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REVIEW ARTICLE

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The role of plant-derived natural antioxidants in reduction of oxidative stress

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Abstract

Free radicals are a group of damaging molecules produced during the normal metabolism of cells in the human body. Exposure to ultraviolet radiation, cigarette smoking, and other environmental pollutants enhances free radicals in the human body. The destructive effects of free radicals may also cause harm to membranes, enzymes, and DNA, leading to several human diseases such as cancer, atherosclerosis, malaria, coronavirus disease (COVID-19), rheumatoid arthritis, and neurodegenerative illnesses. This process occurs when there is an imbalance between free radicals and antioxidant defenses. Since antioxidants scavenge free radicals and repair damaged cells, increasing the consumption of fruits and vegetables containing high antioxidant values is recommended to slow down oxidative stress in the body. Additionally, natural products demonstrated a wide range of biological impacts such as anti-inflammatory, anti-aging, anti-atherosclerosis, and anti-cancer properties. Hence, in this review article, our goal is to explore the role of natural therapeutic antioxidant effects to reduce oxidative stress in the diseases.

KEYWORDS

diseases, free radicals, mass spectrometry, medicinal plants, natural antioxidants, oxidative stress

Abbreviations: ACC, antioxidant activity coefficient; ALE, Artichoke leaf extract; ALT, alanine aminotransferase; AP-1, activator protein 1; AST, aspartate amino transferase; CHD, coronary heart disease; COX, cyclooxygenase; FRAP, ferric reducing ability of plasma; FRAP, ferric reducing activity/antioxidant power; GIT, gastrointestinal tract; HPLC, high-performance liquid chromatography; IL-6, IL-2, IL-8, interleukins; IM-MS, ion mobility mass spectrometry; ITM, Iranian Traditional Medicine; LDH, lactate dehydrogenase; LDL, low-density lipoproteins; MCAS, mast cell activation syndrome; ME/CFS, myalgic encephalomyelitis/chronic fatigue syndrome; MS, mass spectrometry; NER, nucleotide excision repair; NF-κB, nuclear factor-kappaB; NF-κβ, nuclear factor-kappa β; Nrf2, nuclear factor erythroid 2-related factor 2; NSAID, non-steroidal anti-inflammatory drugs; OEO, oregano essential oil; ORAC, oxygen radical absorbance capacity; PBMC, peripheral blood mononuclear cells; *PHA*, mitogen phytohemagglutinin; RAP, reducing antioxidant power; TEAC, Trolox equivalent antioxidant capacity; TGF-β, transforming growth factor beta; TNF-α, tumor necrosis factor-alpha; UPLC, ultra-performance liquid chromatography; ZM, Zhumeria majdae; α-SMA, α-smooth muscle actin.

1 | INTRODUCTION

Free radicals accumulate as a natural byproduct in metabolic pathways resulting in oxidative stress in the body. Such stress may also occur by external sources such as pollution, cigarette smoke, radiation, and medication, leading to cellular damage. Oxidative stress has been associated with the development of some chronic and degenerative diseases such as cancer, autoimmune disorders, age-related disease, cataracts, rheumatoid arthritis, cardiovascular and neurodegenerative diseases. However, this process can be regulated by antioxidants produced in a natural pathway in situ or externally supplied by foods and/or herbal supplements.[1,2] Antioxidants play a pivotal role as scavengers of free radicals or active oxygen species. Almost all organisms are well-protected against free radical damage either by enzymes or compounds, such as ascorbic acid, α-tocopherol, and glutathione, which are essential to protect the human body from oxidation. There are numerous reports of antioxidant activity in fruits, vegetables, and herbal compounds. The higher levels of antioxidants, the more excellent resistance to various types of diseases can be observed.[3,4] For instance, the essence of Eryngium Campestre contains methylated phenylpropanoid, eugenol, methyl isoeugenol, and benzaldehyde derivative[5,6] and/or the essential constituents of Stachys byzantine essence are sesquiterpenes, namely alpha cocaine, spathulenol, and beta-caryophyllene. Research shows that using these plants improves human antioxidant performance.[7,8] Potential antioxidants have been observed in berries, cherries, citrus fruits, prunes, and olives, too.[3] Green and black teas have also been studied extensively for antioxidant properties due to their high flavonoid content, largely catechins (20%–30% of the dry weight). In addition, theophylline and theobromine were primarily reported in black tea at very low values with a reliable range of 0.02%–0.04% dry weight. They can treat respiratory diseases such as bronchitis emphysema because of their antioxidant properties.[8]

Due to the high prevalence of chronic diseases, the use of plants to provide the antioxidants needed for the body is reasonable, especially herbal plants with high phenol and flavonoid levels.[9] For instance, Beta-carotene, which is considered a fat-soluble antioxidant, is found in many orange-colored fruits, including sweet potatoes, carrots,[10] cantaloupes,[11] porridge, apricot, pumpkin,[12] and mango.[13] It is also broadly known for scavenging free radicals and promoting skin health and the immune system.[14] Some leafy green vegetables, such as a stalwart green cabbage with smooth leaves, spinach, and green cabbage (cabbage), are rich in beta-carotene.[12] Furthermore, these vegetables contain lutein, best known as an eye health supplement.[15] Lycopene is one of the most potent antioxidants found in tomato, watermelon, guava, papaya, apricot, pink grapefruit, blood oranges, and other foods. It is estimated that 85% of the lycopene in American diets comes from tomatoes.[16] Vitamins as a broad group of organic compounds are essential for normal body function. The beneficial properties of plants and foods that contain vitamins to improve metabolism and health-promoting activity have been examined extensively.[17] Vitamin A is a critical component of the human diet obtained from foods containing beta-carotene and is observed in three significant forms of retinol or vitamin A1, vitamin A2 (3,4-didehydroretinol), and vitamin A3 (3-hydroxy-retinol). Sweet potato, carrot, milk, egg yolk, and mozzarella cheese could be mentioned as rich sources of vitamin A. Vitamin E has exhibited biological activity primarily attributed to alpha-tocopherol as one of the most commonly available isomers and is found in almonds and oils from wheat germ, safflower, corn, soybeans, mango, jujube, and broccoli. It has been clinically proved that vitamin E is able to decrease the incidence of pneumonia in the elderly effectively. It is also assumed that Vitamin E modulates IL-2 and IL-10 genes as a protective mechanism of decreasing respiratory tract infections in the elderly.[18] Vitamin C, referred to as ascorbic acid, is available abundantly in fruits, vegetables, cereals, beef, chicken, and fish.[11,14] Vitamin C is involved in superoxide and hydroxyl radical scavenging, while vitamin E inhibits the peroxidation of lipids in cellular membranes. Although blood has antioxidants include bilirubin, vitamin E (α-tocopherol), β-carotene, albumin, and uric acid, with 85% of the serum antioxidant capacity caused by uric acid and albumin, exogenous antioxidants such as vitamin C (ascorbic acid), vitamin E, phenols, lecithin from oil, selenium, zinc, and some process such as acetylcysteine are advantageous to reduce the cell damages.[19] Vitamin C plays a critical role in immune function. In 1980, a research study showed that oral administration of ascorbic acid (1 g for 3 days), is able to reduce the blood histamine level which its results motivated the researchers to study further the atopy and allergic diseases, and today, it has been recognized the benefits of vitamin C and quercetin[20] both for prophylaxis high-risk subjects and for the adjunct treatment of COVID-19 patients to pharmacological agents including remdesivir or convalescent plasma.[1,2] Ascorbate could also protect the active antiviral, antiallergic, or even anticancer conformation of certain flavonoids in vivo.[21,22]

Thus far, the coronavirus disease (COVID-19) has spread globally and is recognized as a highly complex illness that suppresses host antiviral and innate immune

response. This virus has also induced oxidative stress causing acute lung injury, tissue fibrosis, and pneumonia. During the writing of this review, significant efforts have been made to control COVID-19. However, further validation studies of vaccine, drug efficacy, and safety are still vital to treat this infectious disease. Until then, exploration of natural compounds with the ability to provide antiviral, antioxidant, and anti-inflammatory potential is highly recommended to boost the immune system and inhibit disease progression to a severe stage. It has been reported that Zn, vitamin D, vitamin C, curcumin, cinnamaldehyde, probiotics, selenium, lactoferrin, and quercetin may prevent COVID-19 spread and further suppression of the hyper inflammation by providing either prophylactic or therapeutic support against COVID-19.[23,24] Therefore, Plant-based antiviral therapies seem attractive for further study and investigation, specifically for the survivors of the CoV-2.

The antioxidant levels vary based on the herbal plants or fruits' collection time, location, and other factors such as climate change, soil, and water quality that affect plants' growth. Also, the isolation, extraction techniques, and mass spectrometry (MS) methods for measuring bioactivities of natural products are critical in herbs and fruits for further enrichment research.[9] Plant species with antioxidant activity provide excellent opportunities to treat a wide range of chronic diseases and coronavirus diseases since the oxidative stress mechanism is the critical element of the inflammatory processes. Moreover, the identification and implementation of antioxidant compounds with low or no side effects for preventive medicine are of global interest. For instance, it is hoped that by assessment of anti-SARS-CoV-2 activity and physicochemical characteristics of natural metabolites and evaluation of their antioxidants based on ion mobility mass spectrometry (IM-MS)[25,26] and/or high-performance liquid chromatography as powerful analytical methods, we can prioritize metabolites for structural information, and accelerate the potential compounds in crude extracts instead of involving a significant amount of time for isolation. So, to fight against many diseases, including coronavirus infection, and study future neuro-therapeutic management of COVID-19, and new therapeutic agents, including natural products (e.g., antioxidants and antiviral activities), we require efficient chemical modern methodologies to introduce a new antioxidant platform for identification of natural antioxidant extracts.

