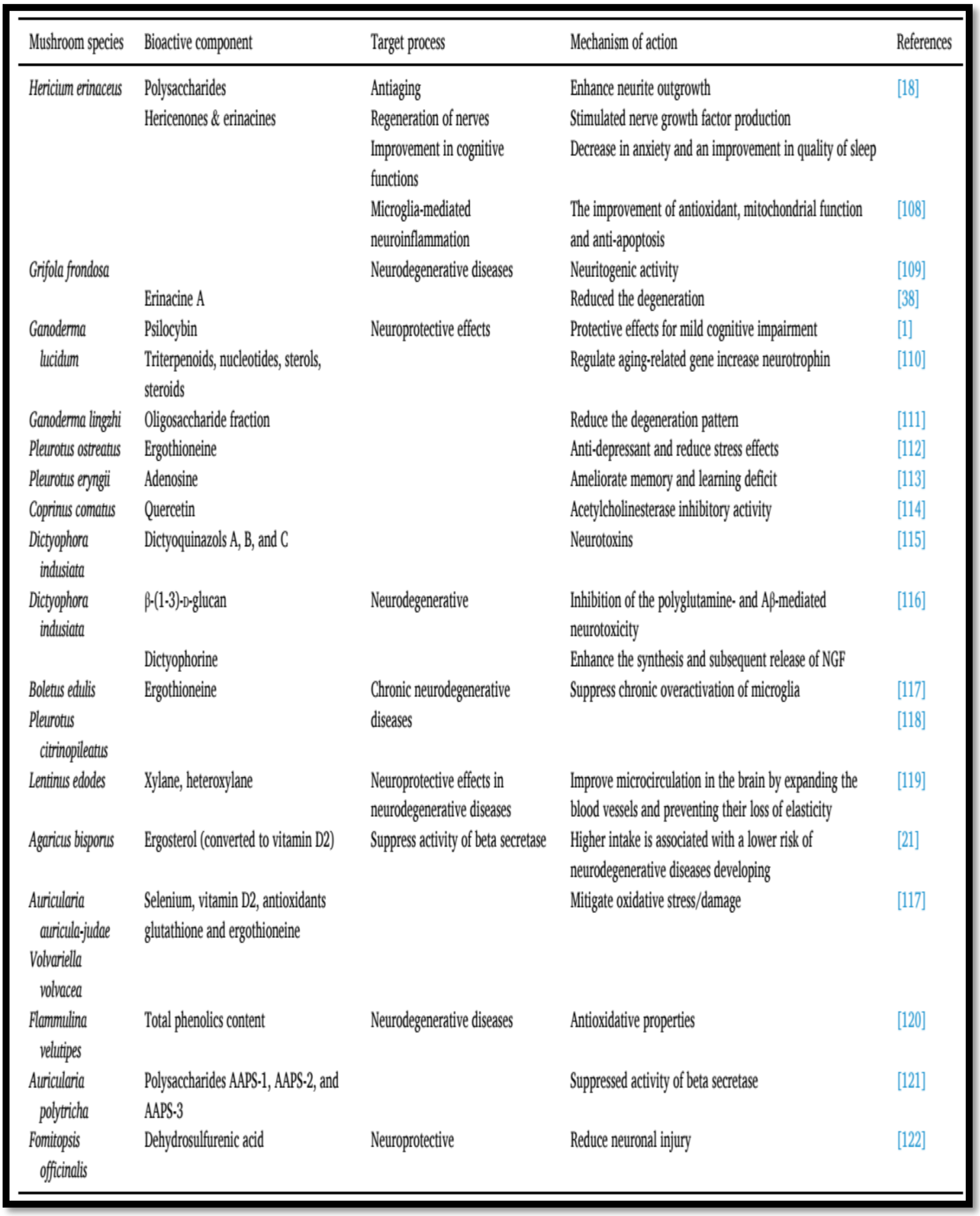


Fig.39. the role of Cc in AD based on the LXA4 ability to reduce the inflammation and how the inflammation that sustains ROS formation could be controlled by the NF-kB in mitochondria.

