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Review

The Role of Selective Flavonoids on Triple-Negative Breast Cancer: An Update

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Abstract: Among the many types of breast cancer (BC), Triple-Negative Breast Cancer (TNBC) is the most alarming. It lacks receptors for the three main biomarkers: estrogen, progesterone, and human epidermal growth factor, hence the name TNBC. This makes its treatment a challenge. Surgical procedures and chemotherapy, performed either alone or in combination, seem to be the primary therapeutic possibilities; however, they are accompanied by severe complications. Currently, the formulation of drugs using natural products has been playing an important role in the pharmaceutical industries, owing to the drugs' increased efficacies and significantly lessened side effects. Hence, treating TNBC with chemotherapeutic drugs developed using natural products such as flavonoids in the near future is much warranted. Flavonoids are metabolic compounds largely present in all plants, vegetables, and fruits, such as blueberries, onions, (which are widely used to make red wine,) chocolates, etc. Flavonoids are known to have enormous health benefits, such as anticancer, antiviral, anti-inflammatory, and antiallergic properties. They are known to arrest the cell cycle of the tumor cells and induces apoptosis by modulating Bcl-2, Bax, and Caspase activity. They show a considerable effect on cell proliferation and viability and angiogenesis. Various studies were performed at both the biochemical and molecular levels. The importance of flavonoids in cancer treatment and its methods of extraction and purification to date have been reported as individual publications. However, this review article explains the potentiality of flavonoids against TNBC in the preclinical levels and also emphasizes their molecular mechanism of action, along with a brief introduction to its methods of extraction, isolation, and purification in general, emphasizing the fact that its quantum of yield if enhanced and its possible synergistic effects with existing chemotherapeutics may pave the way for better anticancer agents of natural origin and significantly lessened side-effects.

Keywords: flavonoids; triple-negative breast cancer; treatment options; side-effects; natural products

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1. Introduction

Cancer is a major disease worldwide with a very high rate of mortality. Mutations caused by changes in lifestyle, genetic inheritance, exposure to carcinogens, etc., are major causes of cancer progression. This deadly disease can occur in any part of the body, leading to unchecked growth of cancerous cells. This huge rate of cell growth in a particular site causes other non-oncogenic cells to starve for nutrients and oxygen [1]. Cancer cells can also migrate from one region of the body to another. Therefore, it spreads all over the host's body—a process termed metastasis. This condition renders cancer a deadly disease. There are several molecular pathways involved in the process of cancer progression, and using these abnormal expressions, the disease is diagnosed and the specific stage is evaluated [2]. There are various types of cancers, based on their site of occurrence—lung, breast, colorectal, blood, brain, etc. Although the causes and treatments for various malignancies are

distinct from one another, the methods used for making the first diagnostic procedures remain the same. These methods include physical screenings, complete blood counts (CBC), imaging procedures such as computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET) scans, and biopsies, among others [3,4]. Tumor biomarkers play an important role in disease diagnosis at an early stage. Treating cancers at the beginning stage is very crucial to save the life of the patient. Hence, the scientific community is attracted to finding an accurate biomarker and its diagnosis technique for every type of cancer [5]. Usually, breast cancer is diagnosed and treated using the detection of cell receptors such as estrogen, progesterone, and human epidermal growth factor. A vast majority of triple-negative cancers comprise the basal-like molecular grouping. Several studies have established molecular categories for TNBC [6]. There are seven molecular subgroups: unstable, basal-like 1, basal-like 2, immunomodulatory, mesenchymal (MES)-like, mesenchymal stem-like (MSL), and luminal androgen receptor. Recently, the immunomodulatory and MSL subtypes were refined. Despite this vast research, the classification of TNBC genetic subgroups has had a minimal clinical effect [7,8]. In TNBC patients, these receptors test negative due to a lack of receptors for these molecules. This complexity induces rapid progression and metastasis of TNBC in a very short period, and hence, treatment for this type of cancer should have higher efficacy within a very short duration of treatment [9]. Recently, it has been reported that among all types of breast cancer, TNBC seems to have the highest death rate seconding lung cancer [10]. It is also reported that TNBC affects younger women more often than the older population. Production of neoantigens is seen in higher levels due to the increased mutation rates and instability in genomes in TNBC cells. This eventually increases immunogenicity [11].

There are several treatment strategies available worldwide to treat cancers. Surgical removal of tumor tissues can be done only at the initial stages before the migration of tumor cells. Radiation therapy is another method that uses high-energy beams to target specific cancer cells and kill them. There are various other therapies such as radiotherapy, chemotherapy, immunotherapy, and hormone therapy that are employed in the treatment of TNBC [12]. Treatment mainly depends on the type of tumor; however, sometimes combination therapies are also employed. One of the common therapies for most cancer treatments is chemotherapy, which kills cancer cells using drugs administered in high doses [13].

Given the lack of hormone receptor and HER2 receptor expression in TNBC, there is a dearth of effective anticancer medications for treating TNBC patients at present [14,15]. As a result, researchers are devoting a great deal of time and energy in investigating the molecular characteristics of the illness in the hopes of uncovering naturally occurring drugs with the potential to cure malignancies such as TNBC. Sixty percent or more of all anticancer medications now are derived from plant or animal sources [16]. Natural products' active components such as flavonoids, alkaloids, polysaccharides, terpenoids, and saponins are proven to be effective against cancer, pain, inflammation, viruses, and germs. Finding new anticancer medications from natural sources is important since chemoresistance is becoming more common and difficult to treat among cancer patients, especially those with TNBC [17]. The cost-effectiveness and ecological friendliness of flavonoids make them an attractive alternative to traditional chemotherapy medicines [18].

Dietary flavonoids, which have showed antitumor activities in preclinical study, are the subject of intense investigation as possible alternative therapeutics [19]. This article examines the synergistic augmentation of conventional chemotherapy by flavonoids. Primary research data on flavonoid–chemotherapeutic synergy in connection to TNBC therapy were obtained from Pubmed and other scientific sources [20]. Flavonoids, such as epigallocatechin-3-gallate (EGCG), icariin, quercetin, silibinin, etc., have the ability to synergistically improve the effects of conventional chemotherapeutics, as shown by this research [21]. Modulation of intracellular signaling systems associated with apoptosis, proliferation, autophagy, motility, and chemoresistance mediates these positive effects. Hence, this review concisely highlights factors in the extraction, isolation, and purification

techniques implemented in increasing the bioavailability of flavonoids and also proving the fact that flavonoids have the potential to improve existing treatment techniques and eventually overcome cancer drug resistance. Despite excellent preclinical findings, further research is required prior to the initiation of clinical trials [22].

Flavonoids are broadly categorized into various subgroups and a broad classification of flavonoids has been depicted in Figure 1.

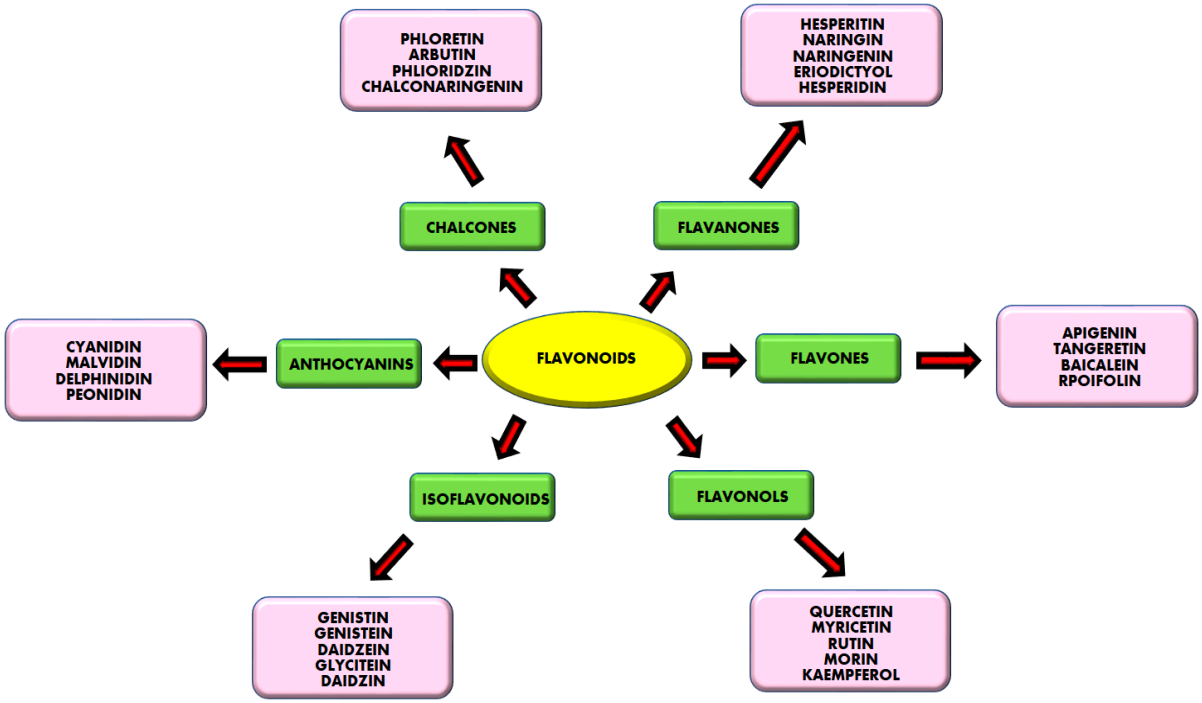

Figure 1. Flavonoids and their broad classifications.

Plants produce secondary metabolites made up of polyphenolic compounds called flavonoids. Numerous fruits and vegetables are rich in flavonoids, such as berries, onions, cherries, etc. In recent days flavonoids are considered one of the best secondary metabolites with many health benefits; hence, scientists are keenly interested in working with these secondary metabolites for various health issues, especially for cancers [23]. Flavonoids are active ingredients of plants that are known to have many health benefits like anticancer, anti-inflammatory, antiallergic, and antiviral properties. It also influences the cell cycle and acts as a chemical messenger [24,25]. Hence many scientists around the world have tested the efficacies of various flavonoids against TNBC cells. In this review, we have consolidated the uses of various flavonoids in TNBC treatment and explained the molecular pathways of action against TNBC by using flavonoids as a drug candidate, as described in Figure 2.

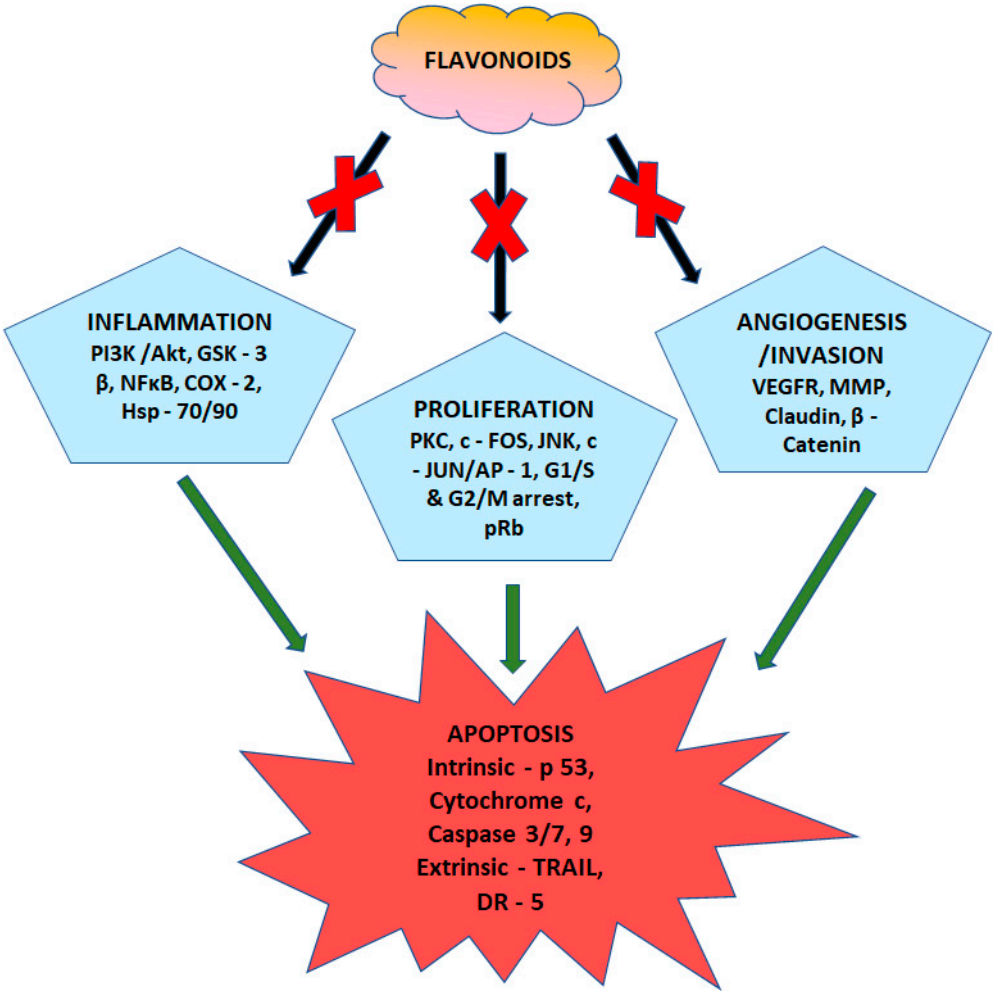

Figure 2. The role of flavonoids in cancer treatment: flavonoids influencing various signaling pathways eventually leading to apoptosis in cancer cells.

2. Natural Products

Flavonoids are secondary metabolites most commonly found in plants. They are polyphenolic natural compounds that have several potential medical, nutritional, and pharmacological uses. They are a vast family of chemicals possessing anti-inflammatory, antioxidant, anticarcinogenic, and antimutagenic characteristics [26], and they may be found in a wide variety of foods and drinks, including vegetables, seeds, fruits, cereals, tea, and even certain alcoholic beverages. Humans may consume large amounts of flavonoids without many risks of adverse effects due to their diversity, dispersion, and low toxicity [25]. There is a large amount of data proving that flavonoids affect a wide range of cancer processes, including growth, proliferation, differentiation, inflammation, angiogenesis, invasion, and metastasis [23], and a few of the prominent ones are mentioned below. Moreover, a figurative representation of the mechanistic action of flavonoids affecting various cancer signaling pathways is represented in Figure 3.