Hence, this present review has aimed to study the potential natural antioxidant compounds in various herbs and fruits due to their special place in medical science, specifically in the prevention and treatment of illnesses.[11,27]

2 | MECHANISM OF ANTIOXIDANTS IN THE HUMAN BODY

Reactive oxygen species (ROS) come from augmented mitochondrial activity as byproducts and promote oxidative stress in the cells. At the low level of ROS, the cellular response facilitates intracellular signaling. However, cell death may occur if the ROS is at a high enough level. Thus, a reliable antioxidant defense system is needed to respond to the accumulated ROS. β-Nicotinamide adenine dinucleotide phosphate (NADPH) and glutathione (GSH) as major antioxidants can maintain the oxygen and oxidation–reduction in cells. NADPH is generated through the pentose phosphate metabolic pathway and other sources and can act as a shared substrate for either GSH regeneration or the production of ROS.[28] Glutathione-S-transferase and glucose-6-phosphate dehydrogenase are natural antioxidant enzymes and scavenge oxidative metabolites to protect the red cells.[19]

In the human body, control of enzymatic and non-enzymatic natures allows ROS such as hydrogen peroxide (H_2O_2), superoxide anion radical (O_2 •–), hypochlorous acid (HOCl), singlet oxygen ($1O_2$), hydroxyl radical (•OH), alkoxyl radical (RO•), and peroxyl radical (ROO•)[29,30] to be inactivated due to the mechanism of antioxidants in a biological system. Enzymatic compounds, such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase, are considered endogenous antioxidants, and non-enzymatic compounds are bilirubin and albumin. If the body is exposed to a high concentration of ROS, exogenous antioxidants such as food, nutritional supplements, or pharmaceuticals are supplied to protect the organisms and slow down oxidative stress. It was reported that phenolic compounds, carotenoids, vitamins C, and some minerals such as selenium and zinc are among the most important exogenous antioxidants. In vitro methods can assess the antioxidant compounds' impacts on plant extracts, blood serum, and so forth through lipophilic, hydrophilic, and amphiphilic media (emulsions). It was suggested that they could be categorized into two major groups due to their high speed and sensitivity: (a) transfer reactions of hydrogen atoms and (b) reactions of a single electron transfer.[30–36]

3 | ROLE OF ANTIOXIDANT DEFENSE IN ORGANISMS

The antioxidant defense can be enzymatic or non-enzymatic, as well as a repair system.

- In the primary enzymatic system, antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and DT-diaphorase are developed by aerobic organisms. The dismutation reaction of O_2 to H_2O_2 is the responsibility of SOD, which in subsequent reactions, catalyzed by catalase or by GPx, resulted in H_2O and O_2. Because of the powerful system of detoxification enzymes, SOD plays a vital role in the cell. SOD, as a metalloenzyme, needs a metal as a cofactor to be activated. Thus, different forms of enzymes are dependent on the metal ion type. Iron or manganese are used in CAT as a cofactor and can catalyze hydrogen peroxide (H_2O_2) to degrade or reduce water and molecular oxygen products. This helps to complete the detoxification process started by SOD. CAT is found in peroxisomes and breaks down numerous H_2O_2 molecules in a second, and eliminates the H_2O_2 when fatty acids are oxidized. GPx, as an intracellular enzyme, breaks down H_2O_2 in water and lipid peroxides based on their alcohols in the mitochondria and sometimes in the cytosol. Selenium is the crucial element to activate GPx. In the human body, at least eight enzymes GPx, GPx1–GPx8 are present, of which GPx1 is the most abundant selenoperoxidase in all cells. Oxidative stress occurs if the human body experiences low GPx, affecting the functional proteins and the fatty acids present in the cell membrane, leading to the development and prevention of diverse diseases.
- The function of the non-enzymatic system is to trap the free radicals and avoid the radical initiation reaction. The radicals are neutralized or captured when the electrons are donated. The role of antioxidants such as Vitamin E, vitamin C, carotenes, ferritin, ceruloplasmin, selenium, reduced glutathione (GSH), manganese, ubiquinone, zinc, flavonoids, coenzyme Q, melatonin, bilirubin, taurine, and cysteine is to prevent or slow damage to cells caused by the free radicals. It is interesting to note that some natural products that contain the flavonoids have direct interactions with the ROS to generate stable or less reactive complex compounds, whereas other flavonoids can act as a co-substrate in the catalysis process of some enzymes.[28,37]
- The system of repair is about the damaged enzymes caused by ROS. Repair enzyme systems of DNA including polymerases, glycosylases, and nucleases, and proteolytic enzymes such as proteinases, proteases, and peptidases present in either the cytosol or the mitochondria of mammalian cells. GPx, glutathione reductase (GR), and methionine sulfoxide reductase (MSR) are also enzymes that have a role as intermediaries in the process of repair of oxidative stress.[30] For instance, UV DNA damage leads to several DNA adducts, including mostly thymine dimers and 6,4-photoproducts. Once the damage is recognized, a short single-stranded DNA segment is removed, composed of the lesion, while the single-stranded DNA that has not been damaged remains. Then, as a template, DNA uses it for the synthesis of a short complementary sequence. The final step for ligation is completing nucleotide excision repair (NER), and a double-stranded DNA is formed by DNA ligase. This is also beneficial for genetically severe human diseases. An undamaged strand will be used as a template for restoration, and the enzyme DNA ligase joins strands. The mechanism of the repair itself includes the use of proteins in DNA synthesis.[38]

4 | ANTIOXIDANT ACTIVITY IN HERBS AND FRUITS AND ITS EFFECTS ON DISEASES

Most plants and their derivatives contain important natural antioxidants because of their high bioactivity and very low toxicity and have been considerably used to prevent oxidative stress.[1–4,23] Table 1 summarizes the bioactivity impacts of the plants and fruits in patients.

Here, we describe how herbs' antioxidant properties can affect oxidative stress:

4.1 | Silymarin

Silymarin is known as a polyphenolic antioxidant, extracted from the seeds of the milk thistle plant and includes a mixture of three structural isomers: (i) silybin and isosilybin, (ii) silydianin and isosilydianin, and (iii) silychristin and isosilychristin and minor components of quercetin and taxifolin. It was found that Silybin or Silibinin is the main component in the silymarin mixture contains antioxidant and anti-inflammatory properties to treat liver diseases, tumors, cardiovascular and neurodegenerative diseases. It has also been described by Khanahmadi et al. that silymarin has higher potential hepatoprotective impacts than aminoguanidine.[39,40] In patients who suffer from β-thalassemia major, excess iron concentrations enhance chronic inflammation oxidative stress and cause cell-mediated immune dysfunction. A study evaluated the potential effect of silymarin, a flavonoid, on intracellular glutathione levels and proliferation of peripheral blood mononuclear cells (PBMC) activated by mitogen phytohemagglutinin (*PHA*) in two groups of participants. One group included 28 patients with a β-thalassemia major, while another included 28 healthy participants with matching ages. Glutathione, a primary

TABLE 1 A summary of herbs and fruits and their natural antioxidants impacts on the diseases

Herbs and fruit	Major bioactive compounds	Diseases	References
Silymarin	Silybin or Silibinin	Liver, tumors, cardiovascular and neurodegenerative diseases	Courderot-Masuyer et al., 2009; Khanahmadi and Rezazadeh, 2010
Teucrium polium L. (Lamiaceae)	Flavonoids, terpenoids, and iridoids	Liver homogenates	Golfakhrabadi et al., 2015
Corn silk	Phenolic and flavonoid	Hyperglycemia, diabetes mellitus, obesity	Zilic et al., 2016
Wheat bran	Phenols and flavonoids	Cardiovascular disease and malignancy risks	Li et al., 2015
Curcumin	Polyphenols, flavonoids, ascorbic acid, and chora	Gastric disorders, dyslipidemia, arthritis, malignancies, and liver diseases	Li et al., 2015 Tanvir et al., 2017
Crataegus	Bioflavonoids and proanthocyanins	Cardiovascular diseases	Li et al., 2015; Li et al., 2015; Salmanian et al., 2014
Rosaceae	Phenolic and terpenoids	Cancer, inflammation, diabetes.	Hao et al., 2015; Baby et al., 2018
Prune	Vitamins (A, B, K), amino acids, carbohydrates, dietary fibers, and minerals	Alleviate anxiety	Pham-Huy et al., 2008
Grape seeds	Proanthocyanidins, which are made of polyhydroxyflavan polymers or oligomers	Anti-cancer, antimicrobial, antioxidant, anti-obesity, anti-diabetic, antiosteoarthritis, anti-neurodegenerative, cardioprotective, oculoprotective effects	Unusan, 2020; Balu et al., 2006
Red grapes	Resveratrol	Malignancies, cardiovascular, neurodegenerative di, viral diseases, and Alzheimer's disease	Keservani et al., 2016
pomegranate	Polyphenols	Alzheimer's disease	Kandylis et al., 2020
Aloe vera	Aloe-emodin	Antioxidant, antiviral, and anti-cancer effects. Protective effect against skin exposure to UV and gamma radiation.	Nejatzadeh-Barandozi, 2013; Surjushe et al., 2008
Chamomile	Azulene	Cardioprotective, anti-inflammatory, antioxidant, anti-diarrhea, anti-cancer, anti-allergic, neuroprotective, and antimicrobial effects. Inhibitory effects on the growth of ovarian and skin malignant cells	Srivastava et al., 2010; Al Dabbagh et al., 2009
Olive leaf	Oleuropein	Inhibits cardiac diseases and obesity problems. Protects enzymes and hypertensive cells from death in cancer patients and antiviral properties	Japon-Lujan et al., 2006
Bitter melon	Alkaloids, glycosides, and ascorbic acid	Treatment of diabetes and jaundice	Horax et al., 2010
Rumex acetosa	Anthocyanin and polyphenol	Neurological diseases such as Alzheimer	Baby et al., 2018
Berries	Polyphenols	Neurological diseases such as Alzheimer's disease	Keservani et al., 2016; Fortalezas et al., 2010

(Continues)

TABLE 1 (Continued)

