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Review Article

Antioxidants from different citrus peels provide protection against cancer

Antioxidantes de diferentes cascas de frutas cítricas como agentes preventivos contra o câncer

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Abstract

Cancer is one of the leading causes of death. Despite significant advancements in the discovery of medications for the treatment of cancer, these drugs are hindered by applicability and efficacy issues and frequently exhibit major side effects that can further impair patients 'quality of life. Therefore, the development of therapeutically sound anti-cancer medicines derived from natural products has gained prominence in the field of functional foods. Some of these compounds have shown efficacy in the prevention and treatment of cancer as well as low toxicity. Additionally, many recent studies have explored the recycling of agro-industrial waste to create bioactive chemicals. Citrus peels are produced in vast quantities in the food processing sector; due to their abundance of flavonoids, they may be inexpensive sources of protection against several cancers. Citrus is a common type of fruit that contains a variety of nutrients. In particular, the antioxidant chemicals found in citrus peel have been identified as potential cancer-fighting agents. Antioxidant substances such as flavonoids prevent the development of cancer by inhibiting the metastatic cascade, decreasing the mobility of cancer cells in the circulatory system, promoting apoptosis, and suppressing angiogenesis. To explore the most effective uses of citrus peel-derived antioxidants, this review presents background information, an overview of the role of citrus antioxidants in cancer therapy, and a discussion of the key underlying molecular mechanisms.

Keywords: citrus peel, antioxidant compounds, flavonoids, nanoparticles, functional foods, anti-cancer.

Resumo

O câncer é uma das principais causas de morte. Apesar dos avanços significativos na descoberta de medicamentos para o tratamento do câncer, esses medicamentos são prejudiciais por questões de aplicabilidade e eficácia e frequentemente apresentam efeitos colaterais importantes que podem afetar ainda mais a qualidade de vida dos pacientes. Portanto, o desenvolvimento de medicamentos anticancerígenos, terapeuticamente adequados derivados de produtos naturais, ganhou destaque no campo dos alimentos funcionais. Alguns desses compostos demonstraram eficácia na prevenção e tratamento do câncer, bem como baixa toxicidade. Além disso, muitos estudos recentes exploraram a reciclagem de resíduos agroindustriais para criar produtos químicos bioativos. As cascas de frutas cítricas são produzidas abundantemente no setor de processamento de alimentos; devido à abundância de flavonoides, e são fontes baratas de proteção contra várias categorias de câncer. *Citrus* é um tipo comum de fruta que contém uma variedade de nutrientes. Em particular, os produtos químicos antioxidantes encontrados na casca de frutas cítricas foram identificados como potenciais agentes de combate ao câncer. Substâncias antioxidantes, como os flavonoides, previnem o desenvolvimento do câncer, inibindo a cascata metastática, diminuindo a mobilidade das células cancerígenas no sistema circulatório, promovendo a apoptose e suprimindo a angiogênese. Para explorar os usos mais eficazes dos antioxidantes derivados da casca de frutas cítricas, esta revisão apresenta informações básicas, uma visão geral do papel dos antioxidantes cítricos na terapia do câncer e uma discussão dos principais mecanismos moleculares subjacentes.

Palavras-chave: casca de frutas cítricas, compostos antioxidantes, flavonoides, nanopartículas, alimentos funcionais, anticâncer.

1. Introduction

Several commercial types of citrus fruit, including orange, grapefruit, and lemon, are thought to contain natural chemicals with a number of health advantages. Citrus is a member of the Rutaceae family. Citrus has long served as the foundation of widely used traditional remedies in several nations. Citrus fruits contain a variety

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of essential nutrients, including vitamin C, vitamin A, and several types of carotenes, as well as a large number of non-nutrient phytochemicals such as diverse flavonoid classes, glycerates, coumarins, monoterpenes, triterpenes, and phenolic acids (Gyawali and Kim, 2014). Citrus peels, byproducts of citrus manufacturing and valuable sources of polyphenols, have been shown to have anti-hyperglycemic properties (Fayek et al., 2017). Specifically, citrus flavonoids found in the flavedo and albedo, such as hesperidin, neohesperidin, and naringin, induced anti-hyperglycemic actions in HepG2 cells (Shen et al., 2012).Moreover, citrus fruits such as the pomelo [*Citrus grandis* (L) Osbeck] have been recognized as rich sources of flavonoids (Tocmo et al., 2020).

Recent research indicates that citrus consumption is linked to a lower incidence of all types of cancer. Citrus fruit and juice consumption appear to be inversely related to a lower risk of various infectious diseases, including malignancies, according to evidence from both experimental and epidemiological research.

2. Antioxidants

Antioxidants function by inhibiting the oxidation of other compounds. Early studies on the biological functions of antioxidants sought to use them to reduce the rancidity of unsaturated lipids. The discovery of vitamins A, C, and E, along with the knowledge of how vitamin E prevents lipid peroxidation, was at urning point in our understanding of antioxidant function in living organisms. Figure 1 displays the different antioxidant categories along with examples of each. These diverse compounds exhibit unique mechanisms of action, sites of action, and results. The network of inter connected antioxidant enzymes exhibits optimal antioxidant defense efficacy. Additionally, antioxidants such as vitamins, coenzymes, carotenes, and minerals neutralize reactive radicals. Natural sources of antioxidants are involved in free radical defenses but are unable to shield organisms from reactive oxygen species (ROS). Prokaryotes and eukaryotes alike are capable of creating bioactive substances (Flieger et al., 2021).

It has been previously demonstrated that the number of active groups, such as OH and NH_2 groups, is highly connected to antioxidant activity (Bendary et al., 2013). Importantly, antioxidants can function through a variety of mechanisms and repair many forms of cellular damage. Antioxidants can be divided into two categories, including primary, or chain-breaking antioxidants, and secondary, or preventative antioxidants (Madhavi et al., 1996). Primary antioxidants scavenge ROS (Bast and Haenen, 2013), whereas inhibition of xanthine oxidase (XO) and NADPH oxidase (NOX),as well as regulation of reductase-sensitive signal transduction pathways, are some of the specific actions of secondary antioxidants (Amarowicz and Pegg, 2019).

2.1. Nanoparticle (NP)-based approaches for the measurement of antioxidant activity

NPs have recently been used to measure antioxidant activity shown in Figure 2. This approach leverages the distinctive optical, electrical, and catalytic characteristics of metallic NPs (1–100 nm) (Baig et al., 2021).

Scampicchio et al. (2006) provided the first description of an NP-based approach for gauging antioxidant activity, the catalytic development of gold (Au) NPs mediated by phenolic acids. The resulting NPs appeared to be related to the antioxidant capacity of the phenolic acids. Specifically, the phenolic acids linearly affected the properties of the AuNPs and were measured with the Folin-Cicolteau spectrophotometric method. Additionally, Özyürek et al. (2012) measured the activity of polyphenols, made possible by the incorporation of silver (Ag) NPs. Silver ions were reduced with trisodium citrate to create the primary seeds. Antioxidants were then added as a second reducing agent, which reduced the Ag^+ ions in the silver seeds and increased the amount of Ag atoms deposited thereon, resulting in the formation of the final core-shell AgNP structures. AgNP growth onmonodisperse seed particles led to a linear,

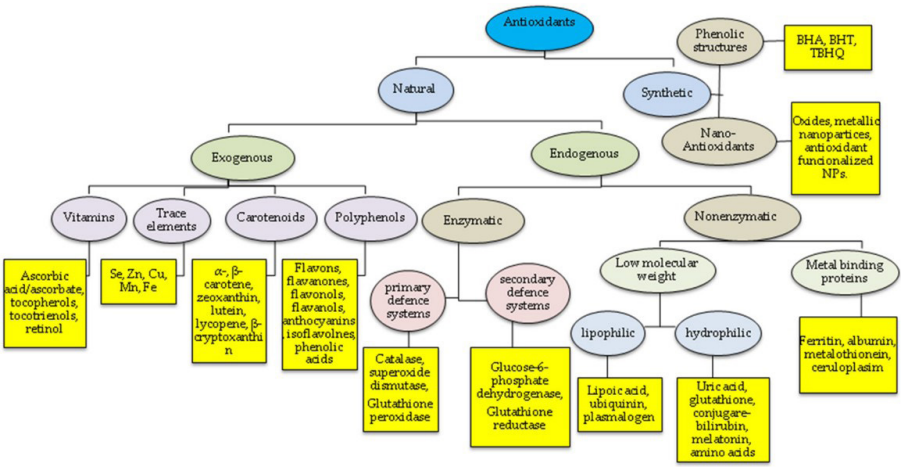

Figure 1. Classification of antioxidants.