5.6.2. 4. Mushrooms and its bioactive components in Huntington's disease : Edible, non-edible, and medicinal mushrooms also show its therapeutic efficacy in Huntington's disease (HD) . The clinical feature of HD is cognitive dysfunction. Polyozellin is a critical biomolecule of the edible mushroom Polyozellus multiplex. Polyozellin significantly alleviates the glutamate-induced mouse hippocampal neuronal HT22 cell death in the HD model. Polyozellin regulates apoptosis through the MAPK pathway. Polyozellin reduced the biochemical abnormalities like ROS and lipid peroxidation in HT22 cells. Thus, Polyozellin, a vital bioactive component in edible mushrooms, might be tested for HD patients shortly .

HD involves motor dysfunction, emotional disturbances, and memory loss. Medicinal mushrooms have a controversial effect on neurodegenerative diseases that have apparent clinical manifestations. They are used to control long-term physiological dysfunctions related to a decrease in the impact of oxidative stress and inflammatory progression that accompanies the neuroprotective effect. For HD, a generally valid action against neurodegenerative dysfunctions has been reported, such as reduced beta-amyloid-induced neurotoxicity and antiacetylcholinesterase . According to Table 9, the species of HE and GL are most often mentioned to contain bioactive components with a role in normalizing HD effects. Oxidative stress, the common cause of neurodegenerative dysfunction, is controlled by complementary methods that include medicinal plants and mushrooms . In this sense, the microbiota is a key element that modulates the anti-inflammatory response through (control) cytokines' production. HE determines the nerve growth factor (NGF) synthesis with direct action in the repair, regeneration, and protection of neurons. Hericenones in the fruiting body and erinacines in the mushroom’s mycelium have neuroprotective effects responsible for maintaining neuronal integrity . Other bioactive components, such as cordysinin (isolated from species of the genus Cordyceps), are multi-targeted compounds but are considered to have the same therapeutic effect. Another compound obtained from HE, dilinoleoyl-phosphatidylethanolamine, reduces endoplasmic reticulum (ER) stress, which decreases the numerical decline of neuronal cells . Typically, for GL, neuroprotective activity (oxidative stress) is closely linked to the immune response’s modulation, mitochondrial protection, which decreases with age, and antioxidant protection, accelerated by dysfunctions of enzymes with antioxidant effect. Extracts of this species contribute to neuronal differentiation, in which polysaccharides (obtained from the mycelium of the mushrooms) help to reduce the presence of free radicals and protect them against lipids peroxidation . Typically, for GL, neuroprotective activity (oxidative stress) is closely linked to the modulation of the immune response, mitochondrial protection, which decreases with age, and antioxidant protection, accelerated by dysfunctions of enzymes with antioxidant effect. Extracts of this species contribute to neuronal differentiation, in which polysaccharides (obtained from the mycelium of the mushrooms) help reduce the presence of free radicals and protection against lipid peroxidation .**(Rai, Mishra et al. 2021)**

Table 9. Bioactive components found in mushrooms used in neurodegenerative diseases and related health problems



Mushroom species	Bioactive component	Target process	Mechanism of action	References
Hericium erinaceus	Polysaccharides	Antiaging	Enhance neurite outgrowth	[18]
	Hericenones & erinacines	Regeneration of nerves	Stimulated nerve growth factor production	
		Improvement in cognitive functions	Decrease in anxiety and an improvement in quality of sleep	
		Microglia-mediated neuroinflammation	The improvement of antioxidant, mitochondrial function and anti-apoptosis	[108]
Grifola frondosa		Neurodegenerative diseases	Neuritogenic activity	[109]
	Erinacine A		Reduced the degeneration	[38]
Ganoderma lucidum	Psilocybin	Neuroprotective effects	Protective effects for mild cognitive impairment	[1]
	Triterpenoids, nucleotides, sterols, steroids		Regulate aging-related gene increase neurotrophin	[110]
Ganoderma lingzhi	Oligosaccharide fraction		Reduce the degeneration pattern	[111]
Pleurotus ostreatus	Ergothioneine		Anti-depressant and reduce stress effects	[112]
Pleurotus eryngii	Adenosine		Ameliorate memory and learning deficit	[113]
Coprinus comatus	Quercetin		Acetylcholinesterase inhibitory activity	[114]
Dictyophora indusiata	Dictyoquinazols A, B, and C		Neurotoxins	[115]
Dictyophora indusiata	β-(1-3)-D-glucan	Neurodegenerative	Inhibition of the polyglutamine- and Aβ-mediated neurotoxicity	[116]
	Dictyophorine		Enhance the synthesis and subsequent release of NGF	
Boletus edulis	Ergothioneine	Chronic neurodegenerative diseases	Suppress chronic overactivation of microglia	[117]
Pleurotus citrinopileatus				[118]
Lentinus edodes	Xylane, heteroxylane	Neuroprotective effects in neurodegenerative diseases	Improve microcirculation in the brain by expanding the blood vessels and preventing their loss of elasticity	[119]
Agaricus bisporus	Ergosterol (converted to vitamin D2)	Suppress activity of beta secretase	Higher intake is associated with a lower risk of neurodegenerative diseases developing	[21]
Auricularia auricula-judae	Selenium, vitamin D2, antioxidants glutathione and ergothioneine		Mitigate oxidative stress/damage	[117]
Volvariella volvacea				
Flammulina velutipes	Total phenolics content	Neurodegenerative diseases	Antioxidative properties	[120]
Auricularia polytricha	Polysaccharides AAPS-1, AAPS-2, and AAPS-3		Suppressed activity of beta secretase	[121]
Fomitopsis officinalis	Dehydrosulfurenic acid	Neuroprotective	Reduce neuronal injury	[122]