Herbs and fruit	Major bioactive compounds	Diseases	References
Blackberry	Anthocyanin and polyphenol		Fortalezas et al., 2010; Keservani et al., 2016
Blueberry	Anthocyanidins, flavonoid	Positive effects on cognition, particularly in the elderly, reduce depression symptoms in adults	Keservani et al., 2016; Olas, 2018
Garden strawberry	Phenolic acids, ellagitannins, and flavonoids	Cardiovascular diseases, malignancies, inflammation, and hypertension	Keservani et al., 2016; Fortalezas et al., 2010; Raudoniūtė, et al., 2011
Raspberry	Anthocyanins	Neurological diseases such as Alzheimer's disease	Keservani et al., 2016; Tan and Ismail, 2020
Mint plants	Phenolic compounds, carotenoids, and riboflavin		Park et al., 2019
Marrubium vulgare	Phenolic compounds and marrubiin	Malignancies, diabetes, and hepatic diseases with its anti-inflammatory, hypotensive, wound-healing, sedative, and lipid-lowering effects, antimicrobial properties	Meamarbashi and Rajabi, 2013; Sweetie et al., 2007
Orange	Flavonoids (such as naringenin), carotenoids (such as lutein, β-carotene, and β-cryptoxanthin)	Neurological disorders, cognitive impairments, and depression	Keservani et al., 2016

antioxidant of intracellular space, is involved in numerous functions of T lymphocytes. In this study, Glutathione levels and PBMC proliferation were significantly decreased in cells from patients with β-thalassemia major, which can be a reason for cell-mediated immune deficiency in this type of patients with iron overload. However, silymarin could restore the glutathione levels and proliferation of PBMCs in the mentioned study. These observations could explain silymarin's antioxidant and immunostimulatory effects, particularly the role of flavonoids in the immune deficiency treatment in β-thalassemia primary patients.[41,42]

4.2 | Artemisia and *Allium latifolium*

Compounds such as *hepatoprotective* agents mitigate tissue injury[43] aminoguanidine have radical scavenging properties and decrease advanced protein glycosylation in diabetes[39] Forty-eight components were identified in Artemisia species. The major components were camphor (12.4%), α-terpineol (9.93%), davana ether (6.24%), and bornyl acetate (3.77%). The high concentration of the extracts is highly related to the chemical techniques, and extraction methodologies. The major constituents of the essential oil of *Allium latifolium* are dimethyl trisulfide (22.8%), 4-methyl-5-thiazole ethanol (17.9%), z-β-ocimene (7.5%), and carvacrol (5.1%). The alk(en)yl substituents and some of the sulfur atoms of the compounds are seen to be important in terms of antioxidative impact.[40]

4.3 | *Teucrium polium* L. (Lamiaceae)

The therapeutic benefits of *Teucrium polium* L. (Lamiaceae) extracts are attributed to their ability to slow down the oxidative processes. For instance, it is reported that hydrogen peroxide could be suppressed by the lipid peroxidation of an alcoholic extract of *T. polium* in red blood cells. It has also been described that the extract can inhibit Beta-carotene oxidation, and Fe^{+2} leading to induction of lipid peroxidation in rat liver homogenates and enhancement of intracellular GSH level.[44]

4.4 | *Achillea wilhelmsii* C. Koch (Asteraceae)

It has also been suggested that *Achillea wilhelmsii* C. Koch (Asteraceae) is full of flavonoids and sesquiterpene lactones, which can lower blood lipids. Asteraceae have not shown any negative impacts on hepatic and hematologic systems.[45,46]

4.5 | *Cupressus semipervirens*, Corn silk (*Zea mays* L.), *Zhumeria majdae*, and *Nepeta ispahanica* Boiss. (Lamiaceae)

The leaves and fruits of 11 various taxons including *Cupressus semipervirens* var. *horizontalis*, *Cupressus semipervirens* var. *semipervirens*, *Cupressus semipervirens* cv. *Cereifeormis*, *Juniperus communis* subsp. *hemisphaerica*, *Juniperus excelsa* subsp. *excelsa*, *Juniperus excelsa* subsp. polycarpos, *Juniperus foetidissima*, *Juniperus oblonga*, *Juniperus sabina*, *Platycladus orientalis*, and *Taxus baccata* were selected and evaluated by Emami et al., showing that the methanol extracts of all these species promoted antioxidant activity. The highest and lowest antioxidant potentials were demonstrated for the methanol extract of C. *semipervirens* fruit and *Cereiformis*, respectively.[47]

Different methods estimated the capacity of Cornsilk (*Zea mays* L.) extract as a strong antioxidant source due to its phenolic and flavonoid contents for potential therapeutic benefits on hyperglycemia, diabetes mellitus, and obesity. The Cornsilk extract showed nitric oxide-scavenging. The extract also showed more effective than 88% inhibition of linoleic acid peroxidation.[48]

The tremendous radical scavenging activity reduced ethyl acetate fraction in *Zhumeria majdae* (ZM) extract. Moein et al. found that the antioxidant activity coefficient (ACC) of ethyl acetate is more than the butanol fraction in ZM crude extract.[49]

Nepeta ispahanica Boiss. (Lamiaceae), known as an endemic herbaceous plant, grows mainly in Iran. Some Nepeta species are implemented as medicinal plants in Iranian traditional medicine (ITM). The biological activity of essential oils and study of Nepta species indicated particular compounds such as 1,8-cineole (45.8%), β-pinene (8.9%), 4aα,7α,7aα-nepetalactone (6.2%), α-terpineol (4.3%), and trans-β-ocimene (3.3%).[50,51]

4.6 | Wheat

Wheat bran has high antioxidant activity and phenolic content, which is significantly higher than that of the debranned wheat grain; however, current milling methods remove a significant part of wheat bran and germ, decreasing the phenols and flavonoids in the flour and bakery products. A research study by Wang et al. found phenolic acid contents of 54 and 695 μg/g in flours produced at 60% and 100% extraction rates, respectively. The whole-wheat or gradual milling method was invented to maintain beneficial biochemicals because regular use of whole wheat products could significantly reduce cardiovascular disease and malignancy risks. However, food processing is also relatively effective in increasing antioxidant properties. For instance, according to Chlopicka et al., flour has higher total flavonoid content than bread (2–4 times higher).

In recent years, attention has focused chiefly on colored wheat cultivars. For example, it was reported that black wheat had elevated radical scavenging capacity and phenolic content, and both black and purple wheat cultivars had higher protein and antioxidant activity due to their phenolic acid and ascorbic acid content. Moreover, green wheat bran shows high antioxidant activity that is associated with pigmentation. Zong et al. found a relationship between wheat color and nutrient quality. They discovered that colored wheat was rich in anthocyanins, which suppressed NO production and in vitro oxidation. However, there are controversies around the association of antioxidant properties, phenolic content, and wheat color. A study by Mpofu et al. reported that wheat color was not relevant to the antioxidant activity parameters.

Moreover, Liu et al. reported some colored cultivars with low antioxidant activity. Also, some white wheat cultivars were found with higher phenolic content and antioxidant activity than the black cultivars. There are studies on rice cultivars with similar results as well.

Li et al. investigated the effects of wheat color or cultivar, milling methods, and food processing on the wheat products' antioxidant activity and antioxidant biochemical content. They evaluated three colored wheat cultivars (black wheat, light purple wheat, and deep purple wheat) and a white wheat cultivar in the forms of refined flour, flour from partially debranded grain, and whole wheat flour. The highest phenolic content, flavonoid content, and antioxidant activity were found in the black wheat cultivar Heibaoshi 1, having 659.8 μg/g gallic acid and 319.3 μg/g rutin. However, the lowest phenolic content and antioxidant activity belonged to the light purple wheat cultivar Shandongzimai 1, with 236.2 μg/g rutin. Also, there was significantly lower phenolic content, flavonoid content, and antioxidant activity in the refined flour than the flour from whole wheat and partially debranded wheat ($P < 0.05$), and also in steamed bread and noodles than the flour, with steamed bread having slightly higher phenols and flavonoids than noodles. The antioxidant activity was measured using the Ferric Reducing Ability of Plasma (FRAP) test, and it was reduced as much as 31.6%, 23.5%, and 21.1% in the steamed bread made from the refined flour, whole wheat flour, partially debranded wheat flour, respectively, than the flour used for baking. Therefore, whole wheat flour and partially debranded wheat flour made from black wheat are considered beneficial for health because of their nutritional and biochemical properties.[52]

Methane dihydrochloride or curcumin ($C_{12}H_{20}O_6$) is a polyphenol with hydrophobic properties and the following formula: 1,7-bis(4-hydroxy-3-methoxyphenyl)-1*E*,6*E*-heptadiene-3,5-dione, or diferuloylmethane. Polyphenolic compounds are potent antioxidant biochemicals effective in free radical neutralization and can improve health by reducing the cytotoxic effects of these radicals.[53]

4.7 | *Curcuma longa* (Turmeric)

Curcumin is found in the rhizome of *Curcuma longa* (Turmeric) and is widely used to treat different diseases. The powdered turmeric rhizome, known as Zard Choobe in Persian, is a spice commonly used in culinary and gives food a yellow color and specific flavor. Moreover, the dried turmeric rhizome is used in traditional medicine due to its antimicrobial, antioxidant, anti-inflammatory, and anti-cancer effects. This medicinal plant also exhibits lipid-lowering, neuroprotective, cardioprotective, and anti-obesity effects. It can be used to treat various diseases such as gastric disorders, dyslipidemia, arthritis, malignancies, and liver diseases.[52,54]

4.8 | Crataegus, Potentilla, and Rubus plants

Crataegus possesses a small number of phenolic acids, 1%–2% flavonoids, and 2%–3% pro-anthocyanidins. Due to the presence of bioflavonoids and proanthocyanins, Crataegus is of particular importance in the pharmaceutical industry and is used in the treatment of cardiovascular diseases as a source of natural antioxidants.[52,55]

Potentilla and rubus plants belonging to the family Rosaceae possess ample secondary metabolites, such as diverse phenolic components and terpenoids. The high antioxidant capacity of the polyphenols of potentilla and Rubus have made them valuable. They have remarkable impacts on preventing various diseases associated with oxidative stress, namely cancer, inflammation, and diabetes. The antioxidant, anti-inflammatory, antimicrobial, anti-cancer, and anti-diabetic characteristics of numerous constituents and potential extracts have been reported.[56,57]

4.9 | Prune

Prune is a dried plum that is usually a European Plum or Prunus domestica. Sometimes, cultivars consumed it for drying proposes named prune as fresh fruit. Prunes are made by drying fresh plums (*Prunus domestica*) at 85–90°C for 18 h and have high amounts of beneficial nutrients such as vitamins (A, B complex, and K), amino acids, carbohydrates, dietary fibers (hemicellulose, pectin, lignins, and cellulose), and minerals (magnesium, calcium, potassium, copper, zinc, selenium, manganese, and boron). The dietary fiber concentration increases with drying. These fruits also have therapeutic applications and can alleviate anxiety because they are rich in chlorogenic acid. This biochemical substance could decrease anxiety in murine models through benzodiazepine receptors in a dose of 20 mg/kg.[1]

Among most other fruits, prunes have the highest phenolic content, which is helpful for health. Neocholorogenic acid and chlorogenic acid are the two main phenolic compounds found in prunes and their juice. These compounds exhibit antioxidant activities against low-density lipoproteins (LDL) oxidation. The Oxygen Radical Absorbance Capacity (ORAC test) showed that prune had the highest antioxidant activity among the other tested fruits, which was 2-fold higher than other fruits with high antioxidant properties such as blueberry and raisin. The antioxidant activity of prune was 7-fold higher than plum, which differences in dry weight can explain.