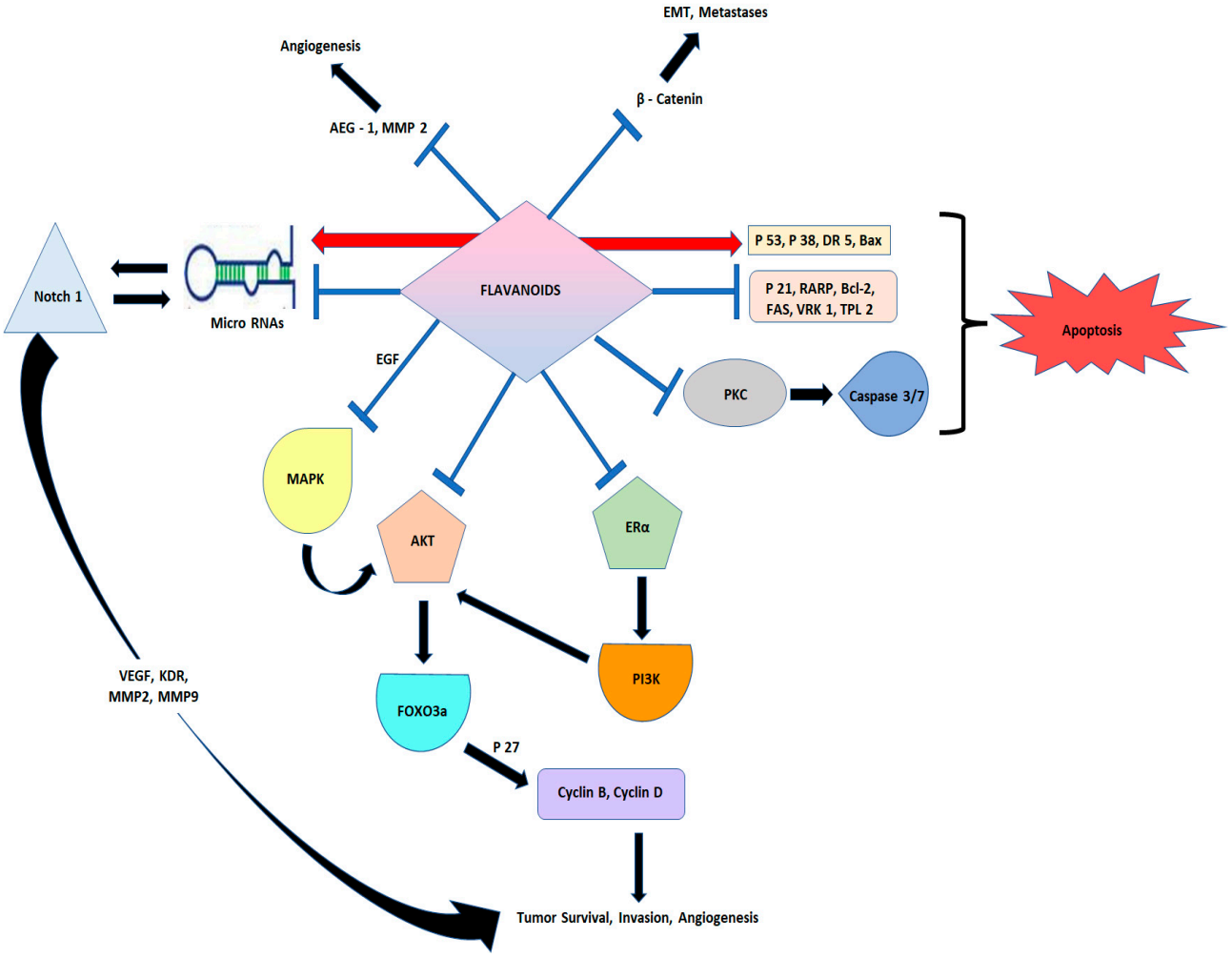

Figure 3. A schematic representation of the mechanism of action of flavonoids on cancers: Flavonoids inhibiting various cellular survival pathways such as MAPK, AKT, and Caspase 3/7, eventually leading to apoptotic cell death in tumor cells.

2.1. Quercetin

Quercetin is a naturally occurring flavonoid found in onions, apples, berries, etc. It has numerous health benefits, such as anti-inflammatory and antiviral properties. It also reduces infection and significantly improves physical and mental health [27]. A recently published report states that quercetin also possesses anticancer properties. It influences the cell cycle and cell proliferation, eventually inducing apoptosis by regulating various biological pathways. This was experimentally tested in both in vivo and in vitro models [28]. Another study reports that quercetin suppresses the migration of MDA-MB-468 and MDA-MB-231 cells. It also inactivates β-catenin and its associated genes. Doxorubicin-induced motility in TNBC cells was decreased upon quercetin treatment. It was also found to modulate E-cadherin and vimentin expressions in TNBC cells. Studies also report that markers of Epithelial to Mesenchymal Transition (EMT) are also regulated by quercetin. It significantly decreases cell growth and its viability. Moreover, it suppresses cell migration by inducing changes in the cell morphology [29]. Quercetin reduces cell viability, increases apoptosis, and arrests the cell cycle in the MDA-MB-231 cells in a time-dependent manner. It was found to activate the JNK signaling pathway and induce the FOXO3a activity [30].

Quercetin dose-dependently inhibits IGF1R and its downstream kinases Akt and Erk1/2 in MDA-MB-231 cells. Quercetin inhibits EMT transcription factors Snail and Slug, reduces IGF1 and enhances IGF-binding protein-3, and disrupts IGF1 autocrine/paracrine

loops. In xenograft mice models, quercetin was found to inhibit MDA-MB-231 tumor development and lung metastasis by inactivating IGF1R and downregulating Snail, Slug, and mesenchymal markers fibronectin and vimentin, thus proving that quercetin prevents TNBC EMT and metastasis by decreasing IGF1/IGF1R signaling [31].

2.2. Combined Effects of Quercetin and Curcumin

Comparative analyses of the combined effects of quercetin and curcumin were recently studied in different cell lines—T4D, MDA-MB-231, MCF-7, BT-20, and MDA-MB-468 cells. BRCA 1 mRNA expression was analyzed using qRT-PCR in all of the cell lines listed above. Results conveyed that the T47D cells show increased expression of BRCA1 when compared to the others. On the contrary, MDA-MB-231 displayed greatly decreased BRCA1 expression [28]. Similarly, the BRCA 1 to β actin ratio was found to be very low in the MDA-MB-231, followed by MDA-MB-486 and BT-20; however, it was very high in the T47D cells. Hence, MDA-MB-231 and MDA-MB-468 were taken for further study involving the use of quercetin and curcumin treatments. Cell proliferation in both MDA-MB-231 and MDA-MB-486 was found to decrease, by around 20% with quercetin and 50% with curcumin when administered individually [29]. However, a significant reduction of cell viability was discovered when combinedly treated with quercetin and curcumin. The viability percentage in the MDA-MB-486 control was higher when compared to the MDA-MB-231 control. Increased BRCA1 expression was seen in both MDA-MB-486 and MDA-MB-231 cell lines when treated with quercetin and curcumin in combination [32].

2.3. Epigallocatechin-3-Gallate (EGCG)

Epigallocatechin-3-gallate (EGCG) is a catechin derived from gallic acid and epigallocatechin esters, mostly found in green tea. EGCG has been reported to possess numerous health benefits against bone diseases, neuron regeneration, and most importantly, it possesses a significant role in cancer treatment [33]. It has been reported that EGCG can modify pathways associated with Parkinson's and Alzheimer's diseases. Effects of EGCG in treating Parkinson's and Alzheimer's diseases were also investigated using nanotechnology [34]. It was also found that EGCG considerably promotes glucose and lipid metabolism used to treat nonalcoholic fatty liver disease [35]. EGCG has also been proven to inhibit the expression of NF-Kappa B and mediate EMT. Importantly, it also regulates cancer stem cell progression and cell proliferation. It was also found to control metalloproteinases, TGFR–II, and other pathways that are associated with cancer cell proliferation and migration [36].

EGCG was reported to downregulate the expression of antiapoptotic genes like insulin-like growth factor-1 receptor (IGF1R) and induced myeloid leukemia cell differentiation protein (MCL1). However, it was found to increase the expression of other genes like Bcl-2 associated athanogene 3 (BAG3), receptor-interacting serine/threonine-protein kinase 2 (RIPK2), and X-linked inhibitor of apoptosis (XIAP). The suppressive effect of EGCG on TNBC cell migration was correlated with the suppression of VEGF production, indicating that EGCG might be deployed to prevent breast tumor invasion [37].

2.4. Fisetin

Fisetin is a flavonoid found in a variety of plants and vegetables such as onions, apples, cucumbers, etc. Fisetin is reported to have many medicinal properties. Recent findings report that it possesses chemo-preventive, anti-inflammatory, and antiaging characteristics [38]. It is also found to modulate various signaling pathways in the initiation and progression of cancers [39]. Stress in the endoplasmic reticulum and pathways associated with mitochondrial stress can be initiated by fisetin to trigger p8-dependent autophagy in the pancreatic cancer cells. It has also been reported that fisetin inhibits the mTOR pathway [40]. Treatment of hepatic steatosis using fisetin was tested in mice with obesity induced by dietary supplements. Results suggest that fisetin regulates signaling pathways of fatty acid β-oxidation and also modulates Sirt1 in hepatic steatosis, which is also called fatty liver, i.e., accumulation of fat in the liver leading to serious illness [41]. As already

mentioned, fisetin is known to possess antiaging properties which are achieved via its senolytic activity on the cells. Senescence is a mechanism activated to suppress tumors, especially to stop DNA replication which has been damaged already. Such a senotherapeutic activity is observed upon fisetin treatment which is believed to help increase the life span and well-being of human beings [42].

Another detailed study reports that the proliferation rate was studied extensively in both MDA-MB-231 and BT594 cell lines which were treated with different concentrations of fisetin. The results show a significant reduction at the highest concentration (100 μm). It is also reported that fisetin suppresses the invasion and migration of TNBC cells when administered in high concentrations. Increased expressions of E-cadherin and claudin, and decreased expressions of N-cadherin and vimentin, were observed with an increase in fisetin concentration. Reduction in the levels of the PI3K-Akt-GSK-3β signaling pathway was observed through immunofluorescence analysis. Similarly, Western blot analysis showed upregulated PTEN expression. Significant reductions in the volume, weight, and lung nodules of tumor masses have been observed in xenografted nude mice models [41].

In MDA-MB-231 and BT549 TNBC cells, fisetin dose-dependently reduced cell proliferation, migration, and invasion. Fisetin also reversed EMT in MDA-MB-231 and BT549 cells. Fisetin suppressed the PI3K-Akt-GSK-3β signaling pathway and increased PTEN mRNA and protein in a dose-dependent manner, limiting TNBC proliferation and metastasis [43].

2.5. Myricetin

Myricetin is a photochemical classified under the family of flavonoids. It is generally found in cabbage, red grapes, and especially in most herbal beverages like green tea [44]. It is found to have several medicinal uses—in diabetes treatment, cardioprotective, antihyperglycemic, antihypertensive, etc. It can also modulate mechanisms associated with cardiovascular diseases [45]. Myricetin displays antitumor effects by arresting the cell cycle and inducing apoptosis [46]. It is reported that myricetin can downregulate several protein expressions and pathways such as cyclin-dependent kinase, TGF-β1, and VGFR-associated primary open-angle glaucoma in rat models [47]. It can also modulate the effects of obesity by increasing the expression of the adipose tissue SIRT3 protein responsible for obesity in humans [44].

It is also reported that myricetin decreased the percentage of cell numbers by approximately more than 50% in MDA-MB-231, MDA-MB-468, MCF-7, and SK-BR-3 cells in a dose-dependent manner. It increased the HDF cell number with an increase in its concentration. A comparative study on the decrease of cell number in MDA-MB-231 and MDA-MB-468 was done between myricetin and other natural compounds like resveratrol, EGCG, doxorubicin, and cisplatin. Myricetin was found to display better inhibition than other compounds. Early apoptosis and late apoptosis were studied in the presence of myricetin, and the results display a considerable increase in apoptosis. Myricetin also generates autooxidation by which hydrogen peroxide is generated in the extracellular space, creating reactive oxygen species, thereby inducing apoptosis [44].

In TNBC cells treated with myricetin, early and late apoptotic cell death as well as cell growth suppression were observed. Cell cycle, proangiogenic, and invasion effects via mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K)/protein kinase B (PKB/also known as AKT) signaling pathways were also found to be regulated upon myricetin treatment. The expressions of MAPK, PI3K/AKT/mTOR, I/NF-B, Hippo, STAT3, GSK-3, Nrf2/HO-1, TLR, eNOS/NO, ACE, and AChE were also found to be regulated by myricetin [48].

2.6. Silibinin

Silibinin is a natural flavonoid found in milk thistle seeds which has numerous medicinal properties, especially as an anticancer agent. It helps in cancer treatment by arresting the cell cycle, inducing mitochondrial fusion, and triggering apoptosis [49]. Silibinin regulates cell differentiation in acute myeloid leukemia. Combination treatments involving silibinin

show great antitumor effects [50]. It is reported that silibinin can modulate the CFLAR-JNK pathway in nonalcoholic steatohepatitis mice and regulate oxidative stress leading to lipid accumulation [51]. It has also been found that silibinin helps in the treatment of nonmelanoma skin cancer cells by activating p53 and inducing apoptosis [52]. Recently it has been reported that silibinin decreases expressions of fibronectin-collagen in renal tissues in the diabetic nephropathy of high fat-induced renal fibrosis mice [51]. Silibinin facilitates chemotherapy by sensitizing cancer cells to chemotherapeutic drugs, as the BC cells are resistant to chemotherapeutic drugs [53].

A comparative study of non-TNBC cells and TNBC cells for the expression of MMP-2, IFN, and TGF-β2 shows higher expression in the TNBC cells than in non-TNBC cells. Silibinin also suppresses metastasis of TNBC cells in xenografted mice models. The expression of TGF-β2 was found to be suppressed by silibinin. Decreased expressions of IFN and MMP-2 induced by TGF- β2 were observed in the presence of silibinin [54]. Invasion and migration of MDA-MB-231 cells were inhibited by silibinin. It was also found to induce mitochondrial fusion, leading to an arrest in the migration of TNBC cells. Activation of the NLRP3 inflammasome was inhibited by decreasing the ROS level [49].

2.7. Luteolin

Luteolin is a flavonoid predominantly found in carrots, broccoli, and black pepper. It has been reported that luteolin has potent activity against various health ailments. Luteolin possesses anticancer, antimicrobial and antiallergen properties [55,56]. Luteolin induces ROS and apoptosis by modulating Wnt/β-catenin signaling, and it also modulates the ATPases levels in colorectal cancer [57–59]. It is reported that the progression of osteoarthritis is significantly decreased upon luteolin administration. Moreover, it is reported that luteolin inhibits inflammation caused by IL-1β in the chondrocytes of rat models [59]. In RAW264.7 macrophage cells stimulated by lipopolysaccharide, luteolin modulates the polarization of macrophages by regulating the activation of the NLRP3 inflammasome [60]. Luteolin modulates p13k/AKT pathways to prevent cancer cell metastasis, especially in BC cells [61]. Another study reports that luteolin has properties to treat several neurological diseases, hence it is also considered a potent neuroprotective agent. It has also been reported that luteolin tends to modulate receptors of adenosine such as A1 and A2A, which promote sleep in mice models [62]. Another recent study reports that peroxiredoxin-II activation can be enabled via luteolin administration for the effective treatment of myocardial ischemia, which has been experimented in rat models [63]. Similarly, another such study reports that the invasion and migration of MDA-MB-231 and BT5-49 have been significantly decreased at various concentrations of luteolin. It is also reported that luteolin decreases N-cadherin, vimentin, and slug expression, while increasing E-cadherin and claudin expression. Another study proves that luteolin reverses EMT in in vitro models by downregulating β-catenin expression in a dose-dependent manner. It is also reported that luteolin suppresses metastasis, which has been proven in in vivo models [64].

As a result of genetic inactivation of the Hippo pathway, YAP/TAZ is found to be hyperactivated in the MDA-MB-231 cells. It was also confirmed that the mRNA levels of CTGF and CYR61, two important YAP/TAZ downstream genes, and YAP/TAZ reporter activities were decreased by luteolin in MDA-MB-231 and 4T1 cell lines. It was also observed that luteolin inhibited YAP and TAZ nuclear translocation, thus lowering the YAP and TAZ levels [65].

2.8. Genistein

Genistein is found abundantly in soy, which falls under the isoflavonoid group of compounds. It has been found that genistein has various antitumor properties. Various reports state that genistein induces apoptosis, arrests cell cycle, inhibits cell proliferation, reduces angiogenesis, etc. Genistein has also been reported to treat symptoms related to menopause and enhance glucose metabolism. It is also reported that genistein is a good natural compound to treat chronic diseases like diabetes, arthritis, cardiovascular

diseases, etc. Genistein has been reported to modulate the activity of estrogen in women with diseases and symptoms related to menopause [66]. It also has the potency to modulate proteins and pathways associated with tumor progression such as those of Bcl-2, Bax, NF-κB, MAPK, P13K/Akt, and KIF20A. It can also sensitize cancer cells to chemotherapeutic drugs like tamoxifen and adriamycin for better treatment [67]. Genistein helps to treat nonalcoholic fatty liver disease by regulating the metabolisms of lipids and glucose [68].

It is reported that female adult mice, when exposed to a lifetime genistein dietary supplements, experience the methylation of BRAC 1 cytosine-guanine dinucleotide and decreased activity of aryl hydrocarbon receptor in the mammary tissue of female mouse offspring. Upregulated expression of ERα was observed upon genistein administration. Antagonism of aryl hydrocarbon receptor demethylates BRCA1 upon genistein treatment. It also decreases the expression of Cyp1b1, a target for the ARH receptor [69]. Genistein also induces apoptosis significantly when its concentration is increased. It also arrests the cell cycle post-72 h in a dose-dependent manner along with decreased levels of Notch-1, Bcl-2, Bcl-xL, and cyclin-1 expressions [70].