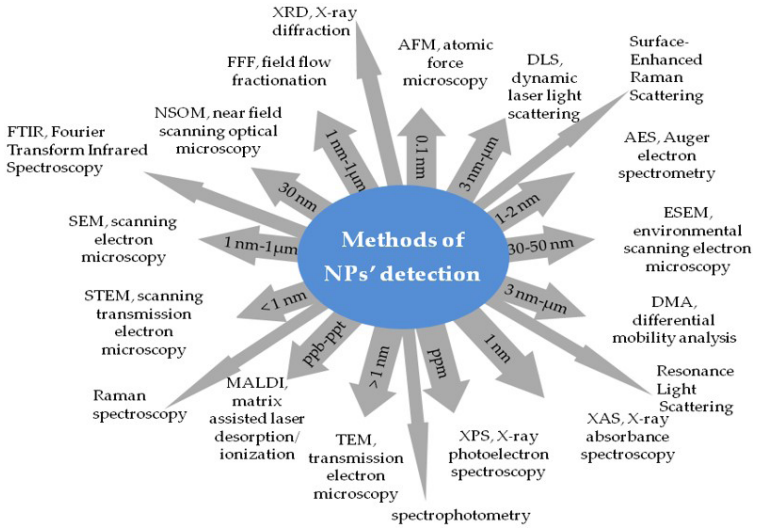

Figure 2. A selection of methods for quantifying and their associated detection limits (Hendrickson et al., 2011 and Mourdikoudis et al., 2018).

concentration-dependent rise in absorbance. This technique is called the "Silver Nanoparticles Antioxidant Capacity".

Until recently, the majority of the assays used to determine antioxidant capability included NPs with gold, silver, Fe_3O_4, quantum dots, or titanium; all are necessary for estimating antioxidant activity. The most widely used substance for this purpose is AuNPs. AuNPs exhibit a distinctive absorbance peak at 517 nm. AuNPs are also soluble and stable in a variety of solvents, including water, dichloromethane, and methanol. Because of the color of AuNPs, which is dependent on their size and shape, the refractive index of the dispersion medium, and interparticle interactions, NP production can be observed visually (Vasilescu et al., 2012).

2.2. Synthesis of NPs from natural antioxidant extracts

Numerous types of metallic nanoparticles are used in industrial and biomedical applications because of their distinctive physicochemical features (Boisselier and Astruc, 2009).In addition to natural extracts, several NPs, including carbon nanotubes, metals, their oxides, and different types of NPs possess antioxidant activity (Eftekhari et al., 2018).Iron nanoparticles have been applied in a variety of fields such as pharmacology, clinical diagnostics, therapy, analytical chemistry, bioprocesses, and industry, among others(Kumar et al., 2020a).

Unfortunately, hazardous reducing and stabilizing chemicals are frequently needed to synthesize NPs. These harmful materials adsorb on to NP surfaces, restricting their use in biological domains (Sharma et al., 2014).Thus, natural synthesis techniques, including the reduction of metal cations by plant extracts and microorganisms, are being exploited to produce nanomaterials. In the first stage of NP synthesis, metal ions are reduced. Subsequently, in the second step, the colloidal suspension aggregates form oligomeric clusters, resulting in the creation of NPs (Kumar et al., 2020b).So-called "green synthesis" is a rapidly developing, environmentally benign method for producing NPs. When compared to NPs manufactured using conventional procedures, those made using green synthesis techniques (Jessl et al., 2018). Electrostatic repulsion is primarily responsible for NP stabilization. Unfortunately, this type of stabilization works best with low-ionic strength extracts because the highly scattered double layer facilitates repelling. Strong van der Waals interactions play a role in aggregation when ionic strength is high (Boström et al., 2001). The installation of new barriers on the surfaces of NPs is another stabilization method. Proteins added to the extracts, as well as polymers applied to the surface (e.g., polyethylene glycol and polyvinyl pyrrolidone), impartsteric stability. The stages of NP formation and stabilization are illustrated in Figure 3.

3. The Antioxidant Components of Citrus

3.1. Vitamins in citrus and their antioxidant activities

Vitamins are organic chemicals that are essential for survival and physiological function. Six of the 13 vitamins, vitamins A, B1, B2, B3, C, and E, are present in citrus fruits (Zhou, 2012). Among these vitamins, vitamins A, C, and E, have been examined for their antioxidant properties (Amitava and Kimberly, 2014).

B-carotene is a vitamin A-class chemical substance that exhibits antioxidant properties by reacting with free radicals and peroxyl radicals (Amitava and Kimberly, 2014). Cryptoxanthin and carotenes are also abundant in citrus fruits. *Citrus sinensis* Osbeck, a candied orange, contains 0.27 mg/kg of vitamin A, whereas *Citrus reticulata* Blanco, a tangerine, contains 2.77 mg/kg (Zhou, 2012).

L-ascorbic acid, also known as vitamin C or ascorbate, is a water-soluble compound. It is an important vitamin present in citrus; it is abundant in both the flesh and peels, both of which have vitamin C in their extracts (Yu et al., 2005). Natural free radical scavengers such as vitamin C can efficiently remove several types of ROS, reduce sulfur, and clear O_2 (Amitava and Kimberly, 2014).

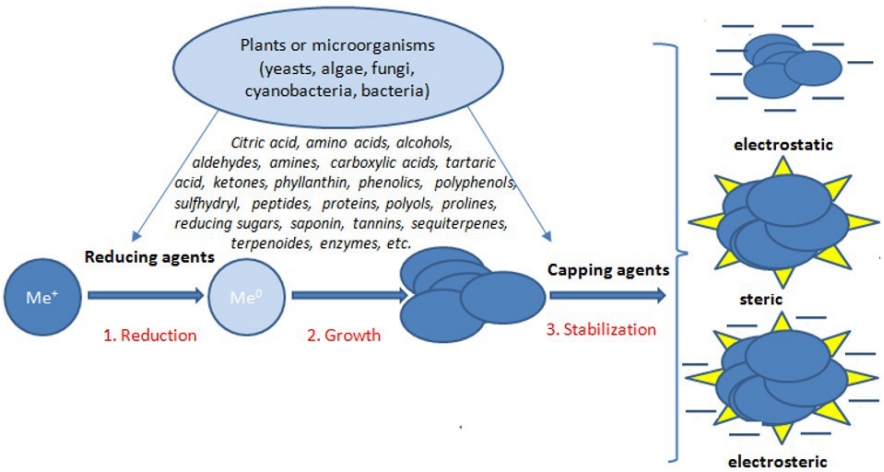

Figure 3. The mechanisms underlying the production and installation of metallic nanoparticles.

Tocopherols and tocotrienols are two lipid-soluble vitamin E molecules. Citrus fruits contain the highest concentrations of vitamin E in their peels and seeds. Vitamin E helps to shield cell membranes from damage induced by lipid peroxidation (Zhou, 2012).

3.2. Elemental minerals in citrus fruits and their antioxidant activities

With the exception of carbon, hydrogen, and oxygen, mineral elements are chemical components that plants absorb from soil that enable their growth and development. The chemical elements present in mammalian bodies are also present in citrus plants and have been linked to increases in a given organism's antioxidant capacity involved in (Amitava and Kimberly, 2014). For example, selenium (Se), a crucial component of the antioxidant enzyme glutathione peroxidase (GSH-Px), can neutralize free radicals in the cytoplasm and shield tissues from oxidative damage. Citrus fruit, tangerine, and lemon contain 0.31, 0.45, and 0.50 mg/100 g of Se, respectively (Zhou, 2012).