Moreover, the LDL oxidation inhibition rate of canned and raw peach (*Prunus persica*) was 56%–87%, with peach peel having lower activity. This antioxidant activity was mainly due to chlorogenic acid, hydroxycinnamic acids, and neochlorogenic acid rather than the carotenoids, including β-cryptoxanthin and β-carotene. However, a study by Plumb et al., using peach and plum extracts, found that hydroxycinnamic acids were not effective in the lipid peroxidation inhibition in the liver and cellular microsomes. However, peach and plum extracts were found to have a slight hydroxyl scavenging ability.[58,59]

4.10 | Grape

Grape seeds are abundant in proanthocyanidins, which are made of polyhydroxyflavan polymers or oligomers. These compounds have health-improving effects attributed to their colonic and conjugated metabolites. A mutual interrelationship is very likely between the intestinal microbial flora and proanthocyanidin in grape seeds. Moreover, many in vivo and in vitro studies have shown the pharmaceutical effect of proanthocyanidins in grape seeds. According to the literature, these compounds exert anti-cancer, antimicrobial, antioxidant, anti-obesity, anti-diabetic, anti-osteoarthritis, anti-neurodegenerative, cardioprotective, and neuroprotective effects. Guo et al.

evaluated the protective effects of polymer and oligomer procyanidin in grape seed against ethanol toxicity. Following the literature, ethanol can lead to oxidative DNA damage in individuals with vulnerable cerebellum and hippocampus. Natural antioxidants such as procyanidins from grape seeds can protect the brain from the genotoxicity caused by ethanol. Moreover, oxidative stress intensifies the aging process by increasing the DNA oxidation and DNA-protein crosslinks in the central nervous system (CNS). Balu et al. investigated the positive effect of grape seed extract on the concentration of products made by oxidative damage to DNA, such as 8-OHdG, and DNA-protein crosslinks in old rats. They found the inhibiting role of this extract on the DNA damage found in the different areas of spinal cords and brains of the rats, including the striatum, cerebral cortex, and hippocampus.[60,61]

Red grapes are commonly used fruit containing several biological activities due to their polyphenolic content, especially in grape seeds (60%–70%) and skin (30%). Unfortunately, large amounts of grape seeds are wasted by food industries producing grape products. Biochemicals present in grapes, such as resveratrol, a fat-soluble, natural phenol, and a phytoalexin compound that several plants produce, have preventive effects in various diseases such as malignancies and cardiovascular diseases, neurodegenerative disease, viral diseases, and Alzheimer's disease. Resveratrol is protective against genotoxicity by oxidative stress. Studies on murine models have shown the inhibitory effect of this biochemical substance on the aging processes in cardiac, skeletal muscle, and cerebral tissue.[3,62]

4.11 | *Punica granatum* (pomegranate)

Punica granatum, known as pomegranate, is a fruit cultivated in the western regions of Asia from ancient times and can also be found in the Mediterranean and other places. Pomegranate (*Punica granatum*) is a stout tree or deciduous shrub with a height of 5–8 m (16–26 ft). The genus name (*Punica*) is the Roman name for pomegranate, which was first used in Carthage. Pomegranate is named grenade in French and Granada in Spanish, meaning seeded (granatus) apple (pomum). The pomegranate seeds have nutritional benefits and are rich in dietary fibers (20% DV).

There have been several human trials and research studies on the protective effect of pomegranate in numerous health-improving conditions, including anti-inflammatory, antimicrobial, and antioxidant properties. This is because Pomegranate is rich in polyphenols and contains hydrolyzable tannins of punicalagin and ellagitannin. Its edible seeds are also abundant in dietary fibers, and its juice has neuroprotective properties due to its antioxidants, the natural properties that are transferrable from mother to baby. Moreover, the oil from pomegranate seeds includes palmitic acid (4.8%), punicic acid (65.3%), linoleic acid (6.6%), oleic acid (6.3%), and stearic acid (2.3%).[63] A study showed that the neuroprotective effects of pomegranate through transgenic mice treatment affected by a pathogenic process to resemble Alzheimer's disease. In this research study, it was observed that mice receiving pomegranate juice had 50% lower amyloid deposition in the hippocampus than those receiving sugar water. A further study reported that pomegranate from Oman (with a concentration of 4%) could reduce the cerebral oxidative damage in transgenic mice affected by Alzheimer's disease.[64]

4.12 | Aloe vera

Aloe vera is rich in biochemicals, including terpenoids, flavonoids, fatty acids, lectins, anthraquinones, carbohydrates (hemicelluloses, pectins, and glucomannan), sterols (β-sitosterol, campesterol), tannins, salicylic acid, and enzymes. Moreover, this plant has abundant minerals, such as chromium, calcium, iron, copper, manganese, magnesium, phosphorus, potassium, zinc, and sodium, as well as vitamins (folic acid, choline, β-carotene, and vitamins A, E, C, B1, B2, B3, B6, and B12). The chemical properties depend on the cultivation, the position of leaves on the stem, climate, species, and leaf harvesting method and time. The best harvesting time is 3 years after the growth of the plant due to the optimal amount of flavonoids (4.70 g/kg) and polysaccharides (6.55 g/kg).[65]

Aloe-emodin, a natural active compound in aloe vera leaves, has many medicinal properties, including antioxidant, antiviral, and anti-cancer effects. There are several active antioxidant components in aloe vera that neutralize free radicals. Aloe vera contains potentially 75 active constituents, including vitamins, enzymes, minerals, sugars, lignin, saponins, salicylic acids, and amino acids. Vitamins A (beta-carotene), C, and E are the most abundant antioxidants in aloe vera. The robust characteristics of aloe vera promote healing when interacting with growth factor receptors on the fibroblast.

Moreover, aloe vera has been reported to have a critical protective effect against skin exposure to UV and gamma radiation[66,67] Aloe-emodin is also a bioactive compound of aloe vera. According to Devi et al., diets rich in aloe-emodin could protect rohu (*Labeo rohita*) against the disease through the pathogen Aphanomyces invadans by improving the innate immune system responses, resistance to the disease, and transcription of

the genes of anti-inflammatory or pro-inflammatory cytokines. They observed these effects in both healthy and infected fishes.[66]

4.13 | Chamomile

Chamomile represented anti-inflammatory, anti-bloating, antioxidant, immune-stimulating, antispasmodic, analgesic, and cholesterol-lowering properties.[68,69] Furthermore, it prevents morphine dependency and anorexia in skin eczema; it reduces menstrual pain and nerve stimulation; and heals headache and gastrointestinal disorders.[59] Azulene in chamomile essence has an inhibitory effect on cell membrane lipid peroxidation and promotes the antioxidant effects of chamomile.[70,71] Chamomile and azulene essences prevent the oxidation of lactate dehydrogenase (LDH), which inhibits the lipid peroxidation process. The major compounds in chamomile are flavonoids, chamomzolin, bisabolol, farnesene, and coumarins.[72] The flowers of this plant contain epinephrine and free quercetin, being used in traditional medicine for gastrointestinal problems.[73] Ardakani et al. suggested that the phenolic compounds in the chamomile structure act as antioxidants, eliminate free radicals, and protect collagen degradation by superoxide anion radicals. These studies showed that the anti-inflammatory effects of chamomile are mainly related to flavonoids and volatile essences, especially chamazulene and alfa-bisabolol, also known as levomenol.[74] A further study aimed to determine the antioxidant activity, total phenols, and flavonoids and evaluate the anti-proliferative activity of ethanolic extract of *Matricaria recutita* L. (chamomile).[71] This medicinal plant with cardioprotective, anti-inflammatory, antioxidant, anti-diarrhea, anti-cancer, anti-allergic, neuroprotective, and antimicrobial effects. Some preclinical studies show its inhibitory effects on the growth of malignant ovarian and skin cells because it induces apoptosis in malignant cells. Moreover, the essential oil from chamomile has the terpenoid of α-bisabolol.[75]

4.14 | Olives

Olive leaf is another medicinal plant known for its antioxidant properties. Olive tree (*Olea europaea*) products and olive leaves have been extensively used in traditional medicine to prevent and treat different diseases in the world, particularly in the Mediterranean region. These leaves contain numerous biochemical compounds with potential lipid-lowering and hypoglycemic properties. According to toxicity studies, they are safe even if used in high dosage. Among the different parts of an olive tree, olive leaves are the richest source of phenolic compounds, and oleuropein is the main phenol-rich compound[74] The bioactive compounds in olive leaves contain antioxidant properties, including hydroxytyrosol, oleuropein, tyrosol, ligstroside, caffeic acid, and mainly oleuropein. These bioactive substances belong to the secoiridoid group, and due to their primary phenolic compound, it gives a bitter taste and unique aroma to olive fruits. Oleuropein, the most prevalent bisphenol, inhibits cardiac diseases and obesity problems by protecting membrane lipid oxidation and improving lipid metabolism.