2.9. Apigenin

Apigenin (5,7,4′-trihydroxyflavone) is a polyphenolic flavonoid with a low molecular weight that is found in parsley, celery, onions, grapefruit, and oranges. However, apigenin is most plentiful in chamomile tea [71]. Recent research indicates that intraperitoneal administration of apigenin to Sprague–Dawley rats protects them against the formation of breast cancers triggered by 7,12-dimethylbenz(a)anthracene [72]. Apigenin promotes apoptosis preferentially in HER2-overexpressing breast cancer cells through suppression of serine/threonine kinase Akt (protein kinase B) [73], as well as disruption of the STAT3 and NFB signaling pathways [74]. Although the impact of apigenin on the in vivo development of HER2-overexpressing breast cancer cells has not yet been examined, subcutaneous injections of apigenin limit the growth of MDA-MB-231 breast cancer cells in nude mice by inhibiting the proteasome and inducing apoptosis [75]. Importantly, apigenin has very few negative effects on cultures of normal human cells and does not seem to be hazardous to mice [76,77].

Recent study reports that apigenin, in combination with gefitinib, one of the EGFR tyrosine kinase inhibitors, inhibits multiple oncogenic factors including c-Myc, hypoxia-inducible factor 1 alpha (HIF-1) and EGFR, and damages glucose uptake and utilization by restricting glucose transporter 1 protein expression, implying that apigenin can significantly influence tumor progression [78].

2.10. Cyanidin-3-Glucoside

Cyanidin-3-glucoside (C3G) is a natural anthocyanin compound found in a variety of fruits and vegetables. It is found to have many health benefits such as anticancer properties, anti-inflammatory properties, etc. Once C3G is consumed, it is broken down in the gastrointestinal tract. Various active metabolites of phenols, such as ferulic acid, vanillic acid, etc., are produced during the catabolism of C3G. The availability of biological barriers such as mucous barriers will be increased by C3G [79]. Photooxidation of A2E causes retinal pigmentation in aged people, which is effectively controlled by the combination of C3G and quercetin [80]. Receptor β in estrogen can be inhibited by C3G, which helps in the prevention of tumor progression reported in mice with melanoma [81]. It is also reported that C3G activates the expression of Sirt1 in MDA-MB-231 and BT-549 cells. It thus decreases the cell viability in a dose-dependent manner and increases the concentration of C3G, leading to a decrease in the cell viability by approximately 40%. C3G also decreases the cell number, invasion, and migration of TNBC cells when subjected to an increase in its dosage. It is also found to downregulate microRNA-138 expression. C3G modulates E-cadherin, vimentin, snail 1, snail 2, and ZO-1 expression in MDA-MB-231 and BT-549 cells. It is found to efficiently block EMT and suppress the invasion and migration of TNBC cells [82].

2.11. Norwogonin

Norwogonin is different from wogonin, owing to the presence of an OH group in its structure at the C-8 position. However, both are flavonoids. Norwogonin is found in *Scutellaria baicalensis*. Norwogonin and wogonin have both been reported to harbor significant antitumor properties, especially against colorectal and breast cancers [83]. Norwogonin can considerably increases the expression of Bax and subsequently lead to activation of caspase-3, thereby inducing apoptosis in cancer cells. Decreased Bcl-2 expression is reported in cancer cells upon norwogonin treatment. These results were determined by comet assay. Norwogonin has also been found to arrest the cell cycle at the G2/M phase, which eventually induces autophagy in in vitro studies conducted on colorectal cancer cells. Hence, norwogonin is considered a potent antitumor agent [84]. Enterovirus 71 causes severe illness related to hand, mouth, and neurological diseases in children. EV71 is usually treated with Ribavirin, which is an antiviral drug used in the treatment of numerous viral infections. It has been reported that norwogonin shows better results when compared to such synthetic drugs. Replication of EV71 is found to be blocked by norwogonin in combination with other flavonoids like Mosloflavone and Oroxylin A. Production of Capsid protein in viruses can be inhibited by using norwogonin to downregulate the expression of VP2 protein in the EV71 virus [85].

A recent study reports that norwogonin significantly arrests the cell cycle in TNBC cells. Norwogonin decreases cell proliferation of TNBC cell lines in a dose-dependent manner. It also modulates cyclin B1, CDK1, and cyclin D1 expressions, increases Bax and Caspase 3 expression in a dose dependent manner, and is also reported to initiate apoptosis. It is also found that norogonin effectively suppresses NF-κB and STAT 3 pathways [83].

Reports suggest that norwogonin upregulates p21 and downregulates CDK4 and cyclin D1 in TNBC cell lines, resulting in G0/G1 cell cycle arrest. Treatment with norwogonin for 48 h increased the binding ability between the promoter of p21 and GATA-binding factor 1 (GATA-1), a zinc finger transcription factor which aids in triggering the differentiation of megakaryocytes and erythrocytes. This suggests that norwogonin induces G0/G1 cell cycle arrest by regulating GATA-1 associated cell cycle checkpoints [78].

2.12. Tangeretin

Owing to its antimetastatic effects on cancer cells [86–88], the citrus flavonoid tangeretin has the potential to be developed into a drug candidate that is specific to cancer. In particular, this flavonoid compound prevents the spread of cancer cells that originate in the skin, breast, and stomach. It suppresses metastasis in 7,12-dimethylbenz anthracene-induced rat breast cancer [89]. In addition, tangeretin prevents breast cancer cells from undergoing epithelial-mesenchymal transition (EMT), invasion, and migration [90]. This is accomplished by downregulating the genes Notch-1, Jagged1/2, Hey-1, and Hes-1 [91].

Another recent study proves that tangeretin targets TP53, PTGS2, MMP9, and PIK3CA, and prevents breast cancer cells from metastasis. Studies using molecular docking techniques showed that tangeretin acts as an inhibitor of MMP9 and PTGS2. In addition, it has also been proven that the PI3K/Akt signaling pathway is a possible target of tangeretin in the process of preventing breast cancer metastasis [92].

2.13. Sophoraflavanone G

Sophoraflavanone G (SG) is extracted from the roots of *Sophora flavescens*, which has been used in China for centuries to treat cold and fever. It has been reported that SG can significantly act as an anti-inflammatory agent, especially against macrophages stimulated by lipopolysaccharides. It also helps in the treatment of leukemia in humans by activating the MAPK pathway, thereby inducing apoptosis in the HL-60 cells. SG can reduce JAK and STAT protein phosphorylation to increase apoptosis in Hodgkin's lymphoma [93]. Neuroinflammation can be inhibited upon SG administration via various signaling pathways such as STAT, MAPKs, Nrf2, and P13K. This effect has been studied in BV2 microglia activated by lipopolysaccharides [94]. It has been recently reported

that infections due to *Staphylococcus aureus* can be ameliorated using SG when used in combination with norfloxacin, which has been studied in both in vivo and in vitro models. Hence, SG with norfloxacin is considered a potential antibiotic against *Staphylococcus aureus* [95]. Recently, mice that were stressed chronically were studied extensively to understand the efficacy of SG for its antidepressant property. The result suggests that SG can significantly reduce stress by modulating the mTOR pathway associated with depression signals [93].

It is also reported that SG increases the intracellular ROS production. It also inhibits the progression of MDA-MB-231 cells. It is reported that upon SG treatment, phosphorylation of the MAPK and AKT pathways occurs. It is also reported that SG increases the production of Bax and also decreases the activity of Bcl-xL and Bcl-2 pathways. Caspase activity has been found to be induced by SG treatment in MDA-MB-231 cells. It is also reported to regulate autophagy. SG significantly induces apoptosis in MDA-MB-231 cells by modulating most of their signaling pathways [93].

SG therapy increased TNBC cell oxidative stress by producing reactive oxygen species, raising malondialdehyde (MDA), and lowering superoxide dismutase activity in TNBC cells. SG inhibited cell migration, invasion, and epithelial–mesenchymal transition, and also inactivated TNBC cell EGFR–PI3K–AKT signaling. Overexpression of EGFR also reduced the inhibitory and promotive effects of SG on cell proliferation, metastasis, apoptosis, and oxidative stress in TNBC cells. SG inhibited tumor development and EGFR–PI3K–AKT signaling in mice models, eventually inhibiting TNBC growth, metastasis, apoptosis, and oxidative stress by targeting the EGFR–PI3K–AKT signaling pathway [96].

2.14. Isorhamnetin

Isorhamnetin (IH) is a flavonoid found in Polygonaceae plants possessing antitumor effects against lung, esophageal, gastric, colorectal, cutaneous, and breast malignancies [97]. IH inhibits migration, invasion, cell proliferation, and apoptosis via multiple signaling pathways (p38/STAT3, MEK, Akt/mTOR). IH modulates PI3K/AKT/mTOR/p70S6K/ULK signaling to promote autophagy in human breast cancer cells [98]. IH inhibits mitophagy and promotes mitochondrial fission and death in TNBC cells but not in the estrogen-dependent breast cancer cell lines. Bax mitochondrial translocation and cytochrome c release followed these events; oxidative stress caused CaMKII (Thr286) and Drp1 (S616) phosphorylation and mitochondrial translocation. IH inhibited tumor development and induced apoptosis in TNBC xenograft mice via activating CaMKII and Drp1 (S616). These data further imply that IH may be a new chemotherapeutic agent of traditional origin in TNBC therapy [99].

Recent findings in MCF7 and BT549 cells report that IH inhibits the proliferation and promotion of apoptosis, induces cycle arrest in G_1 phase, reduces phosphorylation of cell proliferation pathway proteins AKT and ERK and the expression of proliferating nuclear antigen Ki67, decreases expression of Bcl-2, increases expression of Bax, and promotes shearing of caspase-3 [100]. Similar findings in MCF7, T47D, BT474, BT-549, MDA-MB-231, and MDA-MB-468 suggest that IH inhibits proliferation and promotion of apoptosis, as well as inhibits the Akt/mTOR and MEK/extracellular signal-regulated kinase phosphate cascade reaction [101]. Another such research conducted on TNBC cells like MDA-MB-231 and MDA-MB-468 and their consecutive xenograft mouse model studies indicate that IH promotes apoptosis and activates mitochondrial dependent apoptosis pathways [102].

In TNBC cell lines like MCF7, T47D, BT474, BT-549, MDA-MB-231, and MDA-MB-468, isorhamnetin was found to induce cycle arrest in G1 phase, decrease phosphorylation of AKT, ERK, and Ki67, increase expression of Bax, and promote shearing of caspase-3. Furthermore, it was shown to prevent the activation of the mitogen-activated protein kinase/extracellular signal-regulated kinase phosphatase cascade in TNBC cell lines. Furthermore, the mitochondrial dependent apoptotic pathway was shown to be activated in both TNBC cells and their related xenograft mice models [103].

2.15. Genkwanin

Genkwanin is a flavonoid predominantly obtained from *Tephroseris kirilowii* (a perennial plant widely distributed in China) [104], and it was reported to induce cytotoxicity in MDA-MB-231 cells after 24-h treatment. In addition to this, it was also proven that genkwanin induced cell cycle arrest at the G2/M phase, and a significant reduction in the levels of phosphorylated cell division control protein 2 homolog (CDC2) kinase and cyclin B1 were also observed. Genkwanin was also reported to improve the potency of apoptosis induction and decrease the levels of BCL-2 and BCL-XL as well as total PARP-1 expression, while simultaneously raising the levels of p53 and cleaving caspase-3 [105]. Genkwanin also induced autophagy in MDA-MB-231 cells, and treatments resulted in a marked augment in microtubule-associated protein light chain 3 (LC3) puncta formation, accumulation of LC3-II, and an increase in the levels of autophagy-related gene 5 (ATG5), in addition to a decrease in the levels of p62 and the inhibition of PI3K/AKT/mTOR/p70S6K/ULK signaling. According to the results of a molecular docking study, genkwanin was able to dock in the ATP binding pocket of PI3K, which resulted in a further reduction in the PI3K kinase activity [98].

In a similar manner, flavonoids isolated from *Astragalus membranaceus*, such as campanulin, ononin, calycosin, and formononetin, were evaluated for their ability to inhibit the development of breast cancer. Following treatment with genkwanin, there was a substantial increase in the degree of apoptotic induction, although there was a significant decrease in the level of mTOR [106]. Substantial anticancer effects were seen in in vivo research using mice. In addition to this, it was discovered that it inhibited the Akt/mTOR signaling pathway, which was confirmed via Western blot results [107]. This was accomplished by activating caspases and stimulating angiogenic activities [108]. It was also discovered that genkwanin inhibited the Akt/mTOR signaling pathway, which resulted in the inductions of autophagy and apoptosis [109,110].

Genkwanin proved to be lethal to MDA-MB-231 cells. It also caused G2/M phase arrest and cyclin B1 and CDC2 kinase dephosphorylation in them. It also induced apoptosis more potently by decreasing BCL-2, BCL-XL, and total PARP-1 and increased p53 and cleaved caspase-3 levels. It also induced autophagy in MDA-MB-231 cells, which increased LC3 puncta formation, LC3-II accumulation, and ATG5 levels, decreased p62, and inhibited PI3K/AKT/mTOR/p70S6K/ULK signaling [105].

2.16. Kaempferol

One of the most prevalent aglycone flavonoids is kaempferol. It's a yellow-colored tetrahydroxyflavone with four hydroxy groups at positions 3, 5, 7, and 4 [111]. Kaempferol may be found in many different plant components, including seeds, leaves, fruits, flowers, and even vegetables [112]. Cardioprotective, neuroprotective, anti-inflammatory, antidiabetic, antioxidant, antibacterial, antitumor, and anticancer agents are few of the prominent properties of kaempferol and its glycosylated derivatives [111,113]. Epidemiological studies have shown that a high kaempferol consumption is connected with lower incidence of several cancers, such as cancers of the skin, liver, colon, ovary, pancreas, stomach, and bladder [114].

Breast cancer has become more prevalent over the last several decades, and it is now the most common cancer in women [115]. Kaempferol has been reported to successfully suppress the proliferation of breast cancer cell lines VM7Luc4E2, MDA-MB-231, and MCF-7 at micromolar doses [116–118]. Furthermore, kaempferol has been found to significantly suppress bisphenol A (BPA) and triclosan (TCS)-induced antiapoptotic mechanisms [119], trigger cell cycle arrest in the G2/M stage, and even cause apoptosis and DNA fragmentation at the sub-G0 phase.

Kaempferol was also found to increase the levels of proapoptotic enzymes and proteins, such as cleaved caspase-9, -7, -3, p21, p53, Bax, PARP, and p-ATM, [113] and decrease the levels of antiapoptotic proteins Bcl-2, polo-like kinase 1 (PLK-1), pAKT, phosphorylated insulin receptor substrate 1 (pIRS-1), phosphorylated mitogen-activated protein kinase

(pMEK)1/2, cyclin-dependent kinase 1 (CDK1), cyclins A, B, D1, and E, and cathepsin D [116,120]. When compared to non-TNBC cells (control), kaempferol reduced cell migration and invasion stages in TNBC cells. This is explained by the downregulation of RhoA and activation of Rac1 in TNBC cells, as well as the activation of human epidermal growth factor receptor-2 (HER2)-silencing, as well as SK-BR-3 and ER/PR-silencing in non-TNBC cells [117], indicating that kaempferol's antiproliferative action is triggered via the ER-dependent pathway, which mediates cellular processes such as development, differentiation, and proliferation [113].