3.3. Enzymatic antioxidants

3.3.1. GSH-Px

The GSH-Px enzyme family catalyzes the oxidation of GS Hin the presence of a hydroperoxide, such as a lipid hydroperoxide or hydrogen peroxide, as follows (Equation 1):

$$ROH + 2GSH + GSSG + H_2O \quad (1)$$

These enzymes can also metabolize other peroxides, such as lipid hydroperoxides, and are thereby involved in the repair of lipid peroxidation-related damage. This enzyme exists in two different forms; Se and GSH are the most crucial antioxidative defense systems in cells. Humans possess four distinct Se-dependent GSH-Px enzymes, which provide two electrons to reduce peroxides. These antioxidant capabilities allow selenoenzymes to remove peroxides as potential substrates for the Fenton reaction. The tripeptide GSH, which is present in many cells, collaborates with Se-dependent GSH-Px to catalyze the conversion of organic or hydrogen peroxide to water or alcohol while oxidizing GSH. It is the primary defense against mild oxidative/nitrosative stress (Molavian et al., 2015).

3.3.2. Catalase

Catalase was the first antioxidant enzyme to be identified; it catalyzes the transformation of hydrogen peroxide into water and oxygen (Equation 2):

$$H_2O_2 \rightarrow 2H_2O + O_2 \quad (2)$$

The four subunits that comprise catalase each contain an NADPH molecule. The extremely high rate constant (~10^7 M/sec) for the aforementioned reaction suggests that it is difficult to achieve enzyme saturation in vivo. This enzyme is found in the peroxisomes of aerobic cells and converts six million molecules of hydrogen peroxide into water and oxygen per minute. Although all tissues contain some catalase, the liver and erythrocytes exhibit the highest activity (Sies, 2015).

3.3.3. Superoxide dismutase (SOD)

One of the most effective intracellular enzyme antioxidants, SOD, catalyzes the conversion of superoxide anion into dioxygen and hydrogen peroxide (Equation 3):

$$O_2^- + O_2^- + 2H^- \rightarrow H_2O_2 + O_2 \quad (3)$$

Subsequently, hydrogen peroxide can be eliminated with either catalase or GSH-Px. There are various isoforms of SOD that differ in terms of the type of active metal center, amino acid composition, and co-factors, among other characteristics. Humans express extra cellular, mitochondrial, and cytosolic SOD.SOD neutralizes superoxide ions by repeatedly undergoing redox cycles of its active site transition metal ion (Sheng et al., 2014).

4. Bioactive Compounds in Citrus

Peel, pulp, and seeds, collectively known as pomace, are produced in significant quantities as a result of domestic and industrial citrus fruit processing. Extensive research has been performed to extract commercially important chemicals from citrus fruit pomace (Yu et al., 2021).

Citrus peel contains a variety of bioactive substances with excellent antioxidant and health-promoting potential (Long et al., 2021), including essential oils (Singh et al., 2021), carotenoids (Saini et al., 2021), pectin (Nuzzo et al., 2021; Mahato et al., 2018), and flavonoids (El-Kersh et al., 2021). The primary flavonoids in citrus fruit peels include hesperidin, naringin, rutin, and neohesperidin (Abdelghffar et al., 2021). These compounds are found at particularly high concentrations in mandarins, which have significant antioxidant potency (Chen et al., 2021). Surprisingly, citrus fruit peels generally contain more antioxidants and polyphenols than pulp (Singh et al., 2020). As a result, it may be possible to recover these healthy compounds from citrus fruit peels. The orange peel is also a promising substitute for lignocellulosic biomass in the production of biofuels due to its low lignin content (Jeong et al., 2021).Bioactive citrus compounds, particularly polyphenols, vitamins, terpenes, and limonoids, have potential utility against obesity (Huang et al., 2020), inflammatory diseases (Denaro et al., 2021), atherosclerosis (Hu et al., 2021), neurodegenerative diseases (Piccialli et al., 2021), and cancer (Kitagawa et al., 2021) due to their antioxidant activity (Anacleto et al., 2020).

Flavonoids are polyphenolic secondary metabolites that are abundantly present in plants and contribute significantly to the antioxidant components of the human diet. Flavonoids directly scavenge free radicals, increase the activity of antioxidant enzymes in the body, and prevent peroxide production in vivo (Nakao et al., 2011). Citrus fruits contain significant amounts of flavanone-7-O-glycosides, flavones, and polymethoxylated flavones (PMFs) (Peng et al., 2021). PMFs contain more than two methoxy groups (-OCH_3) in their chemical structures (Zhang et al., 2019).Due to their anti-inflammatory (Rong et al., 2021), anti-atherosclerotic (Wang et al., 2021), anti-obesity (Zeng et al., 2020), and anti-cancer capabilities, PMFs have garnered increasing interest in recent years (Song et al., 2020).More flavonoids are found in the flavedo and albedo of citrus fruit than in the juice (Multari et al., 2020).

The bioactive substances found in citrus juices also have antiviral and anti-cancer activity. For example, hesperidin reportedly inhibits influenza virus replication and human cancer spread by inhibiting the pathway (Dong et al., 2014). Key proteases involved in coronavirus replication can also be inhibited by hesperidin, hesperetin, and naringenin, which prevent the virus from entering host cells (Tutunchi et al., 2020). Furthermore, the hydro-ethanolic extract of citrus peels contains flavonoids that exhibit antiproliferative properties against BT-474 human breast cancer cells (Ferreira et al., 2018).

A common class of isoprenoid pigments known as carotenoids is involved in signaling and photosynthesis (Saini et al., 2015). Carotenoids can be classified into one of two groups based on their chemical structures: the hydrocarbon carotenoids, known as carotenes, such as carotene and lycopene; and the oxygenated carotenoids, known as xanthophylls (Saini and Keum, 2018). Xanthophylls can be found in free and esterified fatty acid forms due to their oxygenated functional groups, but carotenes are only found in their free forms because of their simple hydrocarbon structures and lack of oxygenated functional groups. Xanthophylls in citrus fruits are frequently acylated with saturated and unsaturated fatty acids (Etzbach et al., 2020). Citrus fruit peel and pulp are orange-red due to the presence of carotenoids and apocarotenoids (Luan et al., 2020). The most abundant carotenoids in citrus fruits are carotenoid fatty acid esters (xanthophyll esters) (Etzbach et al., 2020). Xanthophyll esters and carotenoids are present depending on the maturation of and on other components in the citrus fruits (Etzbach et al., 2020). Carotenoids are more abundant in citrus fruit peel flavedo than in juice sacs, similar to phenolic chemicals (Multari et al., 2020). Unlike phenolic substances, however, carotenoid concentrations rise with maturation (Petry et al., 2019). Albedo also contains fewer carotenoids than phenolic chemicals; only minute quantities are present (Multari et al., 2020).

Substantial research has been performed to explore the anti-cancer properties of carotenoids (Saini et al., 2020). The antioxidant properties of carotenoids in the typical cellular milieu are well-established (Saini et al., 2015). However, carotenoidsmay also function as strong pro-oxidant chemicals that encourage ROS-mediated cancer cell death (Shin et al., 2020).

Because it contains terpenes, limonoids, polyphenolics, and vitamins, essential oil derived primarily from citrus fruit flavedo is a valuable commercial product (Raspo et al., 2020).Due to their naturally fruity scents, citrus essential oils are frequently employed in the cosmetic and food sectors (Mahato et al., 2019). In addition, citrus essential oils have strong antibacterial, analgesic, anxiolytic, and antioxidant properties (Ambrosio et al., 2019). The bioactive compounds in citrus essential oils are particularly well-known for their possible antibacterial capabilities; their ability to lyse bacterial cell walls and promote leakage of intracellular components ultimately results in cell death (Li et al., 2019).

Limonoids are tetracyclic triterpene secondary metabolite derivatives with high oxygen content. The antioxidant capabilities of different limonoids vary, with some being even superior to vitamin C (Zhou, 2012). Citrus limonoids have been shown to induce apoptosis, inhibit the proliferation of Panc-28 pancreatic cancer cells, and B-cell lymphoma-2 (Bcl-2) by increasing caspase-3 cleavage and lowering mitochondrial membrane potential (Murthy et al., 2021).