5.7.Other medicinal Herbs & fuctional foods :

5.7.1. Herbal drugs showing miscellaneous activity: A detailed analysis on the diverse functions of Rhubarb were reported in a systematic review which showed the significant effects of the plant on restoring the gastrointestinal biological barrier, gastrointestinal mechanical barrier by decreasing intestinal injuries, permeability and improving intestinal microcirculation and metabolism during sepsis. Rhubarb plant effectively inhibit the leakage of leukocyte tissue and protein from vessels to lung tissue thus reducing sepsis related lung injury . A study demonstrated that ethanolic extract of Santalum album possessed neuroprotective behaviour via amelioration of learning and memory and reducing oxidative stress during septic encephalopathy . (Figure 40) depicts therapeutic potentials of above mentioned medicinal plants which can be used in treatment of sepsis with their molecular structures. Evidences from previous studies have suggested a variety of medicines from herbal origin yield some antioxidants to control oxidative stress during inflammation . A study stated that Magnolia officinalis exhibits antioxidant activity which damages reactive oxygen species and peroxides involved in sepsis occurrence, depleted levels of liver GSH were recovered by essential oils extracted from caraway seeds .**(Usmani, Khan et al. 2021)**

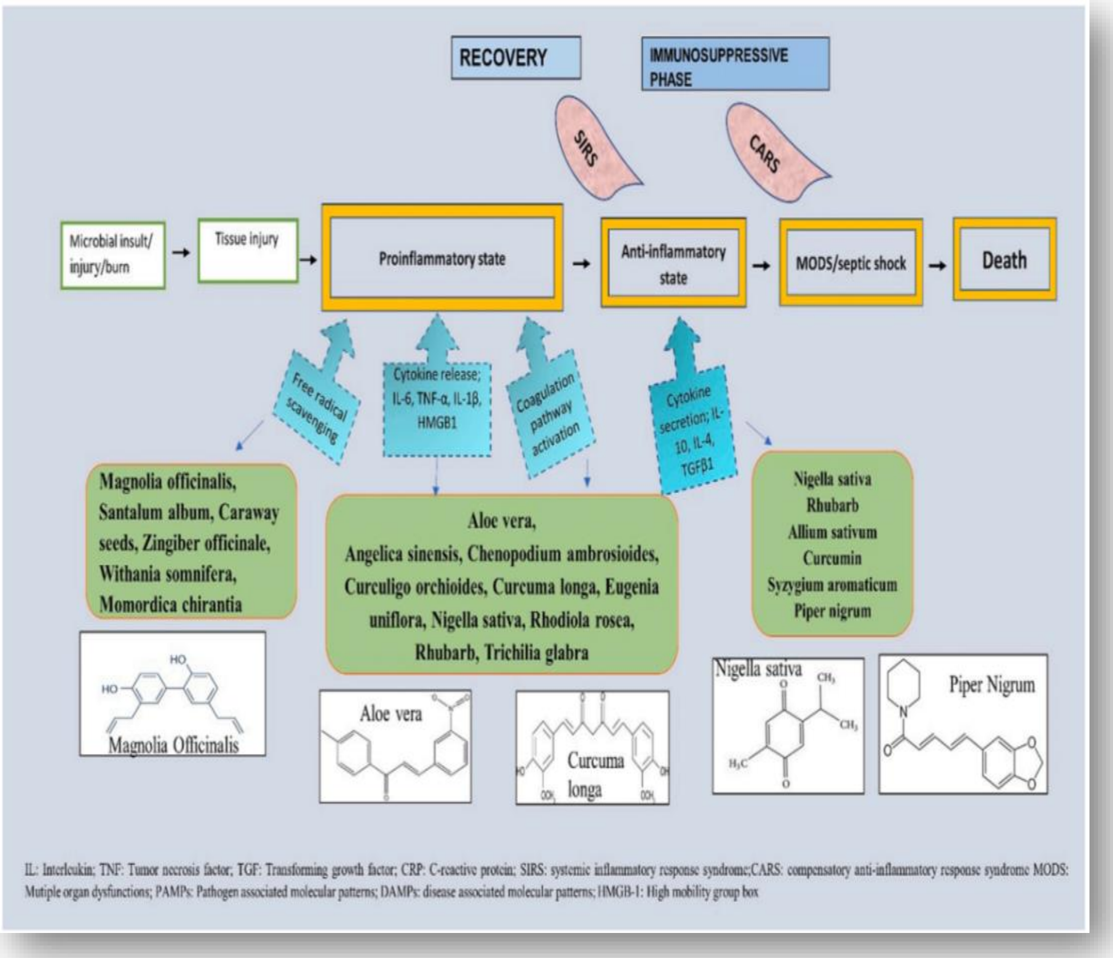


Fig.40. Medicinal plants acting on different pathways of sepsis . plant based are used for the management of sepsis owing to their activity on various pathways of sepsis . molecular structure of plants are depicted in the figure.

6.Bioinformatics: Bioinformatics has become an important part of a variety of biological fields. Bioinformatics methods such as signal processing and image enable the extraction of conclusions that are useful from larger amounts of raw data in experimental and molecular biology. In the realm of genetics, it aids in the annotation and sequencing of genomes as well as their reported mutations. Through biological literature, text mining, and the creation of gene ontologies and biological, it aids in the organisation and querying of biological data. It can also be used to find the expression and control of proteins and genes. Bioinformatics tools help in the analysis, comparison, and interpretation of genomic and genetic data, as well as knowing the evolutionary elements in the molecular biology. It also aids in the investigation and cataloguing of biological pathways and networks on a more integrated level, that are crucial aspects of systems biology. In structural biology, it aids in the