Furthermore, kaempferol has been reported to dramatically stimulate mitogen-activated protein kinase (MAPK) cascades, which are critical signaling pathways involved in the control of normal cell proliferation, survival, and differentiation. Indeed, kaempferol has been demonstrated to activate extracellular signal-regulated kinase (ERK), as well as MEK1 and ELK1, while inhibiting EMT and metastasis. When the MAPK signaling pathway is triggered, it activates the transcription factor activator protein-1 (AP-1), cathepsin B and D, and MMP-2 and -9, which inhibit cell adhesion, migration, and invasion, respectively [121–123]. In addition, kaempferol has been shown to lower glucose transporter 1 (GLUT1) mRNA levels and prevent the uptake of (3)H-deoxy-D-glucose ((3)H-DG) and monocarboxylate transporter 1 (MCT1), resulting in extracellular lactate accumulation [115] and eventually apoptotic cell death in TNBC cells [113].

Kaempferol significantly reduces MDA-MB-231 cell invasion and inhibits matrix metalloproteinase-3 (MMP-3) activity. The hydrolytic activity of MMP-3 casein and the capacity of breast cancer cells to invade are both significantly reduced by kaempferol. Moreover, kaempferol was shown to prevent matrix metalloproteinase-related breast cancer cell invasion. By inhibiting the PKC/MAPK/AP-1 cascade and, in turn, MMP-9 production and activity, kaempferol prevents the invasion of cancer cells [124].

2.17. Icariin

Icariin is a prenylated flavanol glycoside that is extracted from the medicinal plant *Herba epimedii*. It has been reported to have a wide variety of pharmacological effects including aphrodisiac, antidepressant, osteogenic, and cardiovascular protectant. Additionally, it has immunomodulatory activities [125]. It has been found that icariin may act as an efficient NF-B inhibitor, which enhanced Fanconi anaemia hematopoietic stem cell function and reduced murine lupus nephritis [126,127].

Studies conducted in recent years have shown that icariin inhibits growth of cancer cells in many different types of tumors, including osteosarcoma, prostate, lung, and gastric cancer cells [125]. However, the role of icariin in breast cancer and the molecular pathways that are connected to it has not yet been elucidated. Since NF-B is involved in breast cancer, it is proposed that icariin would be a good candidate in treating breast cancer [125].

The tumor microenvironment (TME) is a multifaceted biosphere that is made of immunological, stromal, and malignant cells [128]. Icariin was reported to suppress the immune microenvironment in breast cancer models, which resulted in the production of antitumor effects, according to a number of studies. Indeed, icariin was reported to increase SIRT6 expressions, reduce PD-L1 levels, and inhibit the expression of nuclear NF-B p65 in 4T1 tumors [125].

On the surface of cancer cells, a protein called programmed cell death-ligand 1 (PD-L1) is present, which is essentially an inhibitory molecule. It does damage by attaching itself to a protein called programmed death 1 (PD-1) that is found on immune cells and then prevents the activation of the immune system as a result of this interaction. In addition, it has also been shown that abnormal activation of the NF-kB signaling pathway further begins the PD-1/PD-L1 signaling pathway, which ultimately results in immune evasion by the tumor in TNBC cells via icariin treatment [129].

MDSCs, also known as myeloid-derived suppressor cells (MDSCs) are also found on these cells. MDSCs are extremely diverse immunosuppressive cells that are formed in bone marrow, and they often aggregate in great numbers inside the tumors to block

the antitumor effects of T lymphocytes [130]. An experimental investigation indicated that icariin inhibited the course of illness by significantly reducing the population of MDSCs in tumors and increasing the number of tumor-infiltrating $CD4^+$ and $CD8^+$ T lymphocytes [125].

Icariin preferentially decreased TNBC cell growth and induced apoptosis in both dose- and time-dependent manners, but had minimal cytotoxicity in normal breast cells. Icariin also induced mitochondria-mediated cell death, by increasing Bax/Bcl-2 and ROS levels. Icariin upregulated SIRT6, which inhibited breast cancer cell motility and invasion by inhibiting NF-B/EMT pathway activation. Oss-128167, a SIRT6 inhibitor, greatly reduced icariin's antimigration and antiinvasion activities. Icariin inhibited tumor development and lung metastasis in MDA-MB-231 and 4T1 tumor mice models via modulating the tumors' immunosuppressive microenvironments [125,131].

A cumulative representation of all the above mentioned flavonoids along with their structure and Pubchem ID has been listed below as Figure 4 for better understanding.

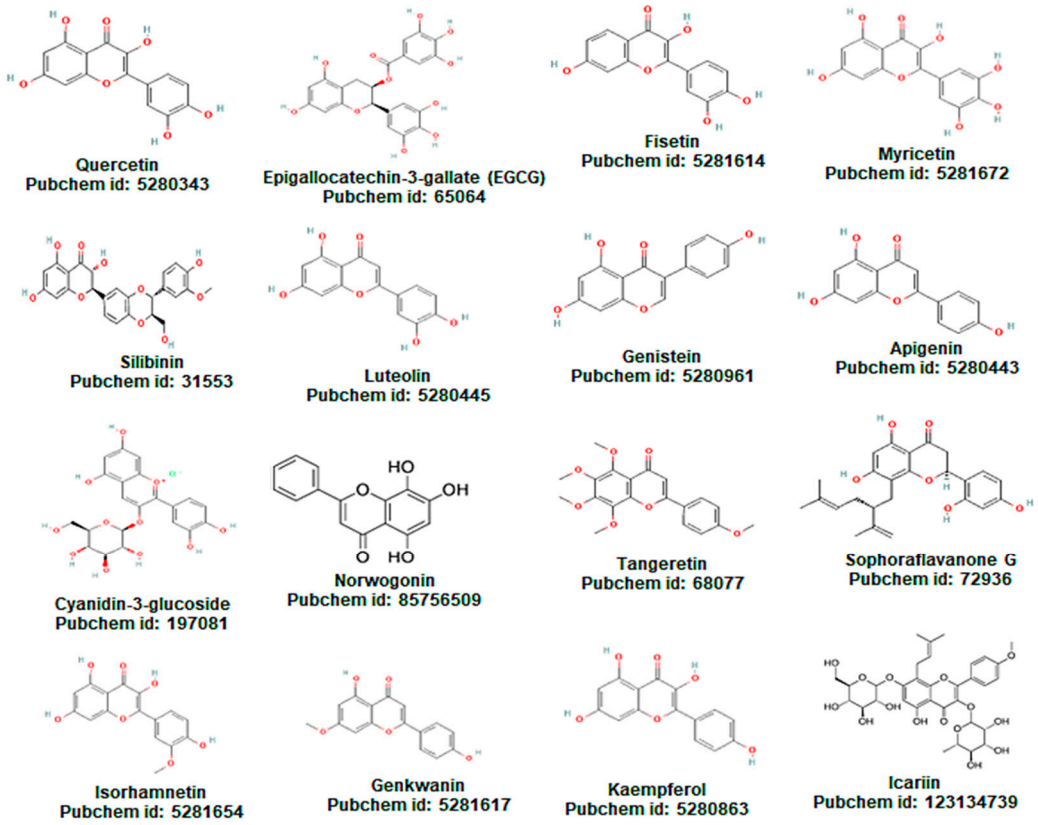

Figure 4. Names, structures, and PubChem IDs of the list of flavonoids listed in this article.

2.18. General Extraction, Separation, and Purification Procedures for Flavonoids

Milling, grinding, and homogenizing are the fundamental steps of every extraction process. This process is affected by variables such as the compound's chemical composition, the extraction technique used, the particle size of the sample, and the existence of any potential interferences [132]. Prior to analysis, extraction is the primary step in the recovery and separation of bioactive phytochemicals from plant sources. If necessary, the removal of undesirable phenolics and nonphenolic compounds such as waxes, lipids, terpenes, and chlorophylls is desired, and further stages may also be performed [133].

Polyphenolic and simple phenolic analysis in natural plants usually begins with liquid-liquid or solid-liquid extraction. Due to their simplicity, effectiveness, and versatility, they remain the most used methods. Methanol, ethanol, acetone, diethyl ether, and ethyl acetate are common extraction solvents [134]. However, pure organic solvents cannot extract extremely polar phenolic acids (benzoic, cinnamic acids), hence alcohol–water or

acetone–water combinations are preferred. Waxes, oils, sterols, and chlorophyll may be extracted from plant matrices using less polar solvents such dichloromethane, chloroform, hexane, and benzene. Factors such as pH, temperature, sample-to-solvent volume ratio, and the duration of extraction also affect the process. Extractions are usually done two to three times and the samples will finally be pooled to obtain the desired volume [133].

Solid flavonoids are often extracted by Soxhlet extraction. Most of the solvents used are water, methanol, or acetonitrile. This extraction technique is claimed to take approximately 12 h. This similar method of extraction yielded quantifiable phenolic acids from *Tilia europea*, *Urtica dioica*, *Mentha spicata*, *Hypericum perforatum*, and *Echinacea purpurea* aerial parts, ultimately yielding flavonoids [135,136]. Supercritical fluid extraction (SFE) removes biodegradable compounds using high temperatures and oxygen. Such extracts lack chlorophyll and other supercritical CO_2-insoluble nonpolar molecules. CO_2 cannot fully extract highly polar flavonoids. Controlling pressure or adding organic modifiers like methanol increases supercritical fluid solvating power and extraction efficiency [137,138]. Pressurized fluid extraction uses common solvents at regulated temperatures and pressures and is frequently used in natural product extraction [139]. It can be mechanized, utilizes less solvent in less time, and keeps samples oxygen- and light-free, making it a strong nutraceutical product. Catechin and epicatechin from tea leaves and grape seeds may be extracted using this method [140]. Isoflavonoids from *Radix astragali* were simultaneously extracted and determined using a microwave-assisted extraction method [141]. This method outperformed Soxhlet, reflux, and ultrasonic extractions. Conventional extraction affects flavonoid glycoside integrity with an extended extraction procedure, thereby reducing its repeatability [142]. Other mechanical methods, such as vortexing followed by centrifugation, mechanical stirring, and continuous rotational extraction, are also used to improve the molecular interactions of flavonoids [143,144].

Thin-layer chromatography is used to determine phenolic acids in natural products [145,146]. Due to its high sample throughput, it is ideal for screening plant extracts for pharmacologically active compounds before instrumental analysis [147]. TLC usually uses silica as a stationary phase and develops plates using 2-(diphenylboryloxy)ethylamine and polyethylene glycol or AlCl3. UV light or densitometry at 350–365 or 250–260 nm is employed for its detection [133].

Gas chromatography, a powerful separation technique, is utilized to purify numerous volatile chemicals. Its sensitivity and selectivity increase when used along with mass spectrometry [148]. The OH group in phenolic compounds increases the chances of hydrogen bonds, eventually raising the melting point. However, the main drawback in this technique is the poor volatility of the phenolic substance [149]. Gas chromatography is often used to analyze plant phenolic acids. Alkali, acid, or enzymatic hydrolysis may liberate phenolics from ester and glycosidic linkages and remove lipids from the extract to prepare samples for GC [150]. Gas phase analysis needs chemical derivatization, sample extraction, isolation, and cleanup. Early studies with derivatized phenolics used flame ionization detection (FID) and mass spectrometry. Most GC–MS work is done in electron impact ionization mode with 70 eV set as the ionization voltage and a scan range around 650 m/z [151].

HPLC has dominated in the field of phenolic compound separation for the past 20 years [145]. HPLC allows simultaneous separation of all components and their derivatives or resulting products [152]. They can detect low analyte concentrations in the presence of multiple interfering and coeluting substances [153]. HPLC is widely used to analyze phenolic compounds from plant-derived and biological matrices due to the vast variety of commercially available columns, including those employed in next-generation sorbents with fit-for-purpose qualities, and (ii) the ability to adjust between two or more columns [154].

Using phosphate or borate buffers, capillaries of 50–100 lm id, voltages of 10–30 kV, and injection volumes of 10–50 nL, capillary electrophoresis (CE), CZE, and MEKC are other equally relevant methods [155]. UV, electrochemical, and MS detectors are usually employed in these techniques. Most capillary electrophoretic phenolic compound investi-

gations include natural product research, including plants, vegetables, herbs, and other plant or fruit-derived items [156]. Tea catechins and theaflavins were analyzed by CE and HPLC with UV detection [157].

Most isolated flavonoids are tested for purity using spectrophotometers. The solvents' and solutions' pH affect simple phenolic absorption maxima in the range of 220 and 320 nm [158]. Both UV and visible spectroscopy methods are used to identify isolated phenolic chemicals, notably flavonoids [159,160]. However, developing a suitable UV test is difficult and highly reliant on the material being analyzed. The Folin–Denis test quantifies total phenolics in plant materials [161]. The process reduces phosphomolybdic–phosphotungstic acid (Folin–Denis) reagent to a blue compound in an alkaline solution. Phosphomolybdic-phosphotungstic-phenol absorbs at 760 nm. Similarly, Folin–Ciocalteu assays measure plant food phenolic content [162,163]. Folin-Denis and Folin-Ciocalteu reagents cannot detect all extract phenolic groups. The vanillin technique is for detecting the purity levels of flavan-3-ols, dihydrochalcones, and proanthocyanidins with a single bond at the 2,3-position and free metahydroxy groups on the B ring [164]. Vanillin test standards include catechin, a monomeric flavan-3-ol. This test detects polymeric proanthocyanidins better than monomeric flavan-3-ols. This test is better known for detecting and quantifying proanthocyanidins in plant materials. The total caffeic acid, total flavonoids, and total tannins may be measured spectrophotometrically by complexing phenolics with Al (III) which complexes with the flavonoid's carbonyl and hydroxyl groups [165,166].

2.19. Limitations

The development of flavonoids is greatly limited by their low extraction yield, complex extraction procedures, high cost, difficulty of epidemiological investigations, and unfavorable pharmacokinetic (PK) properties. To address these restrictions, adaptable solutions are being implemented. Future research is required to assess if these solutions can be deployed safely and economically. Despite preclinical data suggesting that flavonoids have anticancer and cancer-preventive effects, the development of dietary flavonoids as approved drugs for clinical usage has been obstructed by several challenges. The expense and time required for epidemiological research, the extraction and purification of flavonoids from their natural sources, and PK challenges, among others, are predominant difficulties questioning the use of flavonoids in disease treatment [167]. One of the greatest obstacles in the extraction of flavonoids from their natural plant sources is that the yield is very low (micrograms/milligrams concentration per kg of plant material used) implying that the continual extraction of these substances might lead to the extinction of the plant source [168].

In plants, flavonoids are often found complexed with other substances which act together to produce therapeutic effects. Additionally, various secondary metabolites, minerals, and vitamins from the same source are found complexed with flavonoids [167]. Hence, it is reported that the therapeutic activity may be due to the combined effect of a flavonoid's association with other compounds [169]. This flavonoid complexation makes it difficult to separate and identify the precise molecule responsible for specific pharmacological actions. Moreover, after the discovery of the active flavonoid, there is a multistep process required to isolate and purify it from other compounds using various analytical techniques. Multiple procedures, including solvent extraction, column chromatography, medium-pressure liquid chromatography, vacuum column chromatography, and preparative high-performance liquid chromatography (HPLC) may be employed to isolate particular compounds [170,171]. The implementation of such processes is very time-consuming and involves considerable expenditures [172]. Variation in flavonoid composition reduces the predictability of flavonoid yields during extraction, resulting in inconsistent data after each extraction [173]. Another restriction of flavonoid extraction is that these compounds are often unstable, exposing them to a high degree of degradation or change of their chemical structures during purification, resulting in the loss of their activities.

Typically, flavonoids have unsuitable PK profiles [136,174] (i.e., absorption, distribution, metabolism, excretion, and toxicity [ADMET]) that are characterized by low solubility, poor oral absorption, and significant hepatic metabolism by phase I and phase II enzymes [175]. Flavonoids are often consumed along with other dietary components, leading to their complexations or precipitations, thereby reducing their absorptions and bioavailabilities [176,177]. In addition, flavonoids may undergo considerable deglycosylation prior to their absorptions by the epithelial cells of the small intestine [178,179]. The unabsorbed flavonoids might enter the colon and be degraded by intestinal bacteria [180], reduced [181], or hydrolyzed [182]. For example, only 20–30% of an oral dosage of quercetin is bioavailable [183]. Within six hours of incubation under normal physiological circumstances (Hanks' Balanced Salt solution, pH 7.4), quercetin degrades [184]. Similarly, the flavonoid silybin has a limited anticancer impact due to its extensive metabolism and poor oral absorption [185,186]. These PK limitations impede the clinical development of flavonoids, since the needed in vivo levels cannot be attained even with large oral dosages [187,188]. Ingestion of greater quantities of flavonoids for a more potent antiproliferative action may also result in proliferative and inflammatory responses [189,190].