5. Mechanisms of Action of Citrus Peel Antioxidants

5.1. Suppression of proliferation

Cancer cells can multiply unchecked, resist apoptosis, and spread to distant regions of the body. It has been demonstrated that flavonoids in citrus peel extracts (CPEs)

prevent cell proliferation and oncoproteins. For example, CPEs suppressed cell growth and caused apoptosis in A549 human lung cancer cells (Nagappan et al., 2016). Flavonoids extracted from citrus peel also had similar inhibitory effects (Park et al., 2012). Quercetin, an aglycone-type flavanol that is present in fruits and green vegetables, is responsible for the effect of flavonoid compounds on cell proliferation. According to Liao et al. (2015), flavonoids have growth-inhibitory effects on a variety of cancer cell lines.

Nobiletin, tangeretin, quercetin, and sinensetin are PMFs that have shown antiproliferative effects on a variety of cancer cell lines. The antiproliferative effect of naringin is correlated with the prevention of cell growth and DNA synthesis (Kim et al., 2008). In addition, naringenin and hesperetin demonstrated potent antiproliferative activity against a variety of human cancer cell lines (Manthey and Guthrie, 2002). Furthermore, nobiletin, a significant PMF, exhibited cytostatic activity against MCF-7 cancer breast by primary oxidizing enzymes (Surichan et al., 2012). Additionally, nobiletin has demonstrated direct cytotoxicity against gastric cancer cells by inducing cell cycle deregulation (Rawson et al., 2014), and decreases the proliferation of colon cancer cells (Kunimasa et al., 2010).

Cell cycle advancement consists of four tightly regulated stages and cancer development is associated with cell cycle disruption. the coordinated interaction of cyclin-dependent kinases (CDKs) with their subunits results in the formation of active complexes that regulate the transition of cells from one phase to the next. CDK inhibitors control how active complexes are formed. Tumor burden can be diminished or eradicated by stopping the advancement of cells through the cell cycle (Foster, 2008).

Hong et al. (2017) found that a methanol extract from citrus fruit peel reduced phosphorylation in various cancer cell lines. Additionally, anethanolic extract from citrus peels suppressed A549 cell growth in a dose-dependent manner and triggered apoptosis (Adina et al., 2014).Furthermore, in colon tumor-bearing mice, Akt, Ras, ERK1/2, and E-cadherin were found to be responsible for the inhibition of growth signals (Moon et al., 2015).Treated animals had lower levels of catenin buildup in cell nuclei, which inhibited the activity of signaling pathways. Finally, in rats with colorectal cancer, oral CPEs substantially inhibited the enzyme ornithine decarboxylase, which regulates cell growth and proliferation (Lai et al., 2013).

5.2. Cell cycle inhibition

Cell cycle progression is halted by CPEs, which diminish or ablate cell proliferation signaling pathways in cancer cells (Chu et al., 2017). CPEs have been observed to affect MCF-7 breast cancer cells and human SNU-1 gastric cells (Moon et al., 2015). CPE at a concentration of 6 g/mL induced apoptosis (Adina et al., 2014). In human AGS gastric cancer cells, CPEs also induced cell cycle arrest by upregulating and down regulating cyclin B1, in turn modulating the cell division cycle (Hong et al., 2017). CPE, which primarily contains hesperidin and narirutin, also prevented prostate cancer cells from entering S-phase (G0/G1 cells were reduced by 2-3%, compared to a reduction of 12–18% in control cells) (Shammugasamy et al., 2019).

Tangeretin prevented the proliferation of estradiol-stimulated T47D cells and human colon cancer cells. Additionally, nobiletin altered the cell cycle of human gastric carcinoma, MCF-7 breast cancer, and HT-29 colon cancer cells (Wu et al., 2017), whereas hesperetin inhibited the activity of MCF-7 breast cancer cells by inducing aggregation. Moreover, tangeretin and nobiletin inhibited human colon and breast cancer cells, whereas naringin and apigenin stopped both androgen-insensitive PC-3 and androgen-sensitive human prostate cancer cell lines (Vue et al., 2016).

5.3. Inhibition of oxidant enzymes

The bioactive compounds in citrus fruits may exert their antioxidant properties by functioning as oxidant enzyme inhibitors (Figure 4, pathway 1). Oxidant enzymes are the primary producers of cellular ROS/reactive nitrogen species (RNS) and have important functions in the redox reactions of biological systems (López-Alarcón and Denicola, 2013). In addition, one of the primary mechanisms under lying the antioxidant activity of natural compounds is the suppression of XO. Hesperetin can directly reduce cellular free radical generation by inhibiting XO as discovered by Nakao et al. (2011). Additionally, according to Lin et al. (2008), coumarins can directly reduce cellular XO synthesis to reduce the formation of free radicals. As a result, polyphenols and other phytochemicals may bolster the antioxidant capacity of citrus fruits.

5.4. Interaction with redox signaling pathways

Citrus fruits may elicit their antioxidant effects by activating the transcription factor nuclear factor E2-related protein 2 (Nrf-2) and inhibiting nuclear factor kappa B (NF-κB) (Figure 4, pathway 2). These two molecules are crucial regulators of redox signaling pathways in the nucleus and cytoplasm, respectively (López-Alarcón and Denicola, 2013).

Endogenous oxidants, such as H_2O_2, act as second messengers and initiate a series of intracellular signaling events that encourage the production of antioxidants and detoxifying enzymes. In turn, these events control the equilibrium of cellular redox status (Forman et al., 2010).

The redox-sensitive transcription factor Nrf-2 is activated in the cytoplasm and translocates to the nucleus where it binds to antioxidant response elements in DNA. As a result, cytoprotective enzymes such as SOD, glutathione S transferase, and NADPH-quinone oxidase are upregulated (HO-1) (Eggler et al., 2008).

The NF-κB family is composed of a collection of inducible transcription factors that control immunological and inflammatory reactions and protect cells from dying from oxidative stress. NF-κB is kept dormant by interacting with inhibitory IκB proteins in the cytoplasm. However, in response to inflammatory stimuli such as oxidants, the proteasome rapidly degrades IκB proteins, releasing NF-κB proteins into the nucleus where they bind to specific DNA sequences and stimulate the production of pro-inflammatory and anti-apoptotic genes (Renard et al., 2000). Phytochemicals that lower NF-kB synthesis and/or limit its activation impede its nuclear translocation and the resulting activation of pro-oxidant genes.

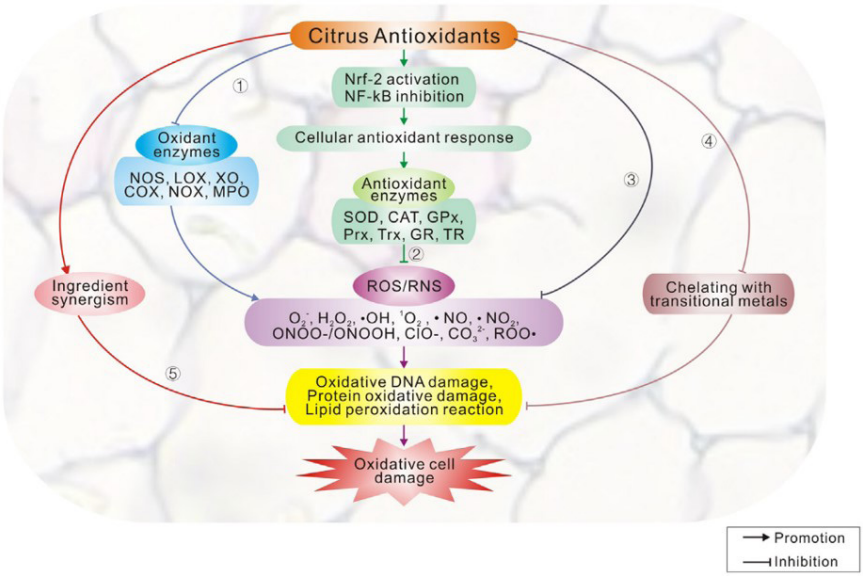

Figure 4. The likely antioxidant mechanisms of action of citrus fruits. There are five possible pathways by which the reduction of oxidative damage can be achieved: (1) inhibition of oxidizing enzymes, which reduces cellular production of ROS/RNS; (2) interaction with redox signaling pathways, which activates cellular antioxidant responses; (3) direct reaction with ROS/RNS as "free radical scavengers"; (4) chelation of transitional metals; and (5) synergistic interaction of the ingredients, which influence the whole antioxidant system. Oxidant enzymes that produce ROS/RNS: NOS (nitric oxide synthase), LOX (lipoxygenase), XO (xanthine oxidase), COX (cyclooxygenase), NOX (NADPH oxidase), MPO (myeloperoxidase). Antioxidant enzymes: SOD (superoxide dismutase), CAT (catalase), GPx (glutathione peroxidase), Prx (peroxiredoxin), Trx (thioredoxin), GR (glutathione reductase), TR (thioredoxin reductase).