modelling and simulation of RNA, proteins, DNA, and biomolecular interactions **(Patil and Gupta 2022)**. Since the beginning of 1970s, biological sciences have made substantial advancements.The emergence of modern biotechnologies, for example, OMICs, have seen to have a positive effect on all areas of life sciences. Before these advances, food and nutritional science,in addition to other food science areas, relied greatly upon the classical chemistry and biochemistry methods, and such techniques stayed relatively constant for a long period of time. Most recently, new improvements in the area, leading to "Omics" technologies, have explored the areas of genomics, transcriptomics, proteomics, metabolomics, nutrigenomics, nutriproteomics, etc., showing many essential biochemical mechanisms and pathways that drive food and nutritional science. Since omics technology help to furtherenvision the modifications that arise when the genetics, environment, or the nutrition ofthe living organisms is altered, the targeted analysis would be an integral part of the food evaluation paradigm where nutrient qualities, anti-nutritional facets, pollutants, or other elements of possible biological activity of living organisms will be quantitatively and qualitatively examined and assessed. Although the targeted compositional analysis provides
the proof required to evaluate food nutrients and their effect on health, omics technologies can add more significance to food quality and safety evaluation processes. Modern agriculture, such as transgenic plants, GMOs, and disease biocontrols, has increased lots of problems, and new omics technologies could be relied on to fix these problems.**(Saif and Iftikhar 2022)** , statistical genetics expertise in preparation for the nutrigenetics research project. The key learning author's acquired from the coursework was th

e global health burden on complex diseases continuously increasing even though the population follows the public health guidelines. Moreover, knowing that human genetic heterogeneity is linked to disease predisposition opens the alternative strategies of personalized nutrition. Combining all of the theories learned in the class, the author's training in statistical analysis of nutrigenetics is valuable to be able to determine the suitable statistical methodology in analyzing the given dataset using SPSS software.**(Nathania 2021)**

7.resultant implementation mechanisms and complementary strategies :

The GAHD/HAMD nutrition system call for ending nutrition problems /nutritional disorders and following a healthy unified diet system that is targets modification of human genes in order to preserve the human race and protect of our genes from deterioration keeping pace with global progress until reaching leadership and role models on the global level by raising the slogan of preserving nature , vital balance and world peace to achieve the highest degree of progress , prosperity and well-being.