Another important limitation of using flavonoids in cancer treatment is owing to their various in vivo interactions. Flavonoids are known to alter the bioavailability and effectiveness of several drugs. Certain flavonoids, for instance, might influence CYPs [191] and conjugation enzymes [192], in addition to other enzymes like amylase [193] and glucosidases [194], bovine hemoglobin [195], multidrug resistance transporters [196], colonic microbiota [197], and plasma proteins [198,199].

2.20. Future Perspectives of Flavonoid Research

Natural health products based on flavonoids need green technology that can scale up to produce large quantities of metabolites while still protecting the consumers and the environment. Caution is needed when giving flavonoid supplements to cancer patients, since flavonoids may counteract the effects of radiation and other chemotherapeutic agents. Consequently, it may be more preferable to conduct research directed towards new delivery systems, such as nano-emulsions and nanoparticles. These delivery systems should be expected to have enhanced target specificity and safety. Improved bioavailability, targeted administration, and increased therapeutic efficiency of specific flavonoids need the cooperation of researchers from a variety of fields to discover more effective and safe delivery mechanisms for these compounds. Although most of the major flavonoids' metabolisms and pharmacokinetics have been reported, the significance of unabsorbed flavonoids in disease prevention and therapy, as well as the interaction of unabsorbed flavonoids with colon microbiota and the consequent metabolites, must be elucidated. It is for this reason that flavonoid nanotechnology, flavonoid-microbiome pharmacology, and flavonoid-inspired therapies are still relatively new areas of study in the field of biomedical sciences.

3. Conclusions

Several studies have been conducted to analyze the effective treatment regimen that can be implemented in treating TNBC like radiotherapy, chemotherapy, etc. All of these treatments have their own side effects, and hence the research community is interested in finding alternatives that have minimalistic toxicity. Flavonoids are metabolic compounds largely present in all plants, vegetables, and fruits. They have various health benefits such as anticancer, antiviral, anti-inflammatory, and antiallergic properties. They display considerable effects on the inhibition of cell proliferation, viability, and angiogenesis. To conclude, TNBC treatment can be effectively done by incorporating the above-mentioned natural products, as they majorly induce apoptosis by modulating Bcl-2, Bax, caspase-3, notch, cyclin, NF-kB, and STAT 3-like pathways. Notable differences can be seen in various cancer cell lines such as the MDA-MB-231, MDA-MB-468, HCC1806, BT-549, HCC70, etc. Hence, these natural products need extensive evaluation in the future in both in vivo and in vitro models for better understanding and development of drugs with minimal toxicity

and great efficacy towards cancer treatments. This review was made as an attempt to concisely highlight the ability of flavonoids in treating TNBC, along with their molecular mechanism of action, a brief introduction to their methods of extraction, isolation, and purification in general, and highlighting their possible synergistic effects with existing chemotherapeutics.

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References

1. Kroemer, G.; Pouyssegur, J. Tumor cell metabolism: Cancer's Achilles' heel. *Cancer Cell* **2008**, *3*, 472–482. [CrossRef]
2. Graham, T.A.; Sottoriva, A. Measuring cancer evolution from the genome. *J. Pathol.* **2016**, *241*, 183–191. [CrossRef]
3. Ferguson, J.L.; Turner, S.P. Bone Cancer: Diagnosis and Treatment Principles. *Am. Fam. Physician* **2018**, *98*, 205–213. [PubMed]
4. Pasechnikov, V.; Chukov, S.; Fedorov, E.; Kikuste, I.; Leja, M. Gastric cancer: Prevention, screening and early diagnosis. *World J. Gastroenterol. WJG* **2014**, *20*, 13842. [CrossRef] [PubMed]
5. Felder, M.; Kapur, A.; Gonzalez-Bosquet, J.; Horibata, S.; Heintz, J.; Albrecht, R.; Fass, L.; Kaur, J.; Hu, K.; Shojaei, H.; et al. MUC16 (CA125): Tumor biomarker to cancer therapy, a work in progress. *Mol. Cancer* **2014**, *13*, 129. [CrossRef] [PubMed]
6. Kjällquist, U.; Acs, B.; Margolin, S.; Karlsson, E.; Kessler, L.E.; Garcia Hernandez, S.; Ekholm, M.; Lundgren, C.; Olsson, E.; Lindman, H.; et al. Real World Evaluation of the Prosigna/PAM50 Test in a Node-Negative Postmenopausal Swedish Population: A Multicenter Study. *Cancers* **2022**, *14*, 2615. [CrossRef]
7. Prat Aparicio, A.; Schettini, F.; Chic, N.; Brasó Maristany, F.; Paré, L.; Pascual, T.; Conte, B.; Martínez Sáez, O.; Adamo, B.; Prat, A. Clinical, pathological, and PAM50 gene expression features of HER2-low breast cancer. *NPJ Breast Cancer* **2021**, *7*, 1.
8. Kao, T.-J.; Wu, C.C.; Phan, N.N.; Liu, Y.H.; Ta, H.D.; Anuraga, G.; Wu, Y.F.; Lee, K.H.; Chuang, J.Y.; Wang, C.Y. Prognoses and genomic analyses of proteasome 26S subunit, ATPase (PSMC) family genes in clinical breast cancer. *Aging* **2021**, *13*, 17970. [CrossRef]
9. Park, J.H.; Ahn, J.-H.; Kim, S.-B. How shall we treat early triple-negative breast cancer (TNBC): From the current standard to upcoming immuno-molecular strategies. *ESMO Open* **2018**, *3*, e000357.
10. Vagia, E.; Mahalingam, D.; Cristofanilli, M. The Landscape of Targeted Therapies in TNBC. *Cancers* **2020**, *12*, 916. [CrossRef]
11. Kwa, M.J.; Adams, S. Checkpoint inhibitors in triple-negative breast cancer (TNBC): Where to go from here. *Cancer* **2018**, *124*, 2086–2103. [CrossRef] [PubMed]
12. Wang, J.-J.; Lei, K.-F.; Han, F. Tumor microenvironment: Recent advances in various cancer treatments. *Eur. Rev. Med. Pharmacol. Sci.* **2018**, *22*, 3855–3864. [CrossRef] [PubMed]
13. Anderson, P.O. Cancer chemotherapy. *Breastfeed. Med.* **2016**, *11*, 164. [CrossRef]
14. Liskova, A.; Koklesova, L.; Samec, M.; Smejkal, K.; Samuel, S.M.; Varghese, E.; Abotaleb, M.; Biringer, K.; Kudela, E.; Danko, J.; et al. Flavonoids in Cancer Metastasis. *Cancers* **2020**, *12*, 1498. [CrossRef]
15. Hsu, Y.; Wu, L.Y.; Hou, M.F.; Tsai, E.M.; Lee, J.N.; Liang, H.L.; Jong, Y.J.; Hung, C.H.; Kuo, P.L. Glabridin, an isoflavan from licorice root, inhibits migration, invasion and angiogenesis of MDA-MB-231 human breast adenocarcinoma cells by inhibiting focal adhesion kinase/Rho signaling pathway. *Mol. Nutr. Food Res.* **2011**, *55*, 318–327. [CrossRef]
16. Ci, Y.; Zhang, Y.; Liu, Y.; Lu, S.; Cao, J.; Li, H.; Zhang, J.; Huang, Z.; Zhu, X.; Gao, J.; et al. Myricetin suppresses breast cancer metastasis through down-regulating the activity of matrix metalloproteinase (MMP)-2/9. *Phyther. Res.* **2018**, *32*, 1373–1381. [CrossRef]
17. Zhang, G.; Wang, Y.; Zhang, Y.; Wan, X.; Li, J.; Liu, K.; Wang, F.; Liu, Q.; Yang, C.; Yu, P.; et al. Anti-Cancer Activities of Tea Epigallocatechin-3-Gallate in Breast Cancer Patients under Radiotherapy. *Curr. Mol. Med.* **2012**, *12*, 163–176. [CrossRef]
18. Noolu, B.; Gogulothu, R.; Bhat, M.; SYH Qadri, S.; Sudhakar Reddy, V.; Bhanuprakash Reddy, G.; Ismail, A. In Vivo Inhibition of Proteasome Activity and Tumour Growth by Murraya koenigii Leaf Extract in Breast Cancer Xenografts and by Its Active Flavonoids in Breast Cancer Cells. *Anti-Cancer Agents Med. Chem.* **2016**, *16*, 1605–1614. [CrossRef]

19. ALaerjani, W.M.A.; Khan, K.A.; Al-Shehri, B.M.; Ghramh, H.A.; Hussain, A.; Mohammed, M.E.; Imran, M.; Ahmad, I.; Ahmad, S.; Al-Awadi, A.S. Chemical Profiling, Antioxidant, and Antimicrobial Activity of Saudi Propolis Collected by Arabian Honey Bee (*Apis mellifera jemenitica)* Colonies. *Antioxidants* **2022**, *11*, 1413. [CrossRef]
20. Arzi, L.; Mollaei, H.; Hoshyar, R. Countering Triple Negative Breast Cancer via Impeding Wnt/β-Catenin Signaling, a Phytotherapeutic Approach. *Plants* **2022**, *11*, 2191. [CrossRef]
21. Adinew, G.M.; Messeha, S.; Taka, E.; Soliman, K.F.A. The Prognostic and Therapeutic Implications of the Chemoresistance Gene BIRC5 in Triple-Negative Breast Cancer. *Cancers* **2022**, *14*, 5180. [CrossRef]
22. Anuraga, G.; Wang, W.J.; Phan, N.N.; An Ton, N.T.; Ta, H.D.; Berenice Prayugo, F.; Minh Xuan, D.T.; Ku, S.C.; Wu, Y.F.; Andriani, V.; et al. Potential prognostic biomarkers of NIMA (Never in Mitosis, Gene A)-Related Kinase (NEK) family members in breast cancer. *J. Pers. Med.* **2021**, *11*, 1089. [CrossRef]
23. Kopustinskiene, D.M.; Jakstas, V.; Savickas, A.; Bernatoniene, J. Flavonoids as anticancer agents. *Nutrients* **2020**, *12*, 457. [CrossRef]
24. Maleki, S.J.; Crespo, J.F.; Cabanillas, B. Anti-inflammatory effects of flavonoids. *Food Chem.* **2019**, *299*, 125124. [CrossRef]
25. Zakaryan, H.; Arabyan, E.; Oo, A.; Zandi, K. Flavonoids: Promising natural compounds against viral infections. *Arch. Virol.* **2017**, *162*, 2539–2551. [CrossRef]
26. Pandey, M.K.; Gupta, S.C.; Karelia, D.; Gilhooley, P.J.; Shakibaei, M.; Aggarwal, B.B. Dietary nutraceuticals as backbone for bone health. *Biotechnol. Adv.* **2018**, *36*, 1633–1648. [CrossRef] [PubMed]
27. Li, Y.; Yao, J.; Han, C.; Yang, J.; Chaudhry, S. Quercetin, inflammation and immunity. *Nutrients* **2016**, *8*, 167. [CrossRef] [PubMed]
28. Tang, S.-M.; Deng, X.-T.; Zhou, J.; Li, Q.-P.; Ge, X.-X.; Miao, L. Pharmacological basis and new insights of quercetin action in respect to its anti-cancer effects. *Biomed. Pharmacother.* **2020**, *121*, 109604. [CrossRef] [PubMed]
29. Srinivasan, A.; Thangavel, C.; Liu, Y.; Shoyele, S.; Den, R.B.; Selvakumar, P.; Lakshmikuttyamma, A. Quercetin regulates β-catenin signaling and reduces the migration of triple negative breast cancer. *Mol. Carcinog.* **2015**, *55*, 743–756. [CrossRef] [PubMed]
30. Nguyen, L.T.; Lee, Y.H.; Sharma, A.R.; Park, J.B.; Jagga, S.; Sharma, G.; Lee, S.S.; Nam, J.S. Quercetin induces apoptosis and cell cycle arrest in triple-negative breast cancer cells through modulation of Foxo3a activity. *Korean J. Physiol. Pharmacol.* **2017**, *21*, 205–213. [CrossRef]
31. Chen, W.-J.; Tsai, J.-H.; Hsu, L.-S.; Lin, C.-L.; Hong, H.-M.; Pan, M.-H. Quercetin blocks the aggressive phenotype of triple-negative breast cancer by inhibiting IGF1/IGF1R-mediated EMT program. *J. Food Drug Anal.* **2021**, *29*, 98. [CrossRef] [PubMed]
32. Kundur, S.; Prayag, A.; Selvakumar, P.; Nguyen, H.; McKee, L.; Cruz, C.; Srinivasan, A.; Shoyele, S.; Lakshmikuttyamma, A. Synergistic anticancer action of quercetin and curcumin against triple-negative breast cancer cell lines. *J. Cell Physiol.* **2019**, *234*, 11103–11118. [CrossRef]
33. Wang, H.; Lou, C.; Ma, N. Forskolin exerts anticancer roles in non-Hodgkin's lymphomas via regulating Axin/β-catenin signaling pathway. *Cancer Manag. Res.* **2019**, *11*, 1685–1696. [CrossRef] [PubMed]
34. Singh, N.A.; Mandal, A.K.A.; Khan, Z.A. Potential neuroprotective properties of epigallocatechin-3-gallate (EGCG). *Nutr. J.* **2015**, *15*, 1–17. [CrossRef] [PubMed]
35. Chen, C.; Liu, Q.; Liu, L.; Hu, Y.-Y.; Feng, Q. Potential Biological Effects of (−)-Epigallocatechin-3-gallate on the Treatment of Nonalcoholic Fatty Liver Disease. *Mol. Nutr. Food Res.* **2018**, *62*, 1–11. [CrossRef]
36. Negri, A.; Naponelli, V.; Rizzi, F.; Bettuzzi, S. Molecular Targets of Epigallocatechin—Gallate (EGCG): A Special Focus on Signal Transduction and Cancer. *Nutrients* **2018**, *10*, 1936. [CrossRef] [PubMed]
37. Bimonte, S.; Cascella, M.; Barbieri, A.; Arra, C.; Cuomo, A. Current shreds of evidence on the anticancer role of EGCG in triple negative breast cancer: An update of the current state of knowledge. *Infect. Agents Cancer* **2020**, *15*, 1–6. [CrossRef]
38. Grynkiewicz, G.; Demchuk, O.M. New Perspectives for Fisetin. *Front. Chem.* **2019**, *7*, 697. [CrossRef]
39. Dharambir, K.; Vivek, K.G.; Hardeep, S.T.; Yerer, M.B.; Sak, K.; Anil, K.S.; Manoj, K.; Vaishali, A.; Sardul, S.S. Fisetin and Quercetin: Promising Flavonoids with Chemopreventive Potential. *Biomolecules* **2019**, *9*, 174.
40. Jia, S.; Xu, X.; Zhou, S.; Chen, Y.; Ding, G.; Cao, L. Fisetin induces autophagy in pancreatic cancer cells via endoplasmic reticulum stress-and mitochondrial stress-dependent pathways. *Cell Death Dis.* **2019**, *10*, 1–15. [CrossRef]
41. Liou, C.-J.; Wei, C.-H.; Chen, Y.-L.; Cheng, C.-Y.; Wang, C.-L.; Huang, W.-C. Fisetin protects against hepatic steatosis through regulation of the Sirt1/AMPK and fatty acid β-oxidation signaling pathway in high-fat diet-induced obese mice. *Cell Physiol. Biochem.* **2018**, *49*, 1870–1884. [CrossRef]
42. Yousefzadeh, M.J.; Zhu, Y.I.; McGowan, S.J.; Angelini, L.; Fuhrmann-Stroissnigg, H.; Xu, M.; Ling, Y.Y.; Melos, K.I.; Pirtskhalava, T.; Inman, C.L.; et al. Fisetin is a senotherapeutic that extends health and lifespan. *Ebiomedicine* **2018**, *36*, 18–28. [CrossRef]
43. Li, J.; Gong, X.; Jiang, R.; Lin, D.; Zhou, T.; Zhang, A.; Li, H.; Zhang, X.; Wan, J.; Kuang, G.; et al. Fisetin Inhibited Growth and Metastasis of Triple-Negative Breast Cancer by Reversing Epithelial-to-Mesenchymal Transition via PTEN/Akt/GSK3β Signal Pathway. *Front. Pharmacol.* **2018**, *9*, 772. [CrossRef]
44. Knickle, A.; Fernando, W.; Greenshields, A.L.; Rupasinghe, H.V.; Hoskin, D.W. Myricetin-induced apoptosis of triple-negative breast cancer cells is mediated by the iron-dependent generation of reactive oxygen species from hydrogen peroxide. *Food Chem. Toxicol.* **2018**, *118*, 154–167. [CrossRef]
45. Wang, L.X.; Shi, Y.L.; Zhang, L.J.; Wang, K.R.; Xiang, L.P.; Cai, Z.Y.; Lu, J.L.; Ye, J.H.; Liang, Y.R.; Zheng, X.Q. Inhibitory Effects of (−)-Epigallocatechin-3-gallate on Esophageal Cancer. *Molecules* **2019**, *24*, 954. [CrossRef]
46. Jiang, M.; Zhu, M.; Wang, L.; Yu, S. Anti-tumor effects and associated molecular mechanisms of myricetin. *Biomed. Pharmacother.* **2019**, *120*, 109506. [CrossRef]