6. Medicinal Properties of Citrus

Citrus fruits with high levels of bioactive chemicals include mandarin, pomelo, orange, lime, lemon, and grapefruit (Darband et al., 2018). These fruits contain bioactive substances such as flavonoids, dietary fiber, folate, and vitamin C in both the pulp and peel. While flavonoids are abundant in many fragrant plants, including mint and tea, they are concentrated in citrus fruits and their peels (Wang et al., 2018). Because citrus peel contains vitamins, volatile oils, pectin, and different natural antioxidant chemicals, it has strong potential as a source of therapeutic ingredients (Tsitsagi et al., 2018).

Epidemiologic studies have demonstrated that a diet high in citrus and vegetables may lower cancer risk by 20% (Cirmi et al., 2016). Indeed, the Mediterranean diet contains abundant citrus, fiber, and natural green polyphenols, which are associated with lower cancer risk (Smeriglio et al., 2019).

Citrus peels have been used medicinally since the 10th century, but only recently have the biological activity of particular compounds been defined (Gómez-Mejia et al., 2019). Polyphenolic chemicals, which are secondary plant metabolites with a variety of vital biological roles, are abundant in citrus peels (Rafiq et al., 2018).

Numerous bioactive substances, such as antioxidants, limonoids, coumarins, essential oils, tannins, lignans, and vitamins, are considered polyphenols (Abudayeh et al., 2019).Citrus peel polyphenolic compounds appear to be important bioactive components, especially in terms of their anti-cancer potential and protection against the risk of viral infection and degenerative diseases (Kim et al., 2017). Although the identification of specific compounds with strong anti-cancer properties is important, accumulating evidence points to the synergy of bioactive chemicals in CPE. Specifically, the anti-cancer activity of whole CPEs is often higher than that of fractionated extracts. In addition, higher levels of total polyphenols are linked to CPE methanolic extracts (Azman et al., 2019).

7. Anti-cancer Compounds

Anti-cancer compounds are generally defined as substances or agents that have strong anti-cancer effects or the ability to stop the spread of cancer. Approximately 174 anti-cancer chemicals have been commercially approved since the 1980s, with 53% (93 medicines) being derived from natural sources (Amaral et al., 2019). Accordingly, anti-cancer substances are often divided into two categories: chemical compounds and natural compounds.

7.1. Chemical compounds

During chemotherapy, substances such as alkylating drugs (e.g., cisplatin), anti-metabolites, and antibiotics typically impact both proliferating cancer cells and healthy cells. Most chemical cytotoxic agents target the skin (hair follicle cells), gonads (sex organs), gastrointestinal system, bone marrow, and other organs, and all have serious adverse effects (Chan and Ismail, 2014). Additionally, their oral route of administration, low water solubility,

acute side effects, and short half-lives limit the utility of these conventional medications (Khan and Gurav, 2017).

7.2. Natural compounds

Fruits, vegetables, green tea, cocoa, and other foods contain polyphenolic substances called flavonoids. It has been demonstrated that certain flavonoids have a variety of anti-cancer actions (Kopustinskiene et al., 2020). Genistein, an isoflavone (4,5,7-trihydroxyisoflavone), is one example of such a flavonoid (Figure 5). Dietary sources of genistein include soy products (e.g., soybeans), dates, and raisins (Forslund and Andersson, 2017). Notably, prostate cancer in men and breast cancer in women are less prevalent in Asian nations, particularly Japan and China, than in western nations such as the United States. This is due to the higher consumption of soy products in these Asian nations, which are the best sources of genistein. Importantly, genistein has anti-cancer effects on additional cancer types as well (Spagnuolo et al., 2015). Genistein slows the spread of cancer by inducing apoptosis, hallmarks of which include formation of cell membrane blebs, fragmentation of cellular DNA, reductions in cell attachment, alterations in the morphology and structure of cells, and cytoplasmic contraction, among other harmful biological changes (Figure 5) (Hsiao et al., 2019).

Genistein promotes cancer cell apoptosis in a number of ways. For example, caspases such as caspase-3 and caspase-9, which are crucial for apoptosis, are induced by genistein (Shafiee et al., 2016). In addition, genistein caused apoptotic cell death in colon cancer cells in vitro by blocking the NF-κB pathway, which controls the expression of pro-inflammatory genes (Zhou et al., 2017). Moreover, in breast cancer cell lines, the combination of genistein and equol, a bioactive metabolite of daidzein, increased the levels of Bax, a pro-apoptotic protein. This combination also reduced the levels of Bcl-2, an anti-apoptotic protein, the primary function of which is to compete with Bax (Ono et al., 2017). Furthermore, genistein impacted the endoplasmic reticulum (ER) of melanoma cells by modulating the p38 mitogen-activated protein kinase signaling pathway, which is activated in response to stress stimuli. Specifically, genistein induced apoptosis by upregulating glucose-regulating protein 78, a molecular chaperon involved in protein folding related to C/EBP (Heo et al., 2018).

Various inflammatory mediators are typically required for the proliferation of cancer cells. In one in vitro study of HaCaT human keratinocytes, genistein inhibited tumor necrosis factor (TNF)-induced NF-κB translocation (Smolińska et al., 2018) .It also reduced the phosphorylation of IB kinase and stimulated the activation of caspase-8 by encouraging the binding of Fas/TNF, a death receptor, to Fas ligand/TNF receptor 1, in turn eliciting apoptotic responses (Tuli et al., 2019).

Natural chemicals are those derived from plants, microorganisms, or animals. These naturally occurring chemicals offer an intriguing mechanism by which to create new cancer treatment options. Interestingly, medicines made from natural substances such as paclitaxel/Taxol, vinblastine, vincristine, camptothecin, and podophyllotoxin, among others, are effective against cancer. In fact, small molecules and naturally derived products account for

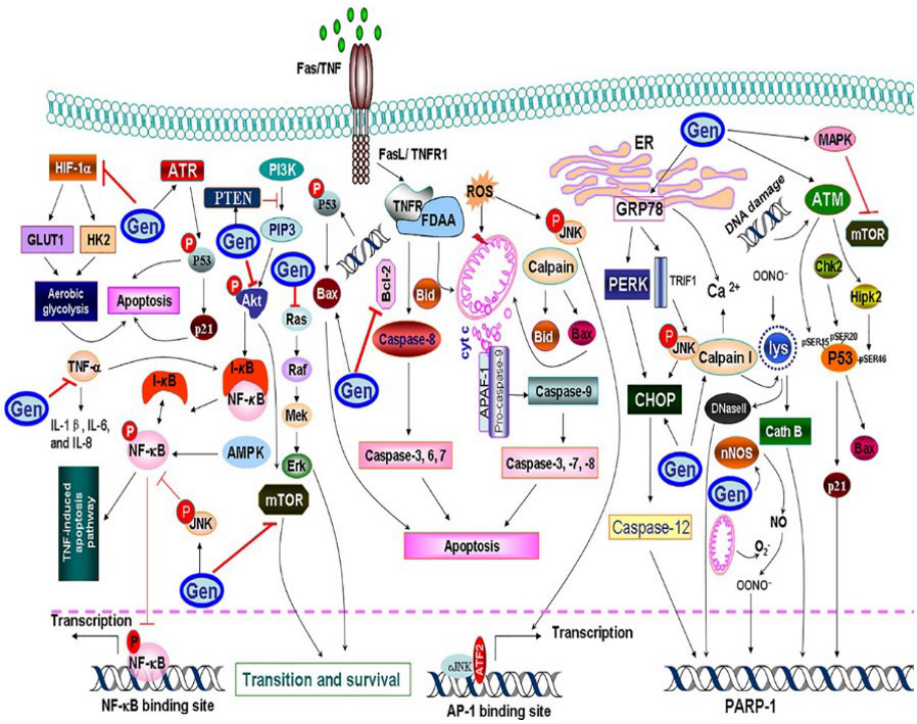

Figure 5. The mechanism by which genistein induces apoptosis in cancer cells (Tuli et al., 2019).

approximately half of approved medications (Khan and Gurav, 2017).