7.1.Ending Nutrition problems/nutritional disorders : this problems is either economic or educational. In Egypt generalizing the implementation of comprehensive health insurance, following up all means of nutritional education , supporting nutrients and nutritional supplements in the basic stages of pregnancy , lactation and neonates , following up on the nutritional education of adolescents and parents , together with supporting Egyptian farmers ,increasing governmental investment in the field of agriculture and more desert reclamation to achieve self-sufficiency of food commodities and fixing their prices.

Actually may end all these food problems gradually and continuously , which will positively reflex on the general economy and progress . Globally, persistent food insecurity, poor growth and micronutrient deficiencies continue to plague school-age children and adolescents, as the new challenge of obesity emerges. Despite this, the persistent absence of these age groups across research, policy and programming means that the limited information available is neither standardized nor comparable. Consensus is urgently needed on methods for assessing nutritional status and its determinants (e.g. dietary intake and quality), in order to set targets and monitor progress. In addition, an understanding of double-duty interventions is needed, to ensure that healthy diets are available, affordable and appealing for all adolescents, alongside efforts to promote healthy behaviours that support optimal growth and development for current and future generations.**(Wrottesley, Mates et al. 2023)**

7.1.1. poverty alleviation studies: poverity alleviation studies should be sponsored by the governments to rise the average income of the citizens at levels of farmers and low-income employees , taking the following studies into consideration

a-this Chinese study : Analysis on the Effect of the Targeted Poverty Alleviation Policy
on Narrowing the Urban-Rural Income Gap: An Empirical Test
Based on 124 Counties in Yunnan Province .**(Yang, Zhong et al. 2022)**

b- Financial Inclusion through Efficient Zakat Distribution for Poverty Alleviation in Malaysia: Using FinTech & Mobile Banking **(Yahaya and Ahmad 2018)**

c-Chinese experience through accurately identifying the degree of poverty and poverty-causing factors of poverty-stricken farmer households is the first key step to alleviating absolute and relative poverty which concluded that The main poverty causing factors under the short-term development goals are per capita net income, safe housing, sanitary toilets, years of education of labor force, and family health. Under the mid- and long-term goals, per capita net income, labor force education, and safe housing are the major development limitations of Fugong County. These factors in the county remain far below the national average levels. These findings have the potential to provide theoretical foundations for practical policy making for national poverty reduction.**(Wang, Jia et al. 2022)**

7.1.2. *The following strategies are proposed in order to meet the global nutrition challenges for optimal human health and well-being in the new millennium:(Uauy, Corvalan et al. 2009)*

1. agree to use the term ‘malnutrition in all its forms’ as a description that encompasses the full spectrum of nutritional disorders when interacting with policy makers and members of the public;

2. develop integrated prevention and control strategies for infant, child and adult under nutrition, and nutrition-related chronic disease throughout the life course;

3. reconsider the concept of dietary quality and optimal growth beyond immediate survival, particularly in relation to life-long health. There remains a critical need to define what is meant in practice by ‘adequate food’, considering not only quantity of energy but also
overall diet quality;

4. address optimal nutrition for healthy aging based on emerging evidence of the impact of nutrition and physical activity interventions on age-related functional and health decline;

5. call for a greater effort by the UN agencies, private and public development partners and other organizations to develop and/or strengthen local, regional and international leadership capacity to support the much needed change in policy and programme activities, focusing on malnutrition in all its forms with a unified agenda.