47. Yang, Q.; Li, Y.; Luo, L. Effect of myricetin on primary open-angle glaucoma. *Transl. Neurosci.* **2018**, *9*, 132–141. [CrossRef]
48. Sharma, P.; Khan, M.A.; Najmi, A.K.; Chaturvedi, S.; Akhtar, M. Myricetin-induced apoptosis in triple-negative breast cancer cells through inhibition of the PI3K/Akt/mTOR pathway. *Med. Oncol.* **2022**, *39*, 248. [CrossRef]
49. Lingling, S.; Jianing, F.; Liu, W.; Toshihiko, H.; Yuheng, N.; Kazunori, M.; Shunji, H.; Hitomi, F.; Satoshi, O.; Takashi, I. Silibinin inhibits migration and invasion of breast cancer MDA-MB-231 cells through induction of mitochondrial fusion. *Mol. Cell Biochem.* **2019**, *463*, 189–201. [CrossRef]
50. Zou, H.; Zhu, X.-X.; Zhang, G.-B.; Ma, Y.; Wu, Y.; Huang, D.-S. Silibinin: An old drug for hematological disorders. *Oncotarget* **2017**, *8*, 89307–89314. [CrossRef]
51. Liu, Y.; Xu, W.; Zhai, T.; You, J.; Chen, Y. Silibinin ameliorates hepatic lipid accumulation and oxidative stress in mice with non-alcoholic steatohepatitis by regulating CFLAR-JNK pathway. *Acta Pharm. Sin. B* **2019**, *9*, 745–757. [CrossRef]
52. Prasad, R.R.; Paudel, S.; Raina, K.; Agarwal, R. Silibinin and non-melanoma skin cancers. *J. Tradit. Complement. Med.* **2020**, *10*, 236–244. [CrossRef]
53. Molavi, O.; Narimani, F.; Asiaee, F.; Sharifi, S.; Tarhriz, V.; Shayanfar, A.; Hejazi, M.; Lai, R. Silibinin sensitizes chemo-resistant breast cancer cells to chemotherapy. *Pharm. Biol.* **2017**, *55*, 729–739. [CrossRef]
54. Kim, S.; Han, J.; Jeon, M.; You, D.; Lee, J.; Kim, H.J.; Bae, S.; Nam, S.J.; Lee, J.E. Silibinin inhibits triple negative breast cancer cell motility by suppressing TGF-β2 expression. *Tumor Biol.* **2016**, *37*, 11397–11407. [CrossRef]
55. Ashokkumar, P.; Sudhandiran, G. Luteolin inhibits cell proliferation during Azoxymethane-induced experimental colon carcinogenesis via Wnt/ β-catenin pathway. *Investig. New Drugs* **2011**, *29*, 273–284. [CrossRef]
56. Pandurangan, A.K.; Esa, N.M. Luteolin, a Bioflavonoid Inhibits Colorectal Cancer through Modulation of Multiple Signaling Pathways: A Review. *Asian Pac. J. Cancer Prev.* **2014**, *15*, 5501–5508. [CrossRef]
57. Pandurangan, A.K.; Ganapasam, S. Cytotoxic effect of luteolin on human colorectal cancer cell line (HCT-15): Crucial involvement of reactive oxygen species. *Middle East J. Cancer* **2013**, *4*, 175–180.
58. Pandurangan, A.K.; Sadagopan, S.K.A.; Dharmalingam, P.; Ganapasam, S. Luteolin, a Bioflavonoid, Attenuates Azoxymethane-Induced Effects on Mitochondrial Enzymes in Balb/c Mice. *Asian Pac. J. Cancer Prev.* **2013**, *14*, 6669–6672. [CrossRef]
59. Fei, J.; Liang, B.; Jiang, C.; Ni, H.; Wang, L. Luteolin inhibits IL-1β-induced inflammation in rat chondrocytes and attenuates osteoarthritis progression in a rat model. *Biomed. Pharmacother.* **2019**, *109*, 1586–1592. [CrossRef]
60. Zhang, B.-C.; Li, Z.; Xu, W.; Xiang, C.-H.; Ma, Y.-F. Luteolin alleviates NLRP3 inflammasome activation and directs macrophage polarization in lipopolysaccharide-stimulated RAW264. 7 cells. *Am. J. Transl. Res.* **2018**, *10*, 265.
61. Cook, M.T. Mechanism of metastasis suppression by luteolin in breast cancer. *Breast Cancer: Targets Ther.* **2018**, *10*, 89–100. [CrossRef]
62. Kim, T.-H.; Custodio, R.J.; Cheong, J.H.; Kim, H.J.; Jung, Y.-S. Sleep Promoting Effect of Luteolin in Mice via Adenosine A1 and A2A Receptors. *Biomol. Ther.* **2019**, *27*, 584–590. [CrossRef]
63. You, W.; Wu, Z.; Ye, F.; Wu, X. Cardamonin protects against adverse cardiac remodeling through mTORC1 inhibition in mice with myocardial infarction. *Die Pharm. Int. J. Pharm. Sci.* **2018**, *73*, 508–512.
64. Lin, D.; Kuang, G.; Wan, J.; Zhang, X.; Li, H.; Gong, X.; Li, H. Luteolin suppresses the metastasis of triple-negative breast cancer by reversing epithelial-to-mesenchymal transition via downregulation of β-catenin expression. *Oncol. Rep.* **2017**, *37*, 895–902. [CrossRef]
65. Cao, D.; Zhu, G.Y.; Lu, Y.; Yang, A.; Chen, D.; Huang, H.J.; Peng, S.X.; Chen, L.W.; Li, Y.W. Luteolin suppresses epithelial-mesenchymal transition and migration of triple-negative breast cancer cells by inhibiting YAP/TAZ activity. *Biomed. Pharmacother.* **2020**, *129*, 110462. [CrossRef]
66. Thangavel, P.; Puga-Olguín, A.; Rodríguez-Landa, J.F.; Zepeda, R.C. Genistein as Potential Therapeutic Candidate for Menopausal Symptoms and Other Related Diseases. *Molecules* **2019**, *24*, 3892. [CrossRef]
67. Spagnuolo, C.; Russo, G.L.; Orhan, I.E.; Habtemariam, S.; Daglia, M.; Sureda, A.; Nabavi, S.F.; Devi, K.P.; Loizzo, M.R.; Tundis, R.; et al. Genistein and cancer: Current status, challenges, and future directions. *Adv. Nutr.* **2015**, *6*, 408–419. [CrossRef]
68. Xin, X.; Chen, C.; Hu, Y.-Y.; Feng, Q. Protective effect of genistein on nonalcoholic fatty liver disease (NAFLD). *Biomed. Pharmacother.* **2019**, *117*, 109047. [CrossRef]
69. Donovan, M.G.; Selmin, O.I.; Doetschman, T.C.; Romagnolo, D.F. Epigenetic Activation of BRCA1 by Genistein In Vivo and Triple Negative Breast Cancer Cells Linked to Antagonism toward Aryl Hydrocarbon Receptor. *Nutrients* **2019**, *11*, 2559. [CrossRef]
70. Pan, H.; Zhou, W.; He, W.; Liu, X.; Ding, Q.; Ling, L.; Zha, X.; Wang, S. Genistein inhibits MDA-MB-231 triple-negative breast cancer cell growth by inhibiting NF-κB activity via the Notch-1 pathway. *Int. J. Mol. Med.* **2012**, *30*, 337–343. [CrossRef]
71. Shukla, S.; Gupta, S. Apigenin: A Promising Molecule for Cancer Prevention. *Pharm. Res.* **2010**, *27*, 962–978. [CrossRef]
72. Mafuvadze, B.; Benakanakere, I.; López Pérez, F.R.; Besch-Williford, C.; Ellersieck, M.R.; Hyder, S.M. Apigenin prevents development of medroxyprogesterone acetate-accelerated 7, 12-dimethylbenz (a) anthracene-induced mammary tumors in Sprague–Dawley rats. *Cancer Prev. Res.* **2011**, *4*, 1316–1324. [CrossRef]
73. Way, T.-D.; Kao, M.-C.; Lin, J.-K. Apigenin induces apoptosis through proteasomal degradation of HER2/neu in HER2/neu-overexpressing breast cancer cells via the phosphatidylinositol 3-kinase/Akt-dependent pathway. *J. Biol. Chem.* **2004**, *279*, 4479–4489. [CrossRef]

74. Seo, H.-S.; Choi, H.S.; Kim, S.R.; Choi, Y.K.; Woo, S.M.; Shin, I.; Woo, J.K.; Park, S.Y.; Shin, Y.C.; Ko, S.K. Apigenin induces apoptosis via extrinsic pathway, inducing p53 and inhibiting STAT3 and NFκB signaling in HER2-overexpressing breast cancer cells. *Mol. Cell. Biochem.* **2012**, *366*, 319–334. [CrossRef]
75. Chen, D.; Landis-Piwowar, K.R.; Chen, M.S.; Dou, Q.P. Inhibition of proteasome activity by the dietary flavonoid apigenin is associated with growth inhibition in cultured breast cancer cells and xenografts. *Breast Cancer Res.* **2007**, *9*, 1–8. [CrossRef]
76. Chen, T.; Li, L.-P.; Lu, X.-Y.; Jiang, H.-D.; Zeng, S. Absorption and excretion of luteolin and apigenin in rats after oral administration of Chrysanthemum morifolium extract. *J. Agric. Food Chem.* **2007**, *55*, 273–277. [CrossRef]
77. Gupta, S.; Afaq, F.; Mukhtar, H. Selective Growth-Inhibitory, Cell-Cycle Deregulatory and Apoptotic Response of Apigenin in Normal versus Human Prostate Carcinoma Cells. *Biochem. Biophys. Res. Commun.* **2001**, *287*, 914–920. [CrossRef]
78. Kikuchi, H.; Yuan, B.; Hu, X.; Okazaki, M. Chemopreventive and anticancer activity of flavonoids and its possibility for clinical use by combining with conventional chemotherapeutic agents. *Am. J. Cancer Res.* **2019**, *9*, 1517–1535.
79. Tan, J.; Li, Y.; Hou, D.-X.; Wu, S. The Effects and Mechanisms of Cyanidin-3-Glucoside and Its Phenolic Metabolites in Maintaining Intestinal Integrity. *Antioxidants* **2019**, *8*, 479. [CrossRef]
80. Wang, Y.; Kim, H.J.; Sparrow, J.R. Quercetin and cyanidin-3-glucoside protect against photooxidation and photodegradation of A2E in retinal pigment epithelial cells. *Exp. Eye Res.* **2017**, *160*, 45–55. [CrossRef]
81. Liu, M.; Du, Y.; Li, H.; Wang, L.; Ponikwicka-Tyszko, D.; Lebiedzinska, W.; Pilaszewicz-Puza, A.; Liu, H.; Zhou, L.; Fan, H.; et al. Cyanidin-3-o-glucoside pharmacologically inhibits tumorigenesis via estrogen receptor β in melanoma mice. *Front. Oncol.* **2019**, *9*, 1–18. [CrossRef]
82. Liang, L.; Liu, X.; He, J.; Shao, Y.; Liu, J.; Wang, Z.; Xia, L.; Han, T.; Wu, P. Cyanidin-3-glucoside induces mesenchymal to epithelial transition via activating Sirt1 expression in triple negative breast cancer cells. *Biochimie* **2019**, *162*, 107–115. [CrossRef]
83. El-Hafeez, A.A.A.; Khalifa, H.O.; Mahdy, E.A.; Sharma, V.; Hosoi, T.; Ghosh, P.; Ozawa, K.; Montano, M.M.; Fujimura, T.; Ibrahim, A.R.; et al. Anticancer effect of nor-wogonin (5, 7, 8-trihydroxyflavone) on human triple-negative breast cancer cells via downregulation of TAK1, NF-κB, and STAT3. *Pharmacol. Rep.* **2019**, *71*, 289–298. [CrossRef]
84. Wang, Z.; Zhang, Q.; Zhou, L.; Liu, G.; Wu, Q.; Chen, C. Norwogonin flavone suppresses the growth of human colon cancer cells via mitochondrial mediated apoptosis, autophagy induction and triggering G2/M phase cell cycle arrest. *J. Buon* **2020**, *25*, 1449–1454.
85. Choi, H.J.; Song, H.-H.; Lee, J.-S.; Ko, H.-J.; Song, J.-H. Inhibitory Effects of Norwogonin, Oroxylin A, and Mosloflavone on Enterovirus 71. *Biomol. Ther.* **2016**, *24*, 552–558. [CrossRef]
86. Cheng, Y.-P.; Li, S.; Chuang, W.L.; Li, C.H.; Chen, G.J.; Chang, C.C.; Or, C.H.; Lin, P.Y.; Chang, C.C. Blockade of STAT3 signaling contributes to anticancer effect of 5-acetyloxy-6, 7, 8, 4′-tetra-methoxyflavone, a tangeretin derivative, on human glioblastoma multiforme cells. *Int. J. Mol. Sci.* **2019**, *20*, 3366. [CrossRef]
87. Morley, K.L.; Ferguson, P.J.; Koropatnick, J. Tangeretin and nobiletin induce G1 cell cycle arrest but not apoptosis in human breast and colon cancer cells. *Cancer Lett.* **2007**, *251*, 168–178. [CrossRef]
88. Surichan, S.; Arroo, R.R.; Tsatsakis, A.M.; Androutsopoulos, V.P. Tangeretin inhibits the proliferation of human breast cancer cells via CYP1A1/CYP1B1 enzyme induction and CYP1A1/CYP1B1–mediated metabolism to the product 4′ hydroxy tangeretin. *Toxicol. Vitr.* **2018**, *50*, 274–284. [CrossRef]
89. Arivazhagan, L.; Pillai, S.S. Tangeretin, a citrus pentamethoxyflavone, exerts cytostatic effect via p53/p21 up-regulation and suppresses metastasis in 7, 12-dimethylbenz (α) anthracene-induced rat mammary carcinoma. *J. Nutr. Biochem.* **2014**, *25*, 1140–1153. [CrossRef]
90. Zhang, X.; Zheng, L.; Sun, Y.; Wang, T.; Wang, B. Tangeretin enhances radiosensitivity and inhibits the radiation-induced epithelial-mesenchymal transition of gastric cancer cells. *Oncol. Rep.* **2015**, *34*, 302–310. [CrossRef]
91. Martínez Conesa, C.; Vicente Ortega, V.; Yáñez Gascón, M.J.; Alcaraz Baños, M.; Canteras Jordana, M.; Benavente-García, O.; Castillo, J. Treatment of metastatic melanoma B16F10 by the flavonoids tangeretin, rutin, and diosmin. *J. Agric. Food Chem.* **2005**, *53*, 6791–6797. [CrossRef]
92. Hermawan, A.; Putri, H.; Hanif, N.; Ikawati, M. Integrative bioinformatics study of tangeretin potential targets for preventing metastatic breast cancer. *Evid.-Based Complement. Altern. Med.* **2021**, *2021*, 2234554. [CrossRef]
93. Huang, W.-C.; Gu, P.-Y.; Fang, L.-W.; Huang, Y.-L.; Lin, C.-F.; Liou, C.-J. Sophoraflavanone G from Sophora flavescens induces apoptosis in triple-negative breast cancer cells. *Phytomedicine* **2019**, *61*, 152852. [CrossRef]
94. Guo, C.; Yang, L.; Wan, C.X.; Xia, Y.Z.; Zhang, C.; Chen, M.H.; Wang, Z.D.; Li, Z.R.; Li, X.M.; Geng, Y.D.; et al. Anti-neuroinflammatory effect of Sophoraflavanone G from Sophora alopecuroides in LPS-activated BV2 microglia by MAPK, JAK/STAT and Nrf2/HO-1 signaling pathways. *Phytomedicine* **2016**, *23*, 1629–1637. [CrossRef] [PubMed]
95. Sun, Z.-L.; Sun, S.-C.; He, J.-M.; Lan, J.-E.; Gibbons, S.; Mu, Q. Synergism of sophoraflavanone G with norfloxacin against effluxing antibiotic-resistant Staphylococcus aureus. *Int. J. Antimicrob. Agents* **2020**, *56*, 106098. [CrossRef] [PubMed]
96. Cheng, W.; Liu, D.; Guo, M.; Li, H.; Wang, Q. Sophoraflavanone G suppresses the progression of triple-negative breast cancer via the inactivation of EGFR–PI3K–AKT signaling. *Drug Dev. Res.* **2022**, *83*, 1138–1151. [CrossRef]
97. Yeh, S.-L.; Lin, Y.-C.; Lin, Y.-L.; Li, C.-C.; Chuang, C.-H. Comparing the metabolism of quercetin in rats, mice and gerbils. *Eur. J. Nutr.* **2016**, *55*, 413–422. [CrossRef]