Furthermore, it protects enzymes and hypertensive cells from death in cancer patients and demonstrates antiviral properties. Hydroxytyrosol, derived from oleuropein, suppresses cardiac diseases and tumors effectively, similar to oleuropein compounds, and prevents atherosclerosis and diabetic neuropathies. Pharmaceutical impacts of this plant in different research studies, particularly in cytological and animal studies, showed the spasmolytic, antiarrhythmic, immunostimulatory, hypotensive, cardioprotective, anti-inflammatory, hypoglycemic, lipid-lowering, and anticoagulative properties. In contrast, the mechanisms involved in the hypoglycemic and cardioprotective effects of these compounds have not been fully understood.

Extracts produced from olive leaves can be dissolved in different organic solvents. The oleuropein content can lead to tablets, capsules, and liquid extracts, and depending on the brand, solvent type, and extraction methods, they might not have the same content. For example, the ethanolic section made from olive leaves has high oleuropein content (almost 20%). A research study found 37.8 mg of oleuropein per gram of dried leaf if the Soxhlet method and methanol are used while its concentration reached 14.2 mg/g of dried leaf the following modification with CO_2 and using the supercritical fluid extraction method. It is important to note that the antioxidant value of olive oil is 0.005%–0.12% due to its low polarity nature.[76] Regardless of the solvent type and extraction method, all the extracts from olive leaves must follow national or local legislation and Pharmacopeia monographs.[77–79]

4.15 | Olive oil

Consumption of extra virgin olive oil is increasing because of its chemical composition, which includes an unsaponifiable fraction, polyunsaturated fatty acids, and a fraction composed of natural antioxidant compounds including carotenoids and phytosterols flavonoids,

α-tocopherol, and other phenolic compounds. The olives mainly contain the polar glycosides oleuropein and ligstroside. Many research studies proposed a protective effect of olive oils as the primary antioxidant sources contain simple phenols like phenolic acid and phenolic alcohols (hydroxytyrosol, tysorol), polyphenols (flavonoids, apigenin, luteolin), lignans (pinoresinol, 1-acetoxypinoresinol), secoiridoids (oleuropein, demethyl oleuropein, elenolic acid, ligstroside) and their aglycones, including 3,4-DHPEA-EA or p-DHPEA-EA, oleacein (3,4-DHPEA-EA) and oleocanthal (p-HPEA-EDA). Consumption of olive oil polyphenols leads to protecting blood lipids from oxidative damage. In addition, oleacein, the main phenol in olive oil, has positive effects on cardiovascular disease, and protective effects against atherosclerosis and oxidation, and anti-inflammatory activity. The biological impacts of olives and virgin olive oil components are protection against cardiovascular diseases, anti-inflammation action, neuro and endothelial protection, and so forth.[3,80–82]

Neuroinflammation is about the activation of the brain's innate immune system in response to an inflammatory challenge and is featured by cellular and molecular host changes across the brain.[83] *Cytokines* can mediate as well as control immune and inflammatory responses. Moreover, neuroinflammation and *cytokines* have impacts on the brain signal patterns.[82,84] Patients undertaking chemotherapy are vulnerable to getting infected with COVID-19. More than 50% of patients under this circumstance develop symptoms identical to the long-COVID syndrome, specifically, cognitive dysfunction, which is referred to as "chemofog" or "chemobrain. While the pathogenesis of brain fog in patients with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) or mast cell activation syndrome (MCAS) is not fully understood, it is assumed that may associate with neuroinflammation through mast cells stimulated by pathogenic and stress stimuli to release mediators. This can activate microglia, leading to inflammation in the brain, specifically, the hypothalamus. The anti-inflammatory activity of natural flavonoids has been reported to be mediated through various mechanisms such as inhibition of releasing several pro-inflammatory cytokines, antioxidant mechanisms, and modulatory activities on transcription factors such as nuclear factor-*kappaB* (NF-κB), nuclear factor erythroid 2-related factor 2 (Nrf2), and activator protein 1 (AP-1).[82]

To treat "chemobrain", the most notable drugs have been suggested thus far: doxorubicin, methotrexate, lenalidomide, rituximab, and trastuzumab which included disrupted neurogenesis, aberrant myelination, interference with prefrontal activity, but most critically neuroinflammation with cytokine dysregulation. However, the natural flavonoid luteolin's phytosomal formulation (presents in olive pomace oil) is proposed to mitigate these processes. Although luteolin and quercetin, the major members of the flavonoid family, are challenging for absorption after oral administration, their pharmacokinetics are immensely improved in liposomal preparations when olive pomace oil is used.[82]

4.16 | Oregano

Oregano, an herb cultivated for centuries in the Mediterranean area, and its extracts and individual constituents have revealed several antioxidants properties which are beneficial toward alleviating inflammation-related diseases, respiratory and digestive disorders, headaches, rheumatism, and diabetes.[85,86] The essential phytochemicals discovered in oregano are categorized into two classes depending on their hydrophilic and hydrophobic properties: essential oils and phenolic compounds. Greek oregano (*Origanum vulgare*), as the most recognized herb globally, has elevated rosmarinic acid content. Oregano essential oil (OEO) possesses antioxidant properties that are effectively retarding lipid peroxidation in fatty foods and can scavenge free radicals and considered as one of the most effective antimicrobial and antioxidant agents.[87]

4.17 | Artichoke

Artichoke leaf extract (ALE), which is referred to as Cynara scolymus was known as one of the few herbal remedies in both clinical and experimental trials. ALE contains bioactive and flavonoid compounds such as caffeoylquinic acids and luteolin glucosides.[88,89]

The potent antioxidant, choleretic, hepatoprotective, bile-enhancing and lipid-lowering effects of this herb have been recognized as well. The research studies demonstrated that artichoke seems to be a beneficial effect on the liver. Its long-standing consumption in humans for digestive and bowel disorders, decreasing cholesterol and, therefore, helping to prevent heart disease have been studied. It has been also indicated that boiled wild artichoke decreased postprandial glycemic and insulinemic responses in normal subjects while not impacting metabolic syndrome patients. The chemical components of artichoke leaves and heads had been reported as a rich source of polyphenolic compounds, inulin, fiber, and minerals. ALE has shown antioxidative, antibacterial, anti-HIV, bile-expelling, hepatoprotective, urinative, and choleretic activities, as well as inhibitory properties of cholesterol biosynthesis and LDL oxidation.

However, antimicrobial agent of this herb has not been fully examined. Many research studies have shown that the potent antioxidant properties of ALE are because of the radical scavenging and metal ion chelating impact of its constituents, including cynarin, chlorogenic acid, and flavonoids. Many polyphenol-type antioxidants in artichoke reported the contribution of this herb to the prevention of prostate cancer, breast cancer, and leukemia. Antioxidants rutin, quercetin, and gallic acid found in ALE can cause apoptosis (cell death) and decrease cancer cells proliferation. The research performed at Comenius University in Slovakia demonstrated that ALE could inhibit the growth of leukemia cells over a 24-h period when they are treated with a variety of concentrations of ALE although inducing apoptosis of these cells were observed. Moreover, at the University of Georg-August in Germany, the research study showed that the many phytochemicals in artichoke could block the secretion of cancer agents, therefore inhibiting angiogenesis associated with the cancer. ALE also has shown a remarkable increase in anti-inflammatory factors, which indicated that serum NF-κB, TNF-α, Cox-2, CD 40, and HGF levels have a significant increase as a result of treatment with both crude aqueous methanolic extract and crude aqueous fraction as in comparison with the nonalcoholic steatohepatitis induced in untreated rats.[88,89]

4.18 | Bitter melon

Bitter melon has two types of fruits that have different shapes and colors. The spindle-shaped yellow color one is the most comprehensive variety. Flavonoid content is lower in ripe fruits than in premature ones. This plant is rich in a group of B vitamins, stearic acid, oleic acid, and fatty acids.[77] Bitter melon (*Momordica charantia*) is a plant abundant in alkaloids, glycosides, and ascorbic acid. Leaves and fruits of this plant have long been used in the traditional medicine of the Indian subcontinent for the treatment of diabetes and jaundice.[90]

4.19 | *Rumex acetosa* (sorrel)

Rumex acetosa (sorrel) is a dioecious, perennial plant that grows in various habitats.[91] Sheep's sorrel (Rumex), known as Acetosella Vulgaris, is a sorrel species that exhibits perennial anti-proliferative, antioxidant, antiviral, anti-mutagenic, and anti-genotoxic impacts.[92,93] A few cultivars and wild types of this plant are commercially available. Its roots and other parts have been generally used in traditional medicine to treat different health problems, including constipation, diabetes, infections, diarrhea, jaundice, edema, scurvy, hepatic diseases, and gallbladder diseases. There have been studies on the pharmaceutical effects of the plants of genus Rumex. It was found that different parts of these plants contain phytochemicals with biological effects, including antioxidant, anti-inflammatory, antimicrobial, diuretic, hypotensive, and analgesic effects. Sorrel and Japanese green tea have almost similar antioxidant activities. Sorrel rhizomes and flowers have bioactive compounds with antitumor properties. Aerial parts of this plant contain polyphenols and flavonoids with antioxidant properties, and its rhizomes contain polysaccharides and anthraquinones with potential antitumor effects. There are also other biochemicals in this plant, including naphthalenes, emodin, triterpenoids, stilbenoids, carotenoids, tannins, geranin, corilagin, vanillic acid, sinapic acid, gallic acid, and pyrogallol.[91]

4.20 | Berry

It has been reported that some fruits (primarily berries) and vegetables have chemopreventive and antioxidant properties. If fruits are consumed in adequate amounts, the risk of major chronic illnesses like cancer, type 2 diabetes mellitus, obesity, and cardiovascular disorders are reduced. Berries are a source of flavonoids known as anthocyanidins, which can cross the blood–brain barrier and concentrate in learning and memory regions, such as the hippocampus. Anthocyanin pigments, ellagic acid (from ellagitannins, e.g., the polyphenol ellagitannin), quercetin, gallic acid, cyanidin, pelargonidin, catechins, kaempferol, and salicylic acid are available in raspberries. The berry ingredients can guard against the damage caused by ROS, particularly in the progress of neurological diseases such as Alzheimer's. Tsuda et al. showed cyanidin 3-glucoside to have the best antioxidant effect among the investigated anthocyanins.[56]