7.1.3.fixing The major nutrition challenges faced today: **which include**

a) addressing the pending burden of under nutrition (low birth weight, severe wasting, stunting) and (Zn, retinol, Fe, iodine and folic acid deficits) affecting those individuals living in conditions of poverty and deprivation;
(b) preventing nutrition-related chronic diseases (obesity, diabetes,
CVD, some forms of cancer and osteoporosis) that, except in sub-Saharan Africa, are the main causes of death and disability globally. This challenge requires a life-course perspective as effective prevention starts before conception and continues at each stage of life. While death is unavoidable, premature death and disability can be postponed by providing the right amount and quality of food and by maintaining an active life;
(c) delaying or avoiding, via appropriate nutrition and physical activity interventions, the functional declines associated with advancing age. To help tackle these challenges, it is proposed that the term ‘malnutrition in all its forms which encompasses the full spectrum of nutritional disorders, should be used to engender a broader understanding of global nutrition problems. This term may prove particularly helpful when interacting with policy makers and the public .**(Uauy, Corvalan et al. 2009)**

7.1.4.cost control to generalize food sufficiency:

7.1.4.1. The World Bank ICP provides a ready avenue for institutionalizing an ongoing monitoring system for the cost of a healthy diet indicator. It is feasible and desirable from the World Bank perspective, and the ICP already has existing links with NSOs in each country. The expectation is that NSOs would be willing and able to provide national prices for all items or for sentinel items on a monthly basis. Establishing regular timely data delivery is the challenge, but one that ICP experience predicts can largely be met., These data are official, which is a major advantage over data collected through parallel efforts and leverages the existing investments of each country in data collection. Once assembled, regular, consistent price data may be useful for other applications as well. WFP may also play a role in a global data hub in providing missing data for states in conflict and in the longer-term, possibly in providing another layer of information: regional or subnational data. These data are collected by variable systems and may not be fully comparable to the NSO data but may be useful for secondary purposes.**(Herforth, Venkat et al. 2022),**

7.1.4.2. Application of such studies on an annual basis
observational study used the International Comparison Program 2017 collection of global food prices to measure cost per day and cost per calorie of meeting nutrient needs, based on least-cost diets within upper and lower bounds for energy and 20 nutrients for healthy populations across 20 demographic groups in 172 countries. We then analysed the composition of these least-cost diets by food groups to estimate how the affordability of foods
for meeting nutrient needs varied by age, sex, and reproductive status **.(Bai, Herforth et al. 2022)**

7.1.5.Nutritional education: World organizations, governments, and scientists reach

the “common person” more efficiently to minimize health issues resulting from a lack of nutrition literacy in public.**(Chandrasekara and Jayasinghe 2022)**

7.2.GAHD/HAMD unified diet for best genetic modification and protection: By following the diet previously explained taking all recommendations previously mentioned in to consideration , always remember not to overeat and knowing that eating dates between meals in exchange with other fruits that have been mentioned as a functional foods in this diet with about 25% of total food eating a day and fasting regularly will lead to best results giving the body the enough power to get rid of free radicals and perfect metabolism.

7.3. green pharmacy application and traditional medicine : by legalizing herbal medicine and generalizing the need to dispense herbal prescriptions to patients from pharmacies for treatment and prevention of many diseases and teaching herbal science in medical colleges and allowing specialists in this field to practice the profession of complementary medicine , to generalize herbal treatment as a firist choice and educating people in public about usefulness of herbs and safety limits of its use in protection and pretreatment , for example necessity of application of this study and others in this field for better health , efficiency and longevity . Traditional Chinese medicine (TCM) includes over ten thousand herbal medicines, some of which were introduced from outside countries and territories. The Silk Road enabled the exchange of merchandise such as teas, silks, carpets, and medicines between the East and West of the Eurasia continent. During this time, the 'Compendium of Materia Medica' (CMM) was composed by a traditional medicine practitioner, Shizhen Li (1,518–1,593) of the Ming Dynasty. This epoch-making masterpiece collected knowledge of traditional medical materials and treatments in China from the 16th century and before in utmost detail, including the origin where a material was obtained. Of 1892 medical materials from the CMM, 46 came from Persia (now Iran). In this study, the basic information of these 46 materials, including the time of introduction, the medicinal value in TCM theory, together with the current status of these medicines in China and Iran, are summarized. It is found that 20 herbs and four stones out of the 46 materials are registered as medicinal materials in the latest China Pharmacopoeia. Now most of these herbs and stones are distributed in China or replacements are available but saffron, ferula, myrrh, and olibanum are still highly dependent on imports. This study may contribute to the further development, exchange, and internationalization of traditional medicine of various backgrounds in the world, given the barriers of transportation and language are largely eased in nowadays.**(Shi, Yang et al. 2022)**.