Commercially available anti-cancer pharmaceuticals are roughly divided into the following categories according to their mode of action: alkylating agents, anti-metabolites, anti-tumor antibiotics, hormone antagonists, natural therapies, and other drugs (Figure 6) (Taskin-Tok and Gowder, 2014).These substances are divided into three major classes based on their metabolic origins: phenolics, terpenoids, and nitrogen/sulfur-containing chemicals (Kumar et al., 2015). Vincristine, paclitaxel, curcumin, and betulinic acid are examples of anti-cancer secondary metabolites that are currently in use and undergoing clinical trials (Seca and Pinto, 2018). Every year, numerous novel cytotoxic secondary metabolites are discovered as potential anti-cancer agents. As a result, altering the structures of these chemicals can offer a cutting-edge method for increasing the specificity of anti-cancer drug activity (Guo, 2017).

8. Anti-cancer Mechanisms of Action of Bioactive Compounds

8.1. Anti-cancer activities of naringin and naringenin

Flavanones, including naringin and naringenin, have been studied for their capacity as anti-cancer agents. The anti-carcinogenic action of flavanones is mediated by a number of cellular signaling mechanisms. The combination of naringin and naringenin with other anti-cancer medications has recently gained popularity and shows synergistic effects compared to monotherapy. Memariani et al. (2021) demonstrated that naringin and naringenin can prevent therapeutics resistance, one of the largest obstacles to cancer therapy. Metastases are less likely to develop when signal transduction pathways and mediators such as vascular endothelial growth factor (VEGF), focal adhesion kinase/protein tyrosine kinase 2, matrix metal loproteases, and Zxb1 are inhibited. VEGF can decrease the blood supply to cancer cells. Numerous tumor types can also form in the context of epidermal growth factor receptor (EGFR) over expression. Interrupting EGFR signaling can halt the growth of EGFR-expressing malignancies. According to Zhao et al. (2019), naringenin prevented breast cancer cells from migrating by halting the cell cycle. Additionally, the successive activation of caspases is essential for mechanisms of cell death (Figure 7). As a result, these flavanones may have the potential to be used as complementary therapies for the prevention and cure of various malignancies.

8.2. Effects of naringin and naringenin on inflammation

Inflammation is the primary adaptive defense mechanism against infection and injury (Tu et al., 2017). TNF, interferon (IFN), NO, and prostaglandins (PGs) are produced by macrophages during inflammation (Li et al., 2014a). Atherosclerosis, rheumatoid arthritis, asthma, pulmonary fibrosis, and septic shock are inflammatory disorders exacerbated by the overproduction of these cytokines and anti-inflammatory mediators (Maleki et al., 2019). When macrophages are stimulated by pathogens and host-derived molecules such as lipopolysaccharide and IFN, inflammatory mediators such as NO, PG-E2, ROS, inducible nitric oxide synthase, and cyclooxygenase-2 are released. Human macrophage activity can be modulated by naringin and naringenin, which reduce inflammation (Liu et al., 2022). When using anti-inflammatory compounds to treat disease, inhibition of these inflammatory mediators is

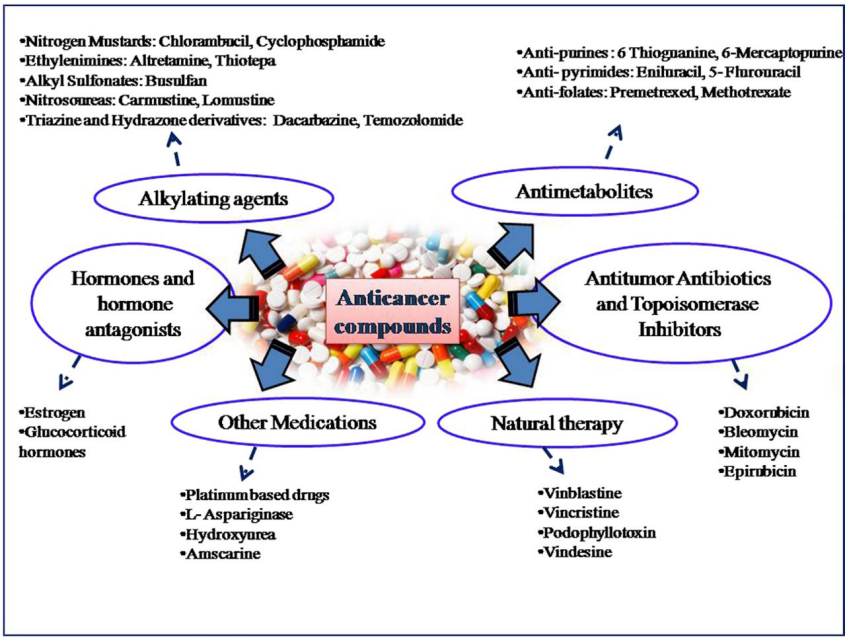

Figure 6. Classification of anti-cancer compounds.

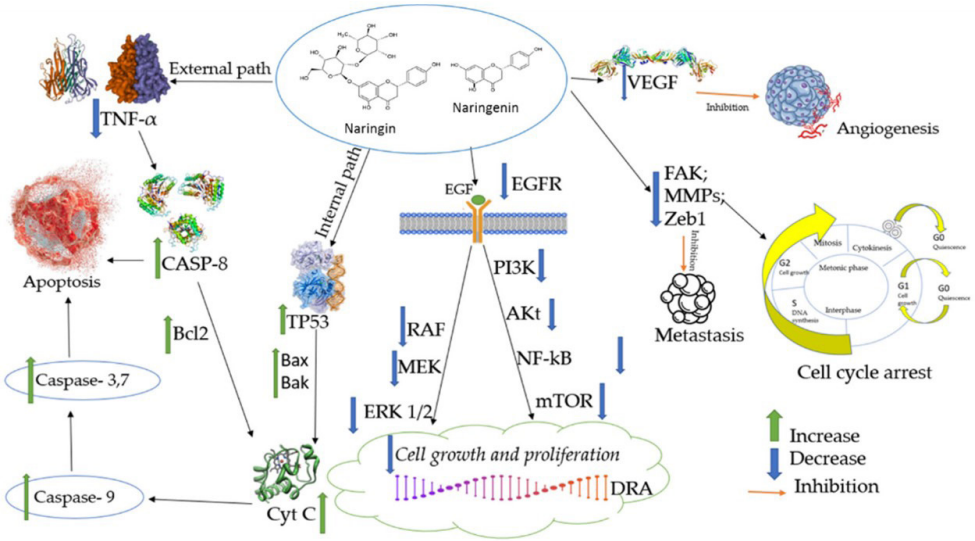

Figure 7. Effects of naringin and naringenin on cancer.

crucial (Kumar and Abraham, 2017). Furthermore, chronic tissue inflammation and associated genomic changes can lead to diseases like cancer, hyperglycemia, heart diseases, immune system disorders, and neurodegenerative diseases. Patients require less toxic and more affordable treatment options because existing treatments for many chronic diseases can have even greater impacts than the diseases themselves.

Since antiquity, flavonoids and flavonoid-containing medicines have been utilized to treat a variety of human ailments (Ginwala et al., 2019).Growing scientific evidence points to the potential anti-inflammatory capacities of polyphenolic natural chemicals (Li et al., 2020). The flavanones naringin and naringenin reduce inflammation in a variety of ways, including by inhibiting regulatory enzymes (Kampschulte et al., 2020), altering the metabolism of arachidonic acid (Escribano-Ferrer et al., 2019), regulating gene expression (Dayarathne et al., 2021), and influencing transcription factors that are crucial for regulating mediators of inflammation (Arafah et al., 2020). Strong antioxidants such as naringin and naringenin can also neutralize free radicals and prevent their production (Yu et al., 2005). They also exert a sizable effect on the immune system, which is a crucial component of inflammatory processes (Figure 8).