Berries have high amounts of phytochemicals such as polyphenols. *Arbutus unedo* (strawberry) is a fruit that can be eaten as fresh fruit or be used in traditional medicine. It is not known as a health-improving fruit; however, it has antioxidant properties due to its phenolic content. Fortalezas et al. investigated the in vitro effects of this fruit in a neurodegeneration cellular model by using *Rubus idaeus* (raspberry) as the control, a fruit with established health-improving products. They found similar polyphenol content and a slightly lower antioxidant activity in strawberry than raspberry. Antioxidant activity of both fruits was almost the same using the chemical methods; however, raspberry could increase the survival of neuroblastoma cells by 36.6%, while strawberry did not affect the survival. Therefore, the antioxidant capacity of

a plant-derived extract can be different from the antioxidant capacity measured using a chemical method.[94] In addition to this, berries have neurologically active biochemicals with antioxidant and anti-inflammatory properties. They are rich in carotenoids, polyphenols, and vitamin C and have the highest antioxidant activity among the standard fruits. Raspberry, black currant fruit, and strawberry have a polyphenol content of 300–1000 mg per 100 g. Berry species and cultivar, cultivation conditions, and processing and handling after harvesting can affect the polyphenol content of the fruits. Therefore, the total antioxidant content of each berry product should be authenticated. The antioxidant content of these fruits can protect the body against oxidative stress by reactive oxygen species, which are probably involved in some neurological diseases such as Alzheimer's disease. Supplementation with cranberry, blueberry, or black currant fruit for 8 weeks could improve the neuronal process indices in old rats.[3]

Blackberry is an edible fruit obtained from some Rubus species, hybrids, and hybrids between Idaeobatus and Rubus subgenera. These fruits have high amounts of vitamin C and K and dietary fibers, including insoluble and soluble fibers. One cup of this fruit (144 g) can provide the body with half of the vitamin C daily recommended dose and contains 7.6 g of fiber. Black and red berries have health-improving benefits due to their high anthocyanin and polyphenol content.[3,94]

Blueberry is a flowering, perennial plant with indigo-colored fruits. It belongs to the family of Cyanococcus, genus Vaccinium, which includes bilberries, cranberries, and gooseberries. A fresh blueberry is made of carbohydrates (9.7%), proteins (0.6%), fat (0.4%), dietary fibers (3–3.5%), and water (84%), and 100 g of blueberry contains 192 kJ energy. This fruit is famous for its taste and high vitamin C content, 10 mg (1/3 of daily recommended dose) in 100 g of blueberries. Additionally, berries have high amounts of anthocyanidins, a flavonoid subgroup. This biochemical can cross the blood–brain barrier in some regions related to memory and learning, such as the hippocampus. According to recent studies, anthocyanins in blueberry and flavanols in cocoa positively affect cognition, particularly in the elderly. For example, it was shown that flavanols in cocoa (520–994 mg) could improve the visual and cognitive functions in young, healthy participants after 2 h, particularly in highly demanding tasks. Moreover, long-term blueberry juice (3 months) could improve working memory and reduce depression symptoms in adults with mild cognitive problems. Also, juices from fruits with high flavonoid content, including blueberry, could improve the cognitive function in the elderly in the short term in some trials with a low sample size (≤15 participants).[3,95]

Garden strawberry (*Fragaria ananassa*) is a hybrid species in the genus Fragaria (strawberry plants). This fruit can reduce the risk of several diseases, including cardiovascular diseases, malignancies, inflammation, and hypertension. A study evaluated the effect of a diet with spinach or strawberry extracts on the F344 rats of 6–15 months of age using a control group receiving a control diet (AIN-93) because spinach and strawberry had high antioxidant capacity measured by vitamin E or oxygen radical absorbance capacity assay. The researchers intended to discover whether this diet could reverse the changes made by the aging process. Also, some initial animal studies showed that strawberries could be helpful for the aging brain. Finally, it was revealed that foods high in polyphenols and antioxidant biochemical in high doses could effectively the cognitive function in both humans and animals in both the long- and short-term.[3,94]

Raspberry is the fruit of the plants of the genus Rubus in the rose family. Most of them are in the subgenus Idaeobatus. Red raspberries are hybrids between *R. strigosus* and *R. idaeus*, while purple raspberries (also called blue raspberry in the Prince Edward Country, Ontario, Canada) are hybrids between black and red raspberries. This hybridization can even occur in the wild environment, such as in Vermont. Also, the hybridization of red raspberry with other species in the genus Rubus has yielded several new cultivars, such as loganberry, boysenberry, and tayberry. Yellow raspberries and other fruits with yellow color have a low amount of anthocyanins; however, they contain carotenoids such as lutein esters. In red raspberries, these biochemicals are covered by anthocyanins. The antioxidant biochemicals in berries have protective effects against Alzheimer's disease due to their ability to neutralize reactive oxygen species. In vitro studies have shown that polyphenols in berries could remodel the amyloid-beta accumulations, which is the primary process of cerebral damage in Alzheimer's disease. Also, blueberry could alleviate the inflammation of microglial cells through inflammatory mediator reduction.[3,96,97]

4.21 | Mint

Mint plants (genus Mentha) are well known for their aromatic and medicinal properties. The metabolites of nine species of this genus have been identified and include 47 hydrophilic, 17 hydrophobic, and 11 phenolic compounds, as well as carotenoids and riboflavin. This genus has significant antioxidant and radical scavenging properties with different degrees between the species. Park et al. showed that the mint plants had the highest

antioxidant capacity after testing antioxidant activity through hydrogen peroxide content, 1,1-diphenyl-2-picryl-hydroxyl (DPPH), and reducing antioxidant power (RAP) assays. However, the samples from nine different Mentha species were not significantly different in the multivariate analysis. The partial least squares method showed that the carotenoid (E-β-carotene, 9Z-β-carotene, 13Z-β-carotene, and lutein) and phenolic contents of the Mentha species in the extract as a good source of electron donors were positively correlated with reducing power.

4.22 | *Marrubium vulgare*

Marrubium vulgare (also called White horehound) is a plant from the mint family. It is used in traditional medicine for gastric disorders and appetite loss, and cooking as a spice.[98] This plant contains phenolic compounds and marrubiin, a labdane diterpene characteristic for the genus Marrubium. Studies have reported that *Marrubium vulgare* has remarkable antioxidant activity and can be used to treat malignancies, diabetes, and hepatic diseases with its anti-inflammatory, hypotensive, wound-healing, sedative, and lipid-lowering effects. Moreover, it has antimicrobial properties against gram-positive bacteria, herpes simplex virus, fungi, and parasites such as *Trichomonas vaginalis*, *Toxoplasma gondii*, and *Plasmodium berghei*. Therefore, there have been tendencies for the cultivation of this plant; however, further studies are needed to establish the use of this plant and its preparations.[99,100] Rezgui et al. investigated the anti-pathogenic, anti-dermatophytes, and antifungal effects of Marrubium vulgare in the forms of acetone extract, methanol extract, and essential oil on the different pathogens in animals and plants. They also investigated the antioxidant activity and chemical composition of these extracts, finding that acetone (272.90 μmol TE/g) and methanol (261.41 μmol TE/g) extracts had remarkable antioxidant activity, while essential oil had relatively low antioxidant activity. They evaluated the antifungal effects of these products at two concentrations (20 and 100 μg/ml) on different dermatophytes and fungi, including *Microsporum canis*, *Microsporum gypseum*, Trichophyton mentagrophytes, *Arthroderma cajetani*, *Botrytis cinerea*, *Trichophyton tonsurans*, *Pythium ultimum*, and *Epidermophyton floccosum*, and found that marrubiin with the concentration of 100 μg/ml had a 50% inhibitory effect on Trichophyton mentagrophytes and Epidermophyton floccosum. Moreover, marrubiin at the highest dose exerted anti-phytopathogenic activity against *Botrytis cinerea* (32.40%), and highly concentrated methanol extracts of marrubiin and *Marrubium vulgare* increased the growth of *Pythium ultimum mycelium* by 40.30% and 45.15%, respectively.[64,101]

4.23 | Citrus

Citrus fruits contain flavonoids such as naringin and hesperidin. Orange is a famous citrus fruit, making up almost 75% of all citrus fruits cultivated. The Queen Orange (*Citrus sinensis*), cultivated in Iran on large scale, is a midseason fruit with red color. It is rich in flavor and dissolved solids and is somehow seedless and grows on trees. The orange trees are highly prolific, strong, and immune to cold weather. A 100 g of orange pulp can supply the human body with 64% of the daily vitamin C recommended dose. Orange includes a variety of phytochemicals, such as carotenoids (e.g., beta-carotene, lutein, and beta-cryptoxanthin), flavonoids (e.g., naringenin), and several volatile organic substances responsible for the orange aroma, namely aldehydes, esters, terpenes, alcohols, and ketones. Antioxidant capacity of orange juices (OJs) from six varieties (Midknight, Delta Seedless, Rohde Red, Seedless, Early, and clone Sambiasi) was assessed by a cellular model (*Saccharomyces cerevisiae*) and chemical methods such as ferric reducing activity/antioxidant power (FRAP), Trolox equivalent antioxidant capacity (TEAC) and total phenols by Folin–Ciocalteu assay in the hydrophilic fraction (phenolic compounds and ascorbic acid). It has been reported that phenolic compounds and ascorbic acids were 370.04 $\pm$ 76.97 mg/L and 52.05 $\pm$ 6.69 mg/100 ml by Ultra Performance Liquid Chromatography (UPLC) and High-Performance Liquid Chromatography (HPLC) respectively.[102] It has also been revealed that ascorbic acid-rich orange- and yellow-colored fruits and vegetables including grapefruit, mango, yellow pepper, orange, banana, pear, nectarine, and pineapple have more antioxidants capacity than the fruits and vegetables rich in chlorophyll and carotenoid.[103]