7.4.modification and development : through continuous research using nutrition questionnaire , nutrivigilance , sequencing , genetic testing and bioinformatics application for epigenetic prediction and personalization of GAHD nutrition for more precise and developmental results .

7.5. ending pollution by all its means : by increasing green landscape areas and development of research and its application through joint cooperation between governments and all research agencies combined. For examble this study application , Air pollution has significant direct (after uptake by the plant) and indirect (through changes in climate and diffuse solar radiation) effects on terrestrial vegetation that lead to visible and invisible vegetation damages. These effects, mostly from exposure to high O_3, have been observed to reduce crop yields, thus affecting agriculture effectiveness and its ability to feed the Earth's population. Plant phenology, functional type, and the seasonality of O_3 have to be taken into account when evaluating the impact of air pollution on the Mediterranean vegetation. Understanding of the interaction between the various stress factors, in particular climate (temperature, droughts, and other extremes) and air pollution (O_3, aerosol, CO_2) and how these factors once combined affect vegetation, is critical for the definition of actions in order to preserve biodiversity and sustain agricultural production. Atmospheric deposition of pollutants provides nutrients and toxic compounds or their products to the vegetation via either direct uptake by the foliage or by indirect uptake through plants' roots. Accumulation of pollutants in the environment has long-term effects on vegetation and soil; thus, it demands long recovery periods after the accumulation has stopped. This is particularly true for N deposition, which leads to N accumulation more than the optimal ecosystem levels in the soils, implies soil acidification, leads to biodiversity reduction, and changes the composition of phytocommunities. Indeed, changes in nutrient stoichiometry have been observed in plants exposed to excessively high N levels in the soil resulting from deposition of anthropogenic reactive nitrogen. As in other locations, human-induced P limitation has been observed in Europe and the Mediterranean due to anthropogenic N deposition. Such alterations of the ecosystem's composition must be carefully evaluated, particularly under conditions of climate change that are potentially increasing the occurrence of severe drought events. Indeed, interactive effects between climate change and N deposition on vegetation have been shown and predicted. Finally, plants' response to air pollution is expressed by symptoms that vary depending on the plant species and variety and the type of pollutant. Thus, plant disturbances caused by air pollution can be utilized to deduce air pollution levels, through the so-called biomonitoring procedure. However, since the use of bioindicators requires an unambiguous relationship between the cause and the plant response, this approach becomes complicated by the nonlinear response of ecosystems to air pollution and climate change. Despite this complexity, the power of biomonitoring to reconstruct past pollution influence, by using, for example, well-preserved herbariums compared with present-day situations, can contribute to the effort to obtain a spatial view of the impact of atmospheric pollution around the Mediterranean regions.**(Kanakidou, Sfakianaki et al. 2022)**

7.6. transforming villages into small cities : by supporting manifestations of civilization keeping green areas space . by providing civil services and facilities and encouraging companies to manage agriculture services and raise their level with the latest scientific methods for example this study and other ways of development for a better future , Human society cannot afford the luxury of the business-as-usual approach when dealing with the emerging challenges of the 21st century. The challenges of food production to meet the pace of population growth in an environmentally-sustainable manner have increased considerably, emphasizing the need to explore newer approaches to agriculture. Agrochemical-based agricultural practices are known to have serious environmental and health implications. Even conventional organic farming is not sustainable in the long run. Although some "age-old" practices are useful, these will not help feed more people on the same or less land more sustainably. Sustainable intensification is the way forward. There is a need to incorporate a customer-centric outlook and make the organic system sustainable. Here, we bring forth the necessity to enhance the efficiency of organic agriculture by the inclusion of robotics and agrochemical-free GM seeds. Such an organic-GM hybrid agriculture system integrated with the use of artificial intelligence (AI) based technologies will have better energy efficiency. The produce from such a system will offer consumers a 'third' choice and create a new food label, 'organically-grown GM produce'.**(Husaini and Sohail 2022)**