98. Zhang, H.-W.; Hu, J.J.; Fu, R.Q.; Liu, X.; Zhang, Y.H.; Li, J.; Liu, L.; Li, Y.N.; Deng, Q.; Luo, Q.S.; et al. Flavonoids inhibit cell proliferation and induce apoptosis and autophagy through downregulation of PI3Kγ mediated PI3K/AKT/mTOR/p70S6K/ULK signaling pathway in human breast cancer cells. *Sci. Rep.* **2018**, *8*, 1–13. [CrossRef]
99. Hu, J.; Zhang, Y.; Jiang, X.; Zhang, H.; Gao, Z.; Li, Y.; Fu, R.; Li, L.; Li, J.; Cui, H.; et al. ROS-mediated activation and mitochondrial translocation of CaMKII contributes to Drp1-dependent mitochondrial fission and apoptosis in triple-negative breast cancer cells by isorhamnetin and chloroquine. *J. Exp. Clin. Cancer Res.* **2019**, *38*, 1–16. [CrossRef]
100. Luczak, E.D.; Anderson, M.E. CaMKII oxidative activation and the pathogenesis of cardiac disease. *J. Mol. Cell. Cardiol.* **2014**, *73*, 112–116. [CrossRef]
101. Zhu, L.J.; Klutho, P.J.; Scott, J.A.; Xie, L.; Luczak, E.D.; Dibbern, M.E.; Prasad, A.M.; Jaffer, O.A.; Venema, A.N.; Nguyen, E.K.; et al. Oxidative activation of the Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) regulates vascular smooth muscle migration and apoptosis. *Vascul. Pharmacol.* **2014**, *60*, 75–83. [CrossRef]
102. Dilshara, M.G.; Bandara, M.M.; Jayawardana, B.C.; Vidanarachchi, J.K.; Jayasooriya, R.G.; Kim, G.Y. Silibinin sensitizes TRAIL-mediated apoptosis by upregulating DR5 through ROS-induced endoplasmic reticulum stress-Ca^{2+}-CaMKII-Sp1 pathway. *Oncotarget* **2018**, *9*, 10324. [CrossRef]
103. Gong, G.; Guan, Y.Y.; Zhang, Z.L.; Rahman, K.; Wang, S.J.; Zhou, S.; Luan, X.; Zhang, H. Isorhamnetin: A review of pharmacological effects. *Biomed. Pharmacother.* **2020**, *128*, 110301. [CrossRef]
104. Liu, W.; Ji, Y.; Sun, Y.; Si, L.; Fu, J.; Hayashi, T.; Onodera, S.; Ikejima, T. Estrogen receptors participate in silibinin-caused nuclear translocation of apoptosis-inducing factor in human breast cancer MCF-7 cells. *Arch. Biochem. Biophys.* **2020**, *689*, 108458. [CrossRef]
105. Vachetta, V.S.; Marder, M.; Troncoso, M.F.; Elola, M.T. Opportunities, obstacles and current challenges of flavonoids for luminal and triple-negative breast cancer therapy. *Eur. J. Med. Chem. Rep.* **2022**, *6*, 100077. [CrossRef]
106. Zhou, R.; Chen, H.; Chen, J.; Chen, X.; Wen, Y.; Xu, L. Extract from Astragalus membranaceus inhibit breast cancer cells proliferation via PI3K/AKT/mTOR signaling pathway. *BMC Complement. Altern. Med.* **2018**, *18*, 83. [CrossRef]
107. Rivera Rivera, A.; Castillo-Pichardo, L.; Gerena, Y.; Dharmawardhane, S. Anti-Breast Cancer Potential of Quercetin via the Akt/AMPK/Mammalian Target of Rapamycin (mTOR) Signaling Cascade. *PLoS ONE* **2016**, *11*, e0157251. [CrossRef]
108. Won, Y.-S.; Seo, K.-I. Lupiwighteone induces caspase-dependent and -independent apoptosis on human breast cancer cells via inhibiting PI3K/Akt/mTOR pathway. *Food Chem. Toxicol.* **2020**, *135*, 110863. [CrossRef]
109. Wang, X.; Song, Z.J.; He, X.; Zhang, R.Q.; Zhang, C.F.; Li, F.; Wang, C.Z.; Yuan, C.S. Antitumor and immunomodulatory activity of genkwanin on colorectal cancer in the APCMin/+ mice. *Int. Immunopharmacol.* **2015**, *29*, 701–707. [CrossRef]
110. Hussain, Y.; Khan, H.; Alam, W.; Aschner, M.; Abdullah, U.; Alsharif, K.F.; Saso, L. Flavonoids Targeting the mTOR Signaling Cascades in Cancer: A Potential Crosstalk in Anti-Breast Cancer Therapy. *Oxidative Med. Cell. Longev.* **2022**, *2022*, 4831833. [CrossRef]
111. Li, H.; Ji, H.S.; Kang, J.H.; Shin, D.H.; Park, H.Y.; Choi, M.S.; Lee, C.H.; Lee, I.K.; Yun, B.S.; Jeong, T.S. Soy leaf extract containing kaempferol glycosides and pheophorbides improves glucose homeostasis by enhancing pancreatic β-cell function and suppressing hepatic lipid accumulation in db/db mice. *J. Agric. Food Chem.* **2015**, *63*, 7198–7210. [CrossRef]
112. Sharifi-Rad, M.; Fokou, P.V.; Sharopov, F.; Martorell, M.; Ademiluyi, A.O.; Rajkovic, J.; Salehi, B.; Martins, N.; Iriti, M.; Sharifi-Rad, J. Antiulcer Agents: From Plant Extracts to Phytochemicals in Healing Promotion. *Molecules* **2018**, *23*, 1751. [CrossRef]
113. Imran, M.; Salehi, B.; Sharifi-Rad, J.; Aslam Gondal, T.; Saeed, F.; Imran, A.; Shahbaz, M.; Tsouh Fokou, P.V.; Umair Arshad, M.; Khan, H.; et al. Kaempferol: A Key Emphasis to Its Anticancer Potential. *Molecules* **2019**, *24*, 2277. [CrossRef]
114. Pei, J.; Chen, A.; Zhao, L.; Cao, F.; Ding, G.; Xiao, W. One-Pot Synthesis of Hyperoside by a Three-Enzyme Cascade Using a UDP-Galactose Regeneration System. *J. Agric. Food Chem.* **2017**, *65*, 6042–6048. [CrossRef]
115. Azevedo, C.; Correia-Branco, A.; Araújo, J.R.; Guimaraes, J.T.; Keating, E.; Martel, F. The chemopreventive effect of the dietary compound kaempferol on the MCF-7 human breast cancer cell line is dependent on inhibition of glucose cellular uptake. *Nutr. Cancer* **2015**, *67*, 504–513. [CrossRef]
116. Zhu, L.; Xue, L. Kaempferol suppresses proliferation and induces cell cycle arrest, apoptosis, and DNA damage in breast cancer cells. *Oncol. Res. Featur. Preclin. Clin. Cancer Ther.* **2019**, *27*, 629–634. [CrossRef]
117. Li, S.; Yan, T.; Deng, R.; Jiang, X.; Xiong, H.; Wang, Y.; Yu, Q.; Wang, X.; Chen, C.; Zhu, Y. Low dose of kaempferol suppresses the migration and invasion of triple-negative breast cancer cells by downregulating the activities of RhoA and Rac1. *Onco. Targets. Ther.* **2017**, *10*, 4809. [CrossRef]
118. Lee, S.-B.; Shin, J.-S.; Han, H.-S.; Lee, H.-H.; Park, C.; Lee, K.-T. Kaempferol 7-O-β-D-glucoside isolated from the leaves of Cudrania tricuspidata inhibits LPS-induced expression of pro-inflammatory mediators through inactivation of NF-κB, AP-1, and JAK-STAT in RAW 264.7 macrophages. *Chem. Biol. Interact.* **2018**, *284*, 101–111. [CrossRef]
119. Lee, G.-A.; Choi, K.-C.; Hwang, K.-A. Treatment with phytoestrogens reversed triclosan and bisphenol A-induced anti-apoptosis in breast cancer cells. *Biomol. Ther.* **2018**, *26*, 503. [CrossRef]
120. Yi, X.; Zuo, J.; Tan, C.; Xian, S.; Luo, C.; Chen, S.; Yu, L.; Luo, Y. Kaempferol, a flavonoid compound from gynura medica induced apoptosis and growth inhibition in mcf-7 breast cancer cell. *Afr. J. Tradit. Complement. Altern. Med.* **2016**, *13*, 210–215. [CrossRef]
121. Lee, G.-A.; Choi, K.-C.; Hwang, K.-A. Kaempferol, a phytoestrogen, suppressed triclosan-induced epithelial-mesenchymal transition and metastatic-related behaviors of MCF-7 breast cancer cells. *Environ. Toxicol. Pharmacol.* **2017**, *49*, 48–57. [CrossRef]

122. Zheng, L.; Zhu, L.; Zhao, M.; Shi, J.; Li, Y.; Yu, J.; Jiang, H.; Wu, J.; Tong, Y.; Liu, Y.; et al. In Vivo Exposure of Kaempferol Is Driven by Phase II Metabolic Enzymes and Efflux Transporters. *AAPS J.* **2016**, *18*, 1289–1299. [CrossRef]
123. Li, C.; Zhao, Y.; Yang, D.; Yu, Y.; Guo, H.; Zhao, Z.; Zhang, B.; Yin, X. Inhibitory effects of kaempferol on the invasion of human breast carcinoma cells by downregulating the expression and activity of matrix metalloproteinase-9. *Biochem. Cell Biol.* **2015**, *93*, 16–27. [CrossRef]
124. Sharma, A.; Sinha, S.; Keswani, H.; Shrivastava, N. Kaempferol and Apigenin suppresses the stemness properties of TNBC cells by modulating Sirtuins. *Mol. Divers.* **2022**, *26*, 3225–3240. [CrossRef]
125. Song, L.; Chen, X.; Mi, L.; Liu, C.; Zhu, S.; Yang, T.; Luo, X.; Zhang, Q.; Lu, H.; Liang, X. Icariin-induced inhibition of SIRT6/NF-κB triggers redox mediated apoptosis and enhances anti-tumor immunity in triple-negative breast cancer. *Cancer Sci.* **2020**, *111*, 4242–4256. [CrossRef]
126. Su, B.; Ye, H.; You, X.; Ni, H.; Chen, X.; Li, L. Icariin alleviates murine lupus nephritis via inhibiting NF-κB activation pathway and NLRP3 inflammasome. *Life Sci.* **2018**, *208*, 26–32. [CrossRef]
127. Li, Y.; Li, X.; Cole, A.; McLaughlin, S.; Du, W. Icariin improves Fanconi anemia hematopoietic stem cell function through SIRT6-mediated NF-kappa B inhibition. *Cell Cycle* **2018**, *17*, 367–376. [CrossRef]
128. Tran, L.; Theodorescu, D. Determinants of resistance to checkpoint inhibitors. *Int. J. Mol. Sci.* **2020**, *21*, 1594. [CrossRef]
129. Bi, Z.; Zhang, W.; Yan, X. Anti-inflammatory and immunoregulatory effects of icariin and icaritin. *Biomed. Pharmacother.* **2022**, *151*, 113180. [CrossRef]
130. Köstlin, N.; Hofstädter, K.; Ostermeir, A.L.; Spring, B.; Leiber, A.; Haen, S.; Abele, H.; Bauer, P.; Pollheimer, J.; Hartl, D.; et al. Granulocytic Myeloid-Derived Suppressor Cells Accumulate in Human Placenta and Polarize toward a Th2 Phenotype. *J. Immunol.* **2016**, *196*, 1132–1145. [CrossRef]
131. Sadik, S.B.S.; Sivaprakasam, P.; Ramasami, N.; Pandurangan, A.K. The Molecular Mechanisms Involved in Suppressing Triple Negative Breast Cancer Using Natural Agents. In *Handbook of Research on Natural Products and Their Bioactive Compounds as Cancer Therapeutics*; IGI Global: Hershey, PA, USA, 2022; pp. 45–71. [CrossRef]
132. Lopez, M.; Martınez, F.; Del Valle, C.; Orte, C.; Miro, M. Analysis of phenolic constituents of biological interest in red wines by high-performance liquid chromatography. *J. Chromatogr. A* **2001**, *922*, 359–363. [CrossRef]
133. Stalikas, C.D. Extraction, separation, and detection methods for phenolic acids and flavonoids. *J. Sep. Sci.* **2007**, *30*, 3268–3295. [CrossRef]
134. Stevens, J.F.; Wollenweber, E.; Ivancic, M.; Hsu, V.L.; Sundberg, S.; Deinzer, M.L. Leaf surface flavonoids of Chrysothamnus. *Phytochemistry* **1999**, *51*, 771–780. [CrossRef]
135. Fiamegos, Y.C.; Nanos, C.G.; Vervoort, J.; Stalikas, C.D. Analytical procedure for the in-vial derivatization? Extraction of phenolic acids and flavonoids in methanolic and aqueous plant extracts followed by gas chromatography with mass-selective detection. *J. Chromatogr. A* **2004**, *1041*, 11–18. [CrossRef]
136. Kempkes, M.; Golka, K.; Reich, S.; Reckwitz, T.; Bolt, H.M. Glutathione S-transferase GSTM1 and GSTT1 null genotypes as potential risk factors for urothelial cancer of the bladder. *Arch. Toxicol.* **1996**, *71*, 123–126. [CrossRef]
137. Lahtinen, M.; Lempa, K.; Salminen, J.-P.; Pihlaja, K. HPLC analysis of leaf surface flavonoids for the preliminary classification of birch species. *Phytochem. Anal.* **2006**, *17*, 197–203. [CrossRef]
138. Lin, M.-C.; Tsai, M.-J.; Wen, K.-C. Supercritical fluid extraction of flavonoids from Scutellariae Radix. *J. Chromatogr. A* **1999**, *830*, 387–395. [CrossRef]
139. Scalia, S.; Giuffreda, L.; Pallado, P. Analytical and preparative supercritical fluid extraction of Chamomile flowers and its comparison with conventional methods. *J. Pharm. Biomed. Anal.* **1999**, *21*, 549–558. [CrossRef]
140. Piñeiro, Z.; Palma, M.; Barroso, C.G. Determination of catechins by means of extraction with pressurized liquids. *J. Chromatogr. A* **2004**, *1026*, 19–23. [CrossRef]
141. Song, J.-Z.; Mo, S.-F.; Yip, Y.-K.; Qiao, C.-F.; Han, Q.-B.; Xu, H.-X. Development of microwave assisted extraction for the simultaneous determination of isoflavonoids and saponins in radix astragali by high performance liquid chromatography. *J. Sep. Sci.* **2007**, *30*, 819–824. [CrossRef]
142. Gao, M.; Song, B.-Z.; Liu, C.-Z. Dynamic microwave-assisted extraction of flavonoids from Saussurea medusa Maxim cultured cells. *Biochem. Eng. J.* **2006**, *32*, 79–83. [CrossRef]
143. Montedoro, G.; Servili, M.; Baldioli, M.; Miniati, E. Simple and hydrolyzable phenolic compounds in virgin olive oil. 1. Their extraction, separation, and quantitative and semiquantitative evaluation by HPLC. *J. Agric. Food Chem.* **1992**, *40*, 1571–1576. [CrossRef]
144. Guillén, D.; Barroso, C.; Pérez-Bustamante, J. Automation of sample preparation as a preliminary stage in the high-performance liquid chromatographic determination of polyphenolic compounds in sherry wines. *J. Chromatogr. A* **1996**, *730*, 39–46. [CrossRef]
145. Ragazzi, E.; Veronese, G. Quantitative analysis of phenolic compounds after thin-layer chromatographic separation. *J. Chromatogr. A* **1973**, *77*, 369–375. [CrossRef]
146. Schulz, J.M.; Herrmann, K. Analysis of hydroxybenzoic and hydroxycinnamic acids in plant material: I. Sample preparation and thin-layer chromatography. *J. Chromatogr. A* **1980**, *195*, 85–94. [CrossRef]
147. Watson, D.G.; Pitt, A.R. Analysis of flavonoids in tablets and urine by gas chromatography/mass spectrometry and liquid chromatography/mass spectrometry. *Rapid Commun. Mass Spectrom.* **1998**, *12*, 153–156. [CrossRef]