9. Antioxidant Therapeutic Strategies in Cancer

Cancer is one of the leading causes of death. Cytotoxic chemotherapy, which is frequently employed, inhibits or kills cancer cells. Substances with anti-cancer activity are derived from synthetic or natural sources (with plant or microbial origins). Plant-derived secondary metabolites recognized for their anti-cancer activities high light the diverse role of plants in the medical field. As a result, efforts to identify and produce new anti-cancer medications for commercial purposes are intensifying and have become a main focus in the industry (Patel et al., 2022).

Figure 9 observed that ROS play a significant role in cancer, controlling ROS levels is a viable anti-cancer therapy. Eliciting oxidative damage and ROS-dependent cell death may prevent the development and spread of ROS-induced cancer (Forman and Zhang, 2021). Therefore, Figure 10 showed the pre-clinical and clinical studies have investigated a variety of antioxidants and mild pro-oxidants. Cancer cells can produce ROS through the aforementioned mechanisms; thus, these cells are more vulnerable than healthy cells to increases in ROS. Pro-oxidants may therefore have anti-cancer properties (Bajor et al., 2018). Additionally, weak pro-oxidants may also play a significant role in antioxidant therapy by increasing internal antioxidant capacity. However, further research is still needed on the use of mild pro-oxidants in this context. In general, antioxidant therapeutic approaches in cancer can be divided into two groups: those that target ROS with non-enzymatic antioxidants, such as NRF-2 activators (Schmidlin et al., 2021) and vitamins (Bakalova et al., 2020), and those that target ROS with enzymatic antioxidants such as NOX inhibitors (Peskin et al., 2021), SOD mimics (Batinic-Haberle et al., 2018), N-acetyl cysteine, and GSH esters (Wu et al., 2019).

10. The Biological Basis for Antioxidant Therapy

According to Galan-Cobo et al. (2019), ROS area group of highly reactive free radicals that includes hydroxyl radical (OH^-), superoxide radical (O_2^-), and H_2O_2. Oxidative stress caused by elevated intracellular ROS levels increases the ability of antioxidants to maintain redox homeostasis by redirecting metabolic or activating genetic pathways. Redox homeostasis is disrupted in a number of human disorders, including cancer. Treatment with antioxidants stops carcinogenesis and slows the spread of cancer. It is well-established that the equilibrium of ROS creation and removal maintains redox homeostasis. As a result, herein,

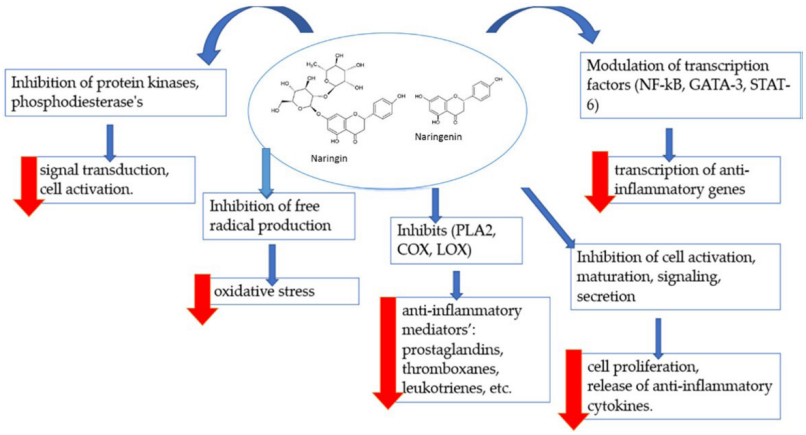

Figure 8. Anti-inflammatory mechanisms of flavonoids.

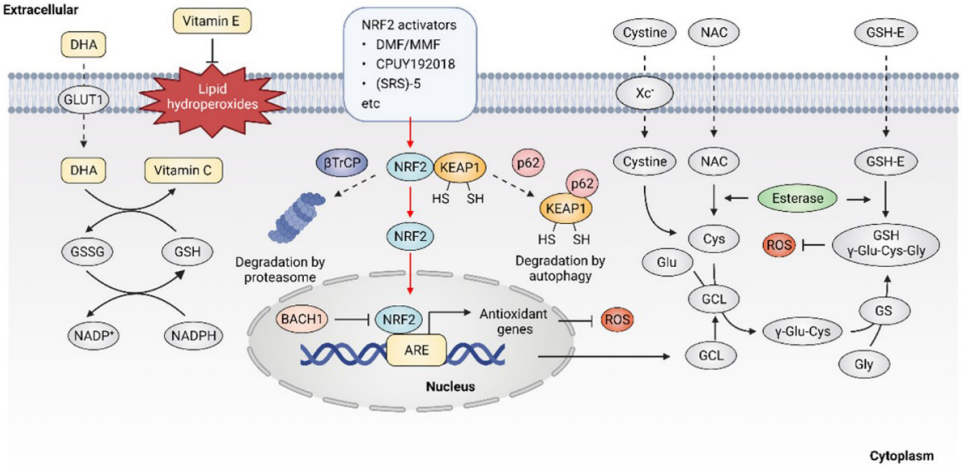

Figure 9. Using non-enzymatic antioxidants to target ROS. Glucose transporter 1 facilitates the intracellular uptake of vitamin C, which is then reduced. Cell membranes contain vitamin E, which protects against lipid hydroperoxide. The KEAP1-NRF-2 interaction may be disrupted by NRF-2 activators, thereby activating antioxidant genes downstream of NRF-2. GSH is made from cysteine, glutamate, and glycine. Supplementation encourages the formation of GSH and protects against excessive ROS.

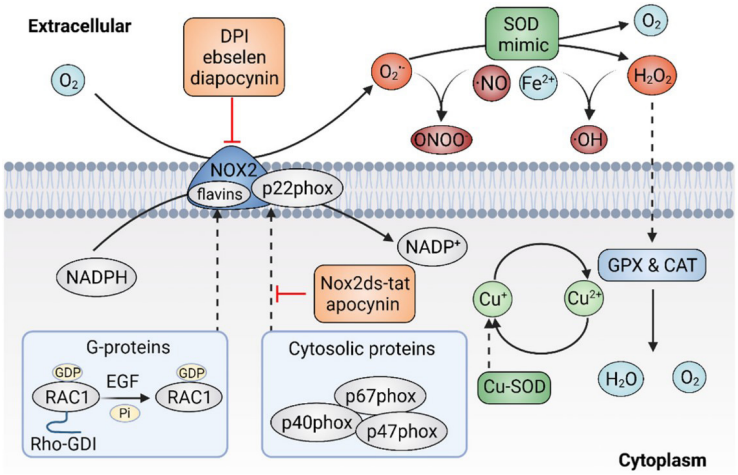

Figure 10. Using enzymatic antioxidants to target ROS. Superoxide (O_2^-) generation can be inhibited by plasma membrane NADPH oxidase 2 (NOX2) inhibitors, whereas O_2^- can be converted to hydrogen peroxide by superoxide dismutase (SOD) mimics.

we outline the fundamental mechanisms that control cellular redox homeostasis (Figure 11).

The diverse oxidases of the mitochondrial electron transport chain (ETC) (Schofield and Schafer, 2021), ER (Cantoni et al., 2021), and peroxisomes (He et al., 2021) are particularly important for ROS production in response to intracellular signaling and external stimuli. The mitochondrion, a highly dynamic organelle, produces ROS via the ETC, a series of proteins positioned on the mitochondrial inner membrane (Nolfi-Donegan et al., 2020). The metabolism of glucose, fatty acids, and amino acids is linked to the formation of mitochondrial ROS, in turn producing metabolic substrates that feed into the ETC (Dambrova et al., 2021). The formation of ROS in the mitochondrial ETC is believed to occur from electron leakage from complexes I, II, and III. One electron is used to reduce oxygen in this process, producing $O2^{-}$, which is contested to be H_2O_2 (Marin et al., 2020). The concentration of the single electron donor is the main determinant of the rate of ROS formation in the mitochondrial ETC. Furthermore, the main function of NOXs is the production of reactive oxygen species, which are activated by a range of conditions and associated with the growth of tumors (Zhang et al., 2020).They do this by delivering electrons to molecular oxygen in different cellular locations (Magnani and Mattevi, 2019).The development of cancer may be accelerated by NOX-derived ROS that activate secondary oxidase systems (Dang et al., 2020).The ER serves as a protein-folding facility and is crucial for cellular physiology (Wadgaonkar and Chen, 2021). Correct protein conformation and post-translational modifications are supported by the oxidizing site in the ER (Bibli and Fleming, 2021).