7.7.Improving all social services and activating the establishment of governmental charitable societies: this will result in elimination of crime ,and rescuing homerless people through governmental charities that aim at social welfare and spreading peace and preserving the environment together with human rights , will end any psychological problems related affect the nutrition and impede the movement of growth and societal prosperity in order to straighten life and achieve the goals of progress . for example this study , We should try to increase the efficiency of economic activity more than that. Reducing the cost of products, achieving energy efficiency, establishing the production of highly profitable productsat the expense of increasing labor productivity, introducing technologies that can quickly adapt to the changing conjuncture of the world market, and ensuring the achievement of these and a positive balance in foreign trade. Creating a marketing mechanism-in a word, raising marketing as a banner of reforms -is one of the most important tasks of today. If we act in this way, we will be able to quickly solve the problem that seems complicated, that is, the problem of eliminating the imbalances caused by the global financial crisis and joining the national economy of Uzbekistan to the ranks of competitive national economies. Achieving this high goal requires the coordination of government bodies, scientists and entrepreneurs.**(Rashid and Mokhichekhra 2022)**

7.8.Improving the road map plan and the economic and industrial direction of progress for governments : to include General trends to support and develop environmentally friendly industries and production of best natural foodstuffs through organic farming and feeding animals and birds used for human nutrition on natural nutrients rich in functional herbs and plants and educating farmers , merchants , industrial pioneers and all people responsible for implementing this , to reach the highest levels of environmental preservation and vital balance which will maximize public health state on all levels. For example this study which found that One Health approaches show quantitative incremental benefits for health services and infrastructure, surveillance–response systems, antimicrobial resistance, food safety, nutrition security, environmental sanitation, and zoonoses control for global health security; however, gaps remain in the realisation of One Health to cover all species of interest. The evidence base is generally strongest for the One Health interventions focused on prevention and preparedness across the spectrum of hazards.**(Zinsstag, Kaiser-Grolimund et al. 2023)**. Also this study which suggested that , Due to popular successes (e.g., ChatGPT) Artificial Intelligence (AI) is on everyone's lips today. When advances in biotechnology are combined with advances in AI unprecedented new potential solutions become available. This can help with many global problems and contribute to important Sustainability Development Goals. Current examples include Food Security, Health and Well-being, Clean Water, Clean Energy, Responsible Consumption and Production, Climate Action, Life below Water, or protect, restore and promote sustainable use of terrestrial ecosystems, sustainably manage forests, combat desertification, and halt and reverse land degradation and halt biodiversity loss. AI is ubiquitous in the life sciences today. Topics include a wide range from machine learning and Big Data analytics, knowledge discovery and data mining, biomedical ontologies, knowledge-based reasoning, natural language processing, decision support and reasoning under uncertainty, temporal and spatial representation and inference, and methodological aspects of explainable AI (XAI) with applications of biotechnology.**(Holzinger, Keiblinger et al. 2023)**.

8.conclusion and future vision:

We can understand from this review article that faith is the most important factor for development and well-being , faith doesn't come easily except with knowledge and certainity . because that nutritional culture cames down with religions , and it was the skill and miracle of prophets and scientists from time immemorial and it was subjected to some whims but there are also well-established sciences that are inherited from the people of trust and religion of islam , these sciences are evident in the Holly Quraan and the noble prophet's sonnah , modern science has confirmed all of these constants , we are now in the process of navigation though more knowledge by systemization , rearrangement ,good matching and continuous research/development for best results to achieve well being and spreading peace to deserve the immortality in the heaven and it won't be the end but only next step for more surprises . firist of all we have to know that it wan't be accomplished without believing of not to ignore any problem even if it was very small and life laws and constats legitimized by the creator and all other life science are not even and needs for more certainty through that constants ,and not stop at certain point of progress .Unfortunately still there are food problems and nutrition /nutritional diseases in our world in the same time where the science reached the coquest of space . and billions of millions are spent on these scientific discoveries instead of finalization of these problems to get ready to do that and more with faith of Allah and believing in that the real treasure is in the compassion and peace which makes the miracles . that’s why every one should start by himself for better results and cooperation in righteousness, piety and charity and the role of governments and the leaders in feeling the responsibility twords protecting humanity and justice , solving all problems in parallel with each other in the same time with developmental steps but giving the health problems the biggest effort , not being satisfied with the solution by short-term and failed methods that's infact worthen the problems , keeping pace with the latest successful scientific methods and long-term strategies which leads to success at all levels to achieve the desired development and advancement .

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