Given the adverse effect of alcohol on the neurobehavior and embryonic development of the zebrafish larvae, Liu et al. evaluated the protective effects of these glycoside flavanones (naringin, hesperidin, and naringenin) on the developmental defects and thigmotaxis induced by alcohol in those larvae. Using behavioral tests, they found that acute exposure to 1% alcohol-induced thigmotaxis in zebrafish larvae 3 and 5 days after fertilization; however, these antioxidants could inhibit this behavior and reduce the alcohol-induced morphological defects and apoptosis if they are administered during its development.[3,96] Furthermore, a diet containing orange juice could improve the cognitive function of

healthy elderly in 8 weeks because it was rich in flavanone.[104,105]

5 | FLAVONOIDS

Flavonoids (Figure 1) are considered as very versatile compounds that have indicated photochemical properties and can protect beverages against light-inducing color deterioration.[106] Flavonoids, as natural compounds with a various phenolic structure, and as critical secondary metabolites, can be found in fruits, vegetables, grains, bark, roots, stems, flowers, tea, and wine.[26,107] These natural products have favorable consequences on the human health. As an indispensable part of nutraceutical, pharmaceutical, medicinal and cosmetic applications, they are attributed to their antioxidative, anti-inflammatory, anti-mutagenic, and anti-carcinogenic properties to regulate key cellular enzyme function. While mechanisms of flavonoids are still unclear, they are globally well-recognized for their broad spectrum of biological activity. Hence, the isolation, identification, characterization, and functions of flavonoids via modern chromatography and mass spectrometry are considerably important. Molecular docking and bioinformatics knowledge are required to predict flavonoids as potential drugs in preventing any chronic diseases.[107–110]

The antioxidant action mechanisms of flavonoids are as follows: (1) direct scavenging of ROS ability, (2) inhibition of ROS formation via the chelation of trace elements (e.g., quercetin with iron-chelating and iron-stabilizing properties), or inhibition of the enzymes in the free radicals production (e.g., glutathione *S*-transferase, microsomal monooxygenase, mitochondrial succinoxidase, NADH oxidase, and xanthine oxidase), and (3) activation of antioxidant defenses (e.g., upregulation of antioxidant enzymes with the radical scavenging capacity). These mechanisms can occur concurrently, for example, radical

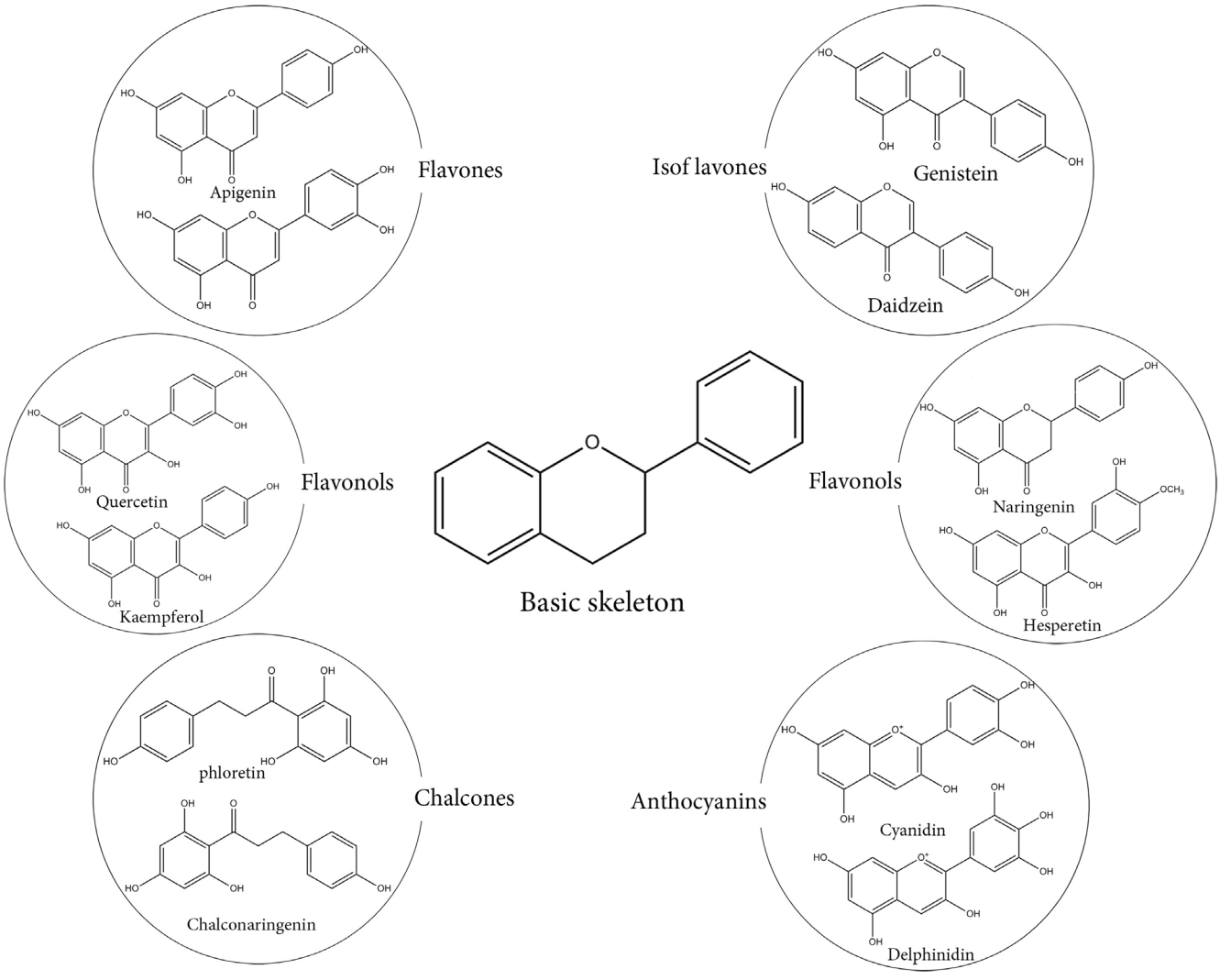

FIGURE 1 The basic structure and main classifications of the flavonoids

scavenging action with some suppressed enzyme functions. Many flavonoids are present as glycosides. The number and position of connections with the sugar influence the flavonoid antioxidant properties. While aglycone forms display a higher antioxidant capacity, a lower bioavailability exists.[106]

Flavanols that are known as flavonoids with a ketone group present abundantly in a variety of fruits and vegetables. The essential flavonols are kaempferol, quercetin, myricetin, and fisetin, and can be found in onions, kale, lettuce, tomatoes, apples, grapes, and berries.[107,111] They are health benefits because of their antioxidant potential and ability to reduce the risk of getting the vascular disease.[112] However, flavonols with a hydroxyl group have various methylation and hydroxylation patterns. Due to the different glycosylation patterns, it is assumed that they are the largest subgroup of flavonoids in fruits and vegetables.[107] For instance, many plant foods rich in quercetin as an antioxidant flavonol belonging to the flavonoid group show antiviral activity against several influenza virus strains. Quercetin has beneficial effects because of its anti-inflammatory, antihypertensive, vasodilator effects, antiobesity, antihypercholesterolemic, and antiatherosclerotic activities.[24,113] Quercetin can inhibit platelet aggregation and is advantageous for the health of the endothelium, and demonstrated a synergistic antiproliferative effect with cisplatin against in vitro cellular drug resistance in leukemia cells.[21] In addition to that, it has a protective action against coronary heart disease (CHD) and decreases the risk of mortality caused by LDL. Studies have reported that quercetin can prevent damage to LDL cholesterol due to its high flavonoids in food supplements. One of the research studies revealed that people who consume quercetin and an alcohol-free red wine extract containing quercetin inhibit LDL oxidation. Another study reported that using quercetin at 150 mg/day lowers the systolic blood pressure and plasma oxidized LDL levels in overweight patients who are prone to high risk of heart disease.[113]

As a natural flavone in many plants, Apigenin also has the potential therapeutic, antioxidant, anti-mutagenic, anti-carcinogenic, anti-inflammatory, and antiproliferative activities, and neuroprotective properties.[114] This bio compound is found in many fruits and vegetables, specifically in parsley, chamomile, celery, vine-spinach, artichokes, and oregano, and the richest sources are in dried forms.[115] Apigenin and luteolin can change ROS signaling and induction of apoptosis in various ovarian cancer cell lines (A2780, OVCAR-3, and SKOV-3).[111,116] The antitumor properties of apigenin have been recognized via the inhibitory activity of several cell proliferation regulating enzymes, nitric oxide inhibition, prostaglandin (PG) production, and selective apoptotic effects on tumor cells. Apigenin treatment restrained the expression of HDAC2, HDAC3, HDAC4, HDAC6, HDAC7, and HDAC8 in skin cancer.[117] In addition to this, apigenin has been able to suppress different human cancers in vitro and in vivo by multiple biological impacts, for instance, inducing cell cycle arrest triggering, cell apoptosis and autophagy, invasion, and suppressing cell migration, and stimulation of an immune response.[118] Considering the side effects and toxicity of current drugs such as life-threatening and long-term malignant infections, herbal compounds including apigenin as an extracting compound of plants play a key role in overcoming diseases such as Parkinson's, Alzheimer's, and different types of autoimmune disease.[114,119]

Another important bioactive molecule is luteolin, a flavonoid with beneficial impacts on cardiovascular protection and cataract prevention. Likewise, luteolin could suppress the DNA oxidative damage and have an antiviral effect on the reactivation of HIV-1. Luteolin metabolites are small molecules and have anti-inflammatory, antioxidant, anticancer, antimicrobial, antiulcer, anti-influenza, cytoprotective, hepatoprotective, neuroprotective, neurotrophic and neurogenesis activity, cardioprotective, and macrophage polarization effects, and free radical scavenging capacity.[120,121]