11. Anti-cancer Activity of Citrus Peel

Uncontrolled cell division and development are hallmarks of cancer. The abnormal energy metabolism of these cells is thought to require glucose as a metabolic substrate. Oxidative stress and its effects, such as DNA alterations and the development of cancer, can be avoided by consuming foods high in antioxidants, phenolic compounds, and antioxidant phytochemicals. Citrus flavonoids are thought to be relatively non-toxic compounds that can modulate tyrosine kinases, which control apoptosis and have antiproliferative properties. Flavanones have also been shown to decrease tumor development and cell cycle arrest, and induce cancer cell apoptosis is via death receptors and mitochondria-associated caspase-dependent pathways (Hwang et al., 2012). The inhibitory effect of citrus flavonoids on oral carcinogenesis in rats was examined by Aranganathan et al. (2008). This study revealed that naringin and naringenin had the ability to prevent various cancer types. Currently, essential oils are also recognized as anticarcinogenic substances. Additionally, it has been confirmed that dietary fiber and vitamin C have positive impacts on cancer prevention and treatment (Moon et al., 2013). Furthermore, flavonoids in CPEs caused human leukemia cells to undergo apoptosis by inhibiting protein kinase B. (Han et al., 2012). The same fruit extract also caused A549 lung cancer cells to undergo cell cycle arrest and apoptosis (Park et al., 2012). Altogether, flavonoids derived from citrus extract had comparable impacts on various cancer cell lines (Nagappan et al., 2016). Finally, although the typical concentrations of flavanones in oranges are not high enough to induce cancer cell apoptosis, they may still be able to ward off the disease (Nagappan et al., 2016).

According to Ianoși et al. (2019), proper management, early detection, accurate diagnosis, and adherence to nursing standards are all necessary for effective cancer treatment. Natural treatments based on bioactive cytotoxic chemicals and complementary alternative medicines (CAM) are beneficial for cancer prevention because chemotherapy has serious adverse effects (Semwal et al., 2022). Cancer patients in the United Kingdom have

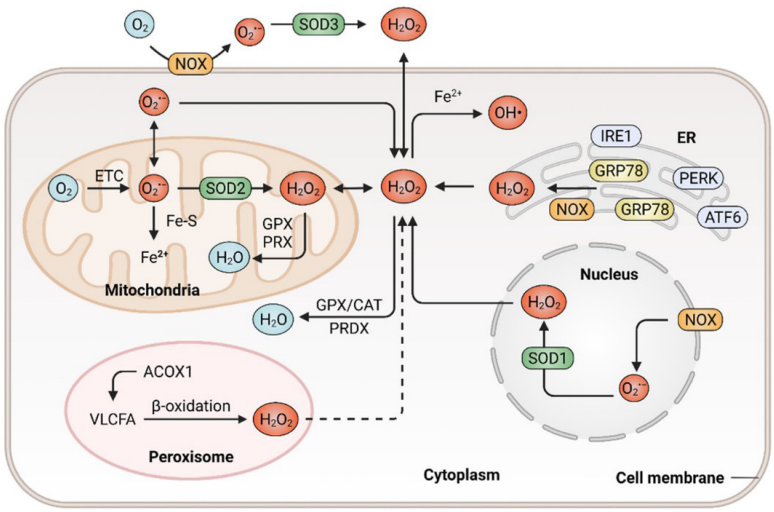

Figure 11. ROS production and removal in mammalian cells. NADPH oxidase (NOX) produces ROS either extra- or intracellularly, such as in the mitochondrial electron transport chain (ETC). Antioxidant systems hydrolyze H_2O_2 to H_2O in the cytosol or mitochondria.

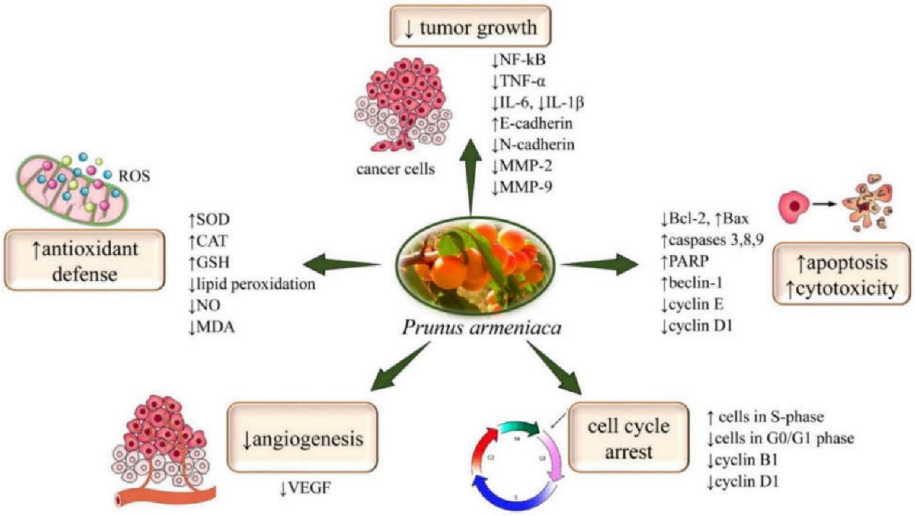

Figure 12. Diagram illustrating the putative anti-cancer effects of *P. armeniaca* bioactive substances (cell cycle arrest, apoptosis, cytotoxicity, and angiogenesis).

reported using CAM products derived from apricots (Zavery et al., 2010). Moreover, according to Quetglas-Llabrés et al. (2022), bioactive compounds can boost resistance to a particular infection and show anti-cancer effects either by directly suppressing angiogenesis or doing so indirectly. This process prevents the growth of tumor cells or metastases. The most prominent mechanisms influencing the anti-cancer activity of *P. armeniaca* L. are shown in Figure 12.

Flavanones and PMFs derived from citrus possess intriguing pharmaceutical qualities, including cancer protection (Bocco et al., 1998). Numerous recent studies have revealed links between dietary flavonoids and their potential therapeutic uses in cancer treatment. For example, Jagetia et al. (2003) showed that flavonoids have anti-mutagenic characteristics, shielding DNA from oxidative damage and dissipating mutation-causing free radicals. Other research suggests that flavonoids may have antiproliferative properties (Tripoli et al., 2007). For example, hesperetin consumption suppressed proliferating cell nuclear antigen expression and inhibited aromatase-positive MCF-7 tumor growth in ovariectomized athymic mice (Li et al., 2014b). Naringenin also exhibited anti-mutagenic properties in human prostate cancer cells, triggering DNA repair after oxidative damage (Gao et al., 2006). Additionally, didymium, a common dietary glycoside flavonoid also known as neoponcirin, has recently been shown to exert antiproliferative effects in breast cancer (Hsu et al., 2016). Furthermore, tangeretin and nobiletin showed anti-angiogenic properties by blocking angiogenic differentiation and imposing cell cycle arrest in breast and human colon cancer cell lines, respectively (Alshatwi et al., 2013). Thus, several studies have shown that flavonoids can prevent the spread of cancer by suppressing the metastatic cascade, inducing apoptosis, inhibiting the cell cycle, and decreasing cancer cell movement in the circulatory system (Wang et al, 2014).

12. Conclusion

Bioactive flavonoids, particularly PMFs, are abundant in citrus fruits. Additionally, citrus fruits and their peels contain high amounts of natural bioactive xanthophylls, pro-vitamin a carotenoids, and apocarotenoids such as violaxanthin esters, cryptoxanthin, and citraurin. These bioactive substances reduced ROS, lowering the risk of metabolic syndrome, hyperglycemia, cancer, heart disease, and neurological illnesses. The establishment of reliable antioxidant activity assays for substances with high antioxidant content is required in light of the critical role antioxidants play in the treatment of oxidative diseases. NP-based antioxidant assays were developed at the beginning of the 21st century, and the use of NPs as optical or electrochemical sensors appears to be a very promising strategy.

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