Flavone luteolin as one of the most prevalent natural polyphenolic flavonoid components, exists in several edible plants.[120] This bio compound is found in celery, broccoli, green pepper, parsley, thyme, dandelion, perilla, chamomile tea, carrots, olive oil, peppermint, rosemary, navel oranges, and oregano. Luteolin and its structural analog methoxyluteolin (3′,4′,5,7-tetramethoxyflavone) have also been offered to treat other neuropsychiatric diseases, such as multiple sclerosis amyotrophic, lateral sclerosis, and an autism spectrum disorder. This compound has numerous beneficial actions in "brain fog" that features some patients who have syndrome of COVID for a long time and patients who undertake or follow chemotherapy for cancer diseases.[122] Luteolin and related flavonoids are commonly safe. A luteolin formulation in olive pomace polyphenols extract has shown a practical approach for improving autism spectrum disorder.[81]

Alzheimer's disease (AD) is considered as the most common age-associated neurodegenerative disease, and because of the high metabolic activity, the brain regions such as the hippocampus are vulnerable to glucose and oxygen supply variations.[123] Brain inflammation could be achieved with natural molecules, specifically polyphenolic flavonoids. The flavone luteolin showed improvement of AD, and other disorders through various mechanisms, including inhibition of microglia activation, AchE133 inhibition, and prevention of Ab42 plaque formation,

inhibition of fibrillary β-amyloid-induced inflammation, decreasing zinc-induced tau phosphorylation, and inhibition of reducing mucin-type O-gycosylation of amyloid precursor protein. Therefore, it is resulted in increasing memory in rodent models that have AD. Thus, certain flavonoids, specifically luteolin which has been formulated in olive pomace oil, together with hydroxytyrosol, propose a promising prophylactic treatment approach.[81] Recent research showed that flavonoids could inhibit serine proteases, such as SARS-CoV 3CL, which is critical for viral infection. For the treatment of COVID-19, antiviral effects and inhibition of furin by luteolin have been suggested. Small natural flavonoid molecules affect the entry of coronavirus and its replication. Another research study performed by Duraisamy Kempuraj et al., in 2020, displays that mast cells are associated with COVID-19 and that luteolin suppresses inflammation such as neuroinflammatory response COVID-19-associated psychological stress effects. If certain plants are consumed that have high polyphenols/flavonoids, the risk of developing neuro-inflammatory disorders in risk groups is reduced.[120]

6 | PHENOLIC COMPOUNDS

6.1 | Absorption and pharmacokinetics

The liver is both involved in metabolism and detoxification and participates in innate immune function. While the liver has the exceptional ability to regenerate and totally recoup from the most acute, non-iterative situation, multiple conditions such as viral hepatitis, non-alcoholic fatty liver disease, long term alcohol abuse, and chronic use of medications cause permanent injury, leading to dysfunctional regenerative capacity resulting in hepatic scaring and cirrhosis.[124–126] Although advancements in medicine, and therapeutics have been able to resolve the concerns, hepatic diseases have remained major problems worldwide. Despite the introduction of many synthetic drugs as strong radical scavengers, the potential carcinogenic risks of these drugs have been reported that cause liver damage. Thus, plant-based medicine has been widely introduced such as Nexavar (sorafenib) as a chemotherapeutic medication for treating advanced renal cell carcinoma but associated with several side effects. Likewise, effective varieties of herbal preparation, including Liv-52, silymarin, and stronger neomin phages against hepatic complications, have been suggested.[125]

Phenolics are important secondary metabolite compounds and categorized into viz, phenolic acids, flavonoids, and lignin. Pears, grapes, apples, and a range of berries are the fruits that naturally showed reasonable amounts of polyphenols (250–400 mg in 100 g). Due to abundant antioxidants in polyphenol, they are considered natural scavengers for toxic elements. Therefore, their intake has been directly linked to a reduced frequency of several hepatic ailments, particularly hepatocellular carcinoma in humans. Phenolics demonstrate anti-inflammatory effects and influence hepatotoxicity and offer protection against oxidative stress via donation of hydrogen or electron to free radicals which aid in the stabilization of cell membrane networks and inhibition of the formation and expression of inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), transforming Growth Factor beta (TGF-β), and varieties of interleukins (IL-6, IL-2, IL-8).[125–127]

To implement any pharmacological actions, phenolic components are primarily absorbed in the gastrointestinal tract (GIT), making it bioavailable to the circulating system. If there is not adequate or no absorption via the GIT, undergoing biotransformation in the colon with the help of resident microbiota culture occurs. Through the GIT, gallic acid, and isoflavones with a small molecular weight are easily absorbed. In some cases, they are absorbed in a rate of 0.3–43% and a low metabolite content circulating in the plasma. As discussed, kaempferol and quercetin belong to flavonols and demonstrated several biological activities. However, low bioavailability as a consequence of low rate of absorption and water solubility, and high instability in alkaline and neutral media such as various organs, that is, colon, small intestine, kidney, and colon are among the reasons that phenolic compounds are not fully utilized as potential health promising compounds.[128,129]

Recent research reports on hepatic inflammation found that phenolics play a crucial role in protecting such inflammation. Phenolic components such as hesperidin act against inflammation through downregulating liver enzyme biomarkers, including aspartate aminotransferase (AST) and alanine aminotransferase (ALT) initially. It holds back oxidative stress and activation of T cells, which is considered a prime instigator of inflammation. Hesperidin, which is a common Citrus flavonoid, aids in the management of various proinflammatory recruiters viz; NF-κβ and α smooth muscle actin (α-SMA). Further well-known flavone, silymarin, and as a subclass of the family of phenolic compounds, helps patients with chronic hepatic carcinoma.[125,129,130]

6.2 | Phenol intolerance and potential treatment

Despite the advantages mentioned above, some patients are not allergic to phenolic compounds, but they are

unable to tolerate, or in some cases, a limited amount of phenolic compounds are tolerable. Exceeding phenolic compounds intake leads to the most common symptoms, such as skin problems, tinnitus, headaches, shortness of breath, as well as mood changes.[126]

Nowadays, plant-based enzyme inhibitors are highly recommended because of the acute side effects of synthetic pharmaceutical agents. Enzyme inhibitors can form an essential class of clinical drugs for cancer, cardiovascular disease, diabetes, neurological disorders, and obesity. Therefore, natural products are extensively paid attention to due to their bioactivity and therapeutic molecules contributing to discovering the drugs from natural product extracts.[127,131] For instance, salicylates are natural ingredients in many fruits, vegetables, and spices. Synthetic salicylates are used as the main ingredient in aspirin and other pain-alleviating medicine. However, a salicylate allergy (also referred to as salicylate intolerance or sensitivity) is a reaction that occurs when the human body is in contact with salicylates. Salicylic acids are phenolic compounds. Salicylate intolerance is considered as a non-specific antigen-induced pseudo-allergic hypersensitivity reaction to salicylic acid, its derivatives, or other related organic or inorganic acids with identical chemical structures. Salicylic acids are present in plant foods and have anti-inflammatory effects.[132,133] Acetylic salicylic acid (aspirin) intolerance correlates to varied metabolism of arachidonic acid and eicosanoids, and prostaglandins and leukotrienes ingestion of salicylates or cyclooxygenase-inhibitors. Salicylates and other anti-inflammatory drugs, specifically the non-steroidal anti-inflammatory drugs (NSAID) chiefly used in rheumatology, can inhibit cyclooxygenase (COX). This reduces prostaglandin synthesis. The patients who cannot tolerate salicylates showed the activation of basophils and eosinophils, macrophages, mast cells, platelets, and lymphocytes. These cells trigger the symptoms. The mechanism is that acetylsalicylate as a potent inhibitor of COX-1 is an isoform of the enzyme COX. This compound can prevent converting arachidonic acid to cyclic prostanoids, while salicylic acid can inhibit COX-2 gene expression.[132] So, COX-2 inhibitors can cause fewer gastrointestinal symptoms than COX-1 inhibitors (for instance, indomethacin or ibuprofen). It was reported that if there are any minor changes in chemical structure, substantial differences would observe in the degree of intolerance or sensitivity.[134]

7 | CONCLUSION

Due to various physicochemical conditions or pathological states, free radicals, reactive oxygen species, and reactive nitrogen species are produced. In this condition, oxidative stress ensues if free radicals are overproduced in the body. However, during normal metabolism, antioxidants including glutathione, ubiquinol, and uric acid begin to regulate the free radicals and delay or inhibit cell damage. To redress the imbalance between free radicals and antioxidants, external sources of nontoxic, natural antioxidants are recommended, which can neutralize the high level of free radicals and assist the human body. Since low-molecular-weight antioxidants can safely interact with free radicals, the chain reaction would terminate before further cell damage. Due to the contribution of oxidative stress to a wide range of diseases such as atherosclerosis, inflammatory condition, certain cancers, and the process of aging, almost all inflammatory diseases (arthritis, vasculitis, glomerulonephritis, lupus erythematous, adult respiratory diseases syndrome), ischemic diseases (heart diseases, stroke, intestinal ischemia), hemochromatosis, acquired immunodeficiency syndrome, emphysema, organ transplantation, gastric ulcers, hypertension and preeclampsia, a neurological disorder (Alzheimer's disease, Parkinson's disease, muscular dystrophy), alcoholism, smoking-related diseases, and many others, attempts should be made to decrease the number of free radicals in human cells.[135–137]

Today, natural compounds with antioxidant properties of various parts of herbs, namely oilseeds, vegetables, leaves, and roots of trees, spices, and seaweed have been utilized in pharmaceuticals and therapies since they can protect human cells from oxidative damage and have a strong potential for scavenging the free radicals. Natural products, plants, and fruits are introduced because of their biological activities, including antioxidant, antimicrobial, and anti-inflammatory effects. Especially recent studies demonstrated that flavonoids possess antiviral activity in some viruses, including SARS-CoV.[138] Although their beneficial role in many diseases, such as cancer, age-related brain diseases, aging, skin, atherosclerosis, Alzheimer's, and Parkinson's illnesses, have been reported in many research studies, greater attention should be paid to the development of extraction methods such as mass spectrometry and liquid chromatography for measurement of antioxidant activity in herbs. Fruits to implement in prevention and/or treatment of diseases.

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CONFLICT OF INTEREST

The authors have declared no conflicts of interest for this article.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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