148. Queiroz, E.F.; Ioset, J.; Ndjoko, K.; Guntern, A.; Foggin, C.M.; Hostettmann, K. On-line identification of the bioactive compounds from Blumea gariepina by HPLC-UV-MS and HPLC-UV-NMR, combined with HPLC-micro-fractionation. *Phytochem. Anal. An Int. J. Plant Chem. Biochem. Tech.* **2005**, *16*, 166–174. [CrossRef]
149. Xie, J.; Zhu, L.; Luo, H.; Zhou, L.; Li, C.; Xu, X. Direct extraction of specific pharmacophoric flavonoids from gingko leaves using a molecularly imprinted polymer for quercetin. *J. Chromatogr. A* **2001**, *934*, 1–11. [CrossRef]
150. Xiao, H.; Krucker, M.; Albert, K.; Liang, X. Determination and identification of isoflavonoids in Radix astragali by matrix solid-phase dispersion extraction and high-performance liquid chromatography with photodiode array and mass spectrometric detection. *J. Chromatogr. A* **2004**, *1032*, 117–124. [CrossRef]
151. Tian, G.; Zhang, U.; Zhang, T.; Yang, F.; Ito, Y. Separation of flavonoids from the seeds of Vernonia anthelmintica Willd by high-speed counter-current chromatography. *J. Chromatogr. A* **2004**, *1049*, 219–222. [CrossRef]
152. Soczewiński, E.; Wojciak-Kosior, M.; Matysik, G. Analysis of glycosides and aglycones of flavonoid compounds by double-development thin-layer chromatography. *JPC–J. Planar Chromatogr. TLC* **2004**, *17*, 261–263. [CrossRef]
153. Jamshidi, A.; Adjvadi, M.; Husain, S.W. Determination of kaempferol and quercetin in an extract of Ginkgo biloba leaves by high-performance thin-layer chromatography (HPTLC). *J. Planar Chromatogr. TLC* **2000**, *13*, 57–59.
154. Bagul, M.; Srinivasa, H.; Padh, H.; Rajani, M. A rapid densitometric method for simultaneous quantification of gallic acid and ellagic acid in herbal raw materials using HPTLC. *J. Sep. Sci.* **2005**, *28*, 581–584. [CrossRef]
155. Głowniak, K.; Zgórka, G.; Kozyra, M. Solid-phase extraction and reversed-phase high-performance liquid chromatography of free phenolic acids in some Echinacea species. *J. Chromatogr. A* **1996**, *730*, 25–29. [CrossRef]
156. Herrero, M.; Ibáñez, E.; Cifuentes, A. Analysis of natural antioxidants by capillary electromigration methods. *J. Sep. Sci.* **2005**, *28*, 883–897. [CrossRef]
157. Lee, B.-L.; Ong, C.N. Comparative analysis of tea catechins and theaflavins by high-performance liquid chromatography and capillary electrophoresis. *J. Chromatogr. A* **2000**, *881*, 439–447. [CrossRef]
158. Owades, J.L.; Rubin, G.; Brenner, M.W. Food tannins measurement, determination of food tannins by ultraviolet spectrophotometry. *J. Agric. Food Chem.* **1958**, *6*, 44–46. [CrossRef]
159. Mabry, T.J.; Markham, R.R.; Thomas, M.B. *The Systematic Identification of Flavonoids*; Springer: Berlin/Heidelberg, Germany; New York, NY, USA, 1970.
160. Macheix, J.J.; Fleuriet, A.; Billot, J. *Fruit Phenolics*; CRC Press: Boca Raton, FL, USA, 1990.
161. OFolin, O.; Denis, W. On phosphotungstic-phosphomolybdic compounds as color reagents. *J. Biol. Chem.* **1912**, *12*, 239–243.
162. Singleton, V.L.; Rossi, J.A. Colorimetry of total phenolics with phosphomolybdic-phosphotungstic acid reagents. *Am. J. Enol. Vitic.* **1965**, *16*, 144–158.
163. Brune, M.; Hallberg, L.; Skånberg, A.-B. Determination of Iron-Binding Phenolic Groups in Foods. *J. Food Sci.* **1991**, *56*, 128–131. [CrossRef]
164. Goldstein, J.L.; Swain, T. Changes in tannins in ripening fruits. *Phytochemistry* **1963**, *2*, 371–383. [CrossRef]
165. Lamaison, J.L.; Carnart, A. Teneurs en principaux falvonoïdes des fleurs et des feuilles de Crataegus monogyna Jacq. et de Crataegus laevigata (Poiret) DC. en fonction de la période de vegetation. *Plantes Médicinales Phytothérapie* **1991**, *25*, 12–16.
166. Zaporozhets, O.A.; Krushynska, O.A.; Lipkovska, N.A.; Barvinchenko, V.N. A New Test Method for the Evaluation of Total Antioxidant Activity of Herbal Products. *J. Agric. Food Chem.* **2004**, *52*, 21–25. [CrossRef]
167. Amawi, H.; Ashby, C.R., Jr.; Tiwari, A.K. Cancer chemoprevention through dietary flavonoids: What's limiting? *Chin. J. Cancer* **2017**, *36*, 50. [CrossRef]
168. Zhou, J.; Du, G.; Chen, J. Novel fermentation processes for manufacturing plant natural products. *Curr. Opin. Biotechnol.* **2014**, *25*, 17–23. [CrossRef]
169. Ross, J.A.; Kasum, C.M. DIETARY FLAVONOIDS: Bioavailability, Metabolic Effects, and Safety. *Annu. Rev. Nutr.* **2002**, *22*, 19–34. [CrossRef]
170. Zhu, Y.; Liu, Y.; Zhan, Y.; Liu, L.; Xu, Y.; Xu, T.; Liu, T. Preparative Isolation and Purification of Five Flavonoid Glycosides and One Benzophenone Galloyl Glycoside from Psidium guajava by High-Speed Counter-Current Chromatography (HSCCC). *Molecules* **2013**, *18*, 15648–15661. [CrossRef]
171. Markham, K. Isolation techniques for flavonoids. In *The Flavonoids*; Springer: Berlin/Heidelberg, Germany, 1975; pp. 1–44.
172. Cragg, G.M.; Newman, D.J. Natural products: A continuing source of novel drug leads. *Biochim. Biophys. Acta BBA Gen. Subj.* **2013**, *1830*, 3670–3695. [CrossRef]
173. Quattrocchio, F.; Baudry, A.; Lepiniec, L.; Grotewold, E. The regulation of flavonoid biosynthesis. In *The Science of Flavonoids*; Springer: Berlin/Heidelberg, Germany, 2006; pp. 97–122.
174. Yu, C.-P.; Shia, C.-S.; Tsai, S.-Y.; Hou, Y.-C. Pharmacokinetics and Relative Bioavailability of Flavonoids between Two Dosage Forms of Gegen-Qinlian-Tang in Rats. *Evid.-Based Complement. Altern. Med.* **2012**, *2012*, 308018. [CrossRef]
175. Cai, X.; Fang, Z.; Dou, J.; Yu, A.; Zhai, G. Bioavailability of Quercetin: Problems and Promises. *Curr. Med. Chem.* **2013**, *20*, 2572–2582. [CrossRef]
176. Gil-Izquierdo, A.; Gil, M.I.; Ferreres, F.; Tomás-Barberán, F.A. In Vitro Availability of Flavonoids and Other Phenolics in Orange Juice. *J. Agric. Food Chem.* **2001**, *49*, 1035–1041. [CrossRef]

177. Mandalari, G.; Tomaino, A.; Rich, G.T.; Curto, R.L.; Arcoraci, T.; Martorana, M.; Bisignano, C.; Saija, A.; Parker, M.L.; Waldron, K.W.; et al. Polyphenol and nutrient release from skin of almonds during simulated human digestion. *Food Chem.* **2010**, *122*, 1083–1088. [CrossRef]
178. King, R.A.; Bursill, D.B. Plasma and urinary kinetics of the isoflavones daidzein and genistein after a single soy meal in humans. *Am. J. Clin. Nutr.* **1998**, *67*, 867–872. [CrossRef]
179. Gee, J.M.; DuPont, M.S.; Day, A.J.; Plumb, G.W.; Williamson, G.; Johnson, I.T. Intestinal Transport of Quercetin Glycosides in Rats Involves Both Deglycosylation and Interaction with the Hexose Transport Pathway. *J. Nutr.* **2000**, *130*, 2765–2771. [CrossRef]
180. Aura, A.-M.; Martin-Lopez, P.; O'Leary, K.A.; Williamson, G.; Oksman-Caldentey, K.M.; Poutanen, K.; Santos-Buelga, C. In vitro metabolism of anthocyanins by human gut microflora. *Eur. J. Nutr.* **2005**, *44*, 133–142. [CrossRef]
181. Gonthier, M.-P.; Verny, M.-A.; Besson, C.; Rémésy, C.; Scalbert, A. Chlorogenic acid bioavailability largely depends on its metabolism by the gut microflora in rats. *J. Nutr.* **2003**, *133*, 1853–1859. [CrossRef]
182. Kim, D.-H.; Jung, E.-A.; Sohng, I.-S.; Han, J.-A.; Kim, T.-H.; Han, M.J. Intestinal bacterial metabolism of flavonoids and its relation to some biological activities. *Arch. Pharmacal Res.* **1998**, *21*, 17–23. [CrossRef]
183. Ueno, I.; Nakano, N.; Hirono, I. Metabolic fate of [14C] quercetin in the ACI rat. *Jpn. J. Exp. Med.* **1983**, *53*, 41–50.
184. Boulton, D.W.; Walle, U.K.; Walle, T. Fate of the flavonoid quercetin in human cell lines: Chemical instability and metabolism. *J. Pharm. Pharmacol.* **1999**, *51*, 353–359. [CrossRef]
185. Zhu, H.-J.; Brinda, B.J.; Chavin, K.D.; Bernstein, H.J.; Patrick, K.S.; Markowitz, J.S. An Assessment of Pharmacokinetics and Antioxidant Activity of Free Silymarin Flavonolignans in Healthy Volunteers: A Dose Escalation Study. *Drug Metab. Dispos.* **2013**, *41*, 1679–1685. [CrossRef]
186. Dixit, N.; Baboota, S.; Kohli, K.; Ahmad, S.; Ali, J. Silymarin: A review of pharmacological aspects and bioavailability enhancement approaches. *Indian J. Pharmacol.* **2007**, *39*, 172. [CrossRef]
187. Gawande, S.; Kale, A.; Kotwal, S. Effect of nutrient mixture and black grapes on the pharmacokinetics of orally administered (−) epigallocatechin-3-gallate from green tea extract: A human study. *Phyther. Res. An Int. J. Devoted to Pharmacol. Toxicol. Eval. Nat. Prod. Deriv.* **2008**, *22*, 802–808. [CrossRef]
188. Nunes, T.; Almeida, L.; Rocha, J.F.; Falcão, A.; Fernandes-Lopes, C.; Loureiro, A.I.; Wright, L.; Vaz-da-Silva, M.; Soares-da-Silva, P. Pharmacokinetics of trans-resveratrol following repeated administration in healthy elderly and young subjects. *J. Clin. Pharmacol.* **2009**, *49*, 1477–1482. [CrossRef]
189. Decker, A. Phenolics: Prooxidants or Antioxidants? *Nutr. Rev.* **1997**, *55*, 396–398. [CrossRef]
190. Fresco, P.; Borges, F.; Diniz, C.; Marques, M. New insights on the anticancer properties of dietary polyphenols. *Med. Res. Rev.* **2006**, *26*, 747–766. [CrossRef]
191. Křížková, J.; Burdová, K.; Stiborová, M.; Křen, V.; Hodek, P. The effects of selected flavonoids on cytochromes P450 in rat liver and small intestine. *Interdiscip. Toxicol.* **2009**, *2*, 201–204. [CrossRef]
192. Jiang, W.; Hu, M. Mutual interactions between flavonoids and enzymatic and transporter elements responsible for flavonoid disposition via phase II metabolic pathways. *RSC Adv.* **2012**, *2*, 7948–7963. [CrossRef]
193. Xiao, J.; Ni, X.; Kai, G.; Chen, X. A review on structure–activity relationship of dietary polyphenols inhibiting α-amylase. *Crit. Rev. Food Sci. Nutr.* **2013**, *53*, 497–506. [CrossRef]
194. Xiao, J.; Kai, G.; Yamamoto, K.; Chen, X. Advance in dietary polyphenols as α-glucosidases inhibitors: A review on structure-activity relationship aspect. *Crit. Rev. Food Sci. Nutr.* **2013**, *53*, 818–836. [CrossRef]
195. Xiao, J.B.; Huo, J.L.; Yang, F.; Chen, X.Q. Noncovalent Interaction of Dietary Polyphenols with Bovine Hemoglobin in Vitro: Molecular Structure/Property–Affinity Relationship Aspects. *J. Agric. Food Chem.* **2011**, *59*, 8484–8490. [CrossRef]
196. Morris, M.E.; Zhang, S. Flavonoid–drug interactions: Effects of flavonoids on ABC transporters. *Life Sci.* **2006**, *78*, 2116–2130. [CrossRef]
197. Duda-Chodak, A.; Tarko, T.; Satora, P.; Sroka, P. Interaction of dietary compounds, especially polyphenols, with the intestinal microbiota: A review. *Eur. J. Nutr.* **2015**, *54*, 325–341. [CrossRef]
198. Xiao, J.; Kai, G. A review of dietary polyphenol-plasma protein interactions: Characterization, influence on the bioactivity, and structure-affinity relationship. *Crit. Rev. Food Sci. Nutr.* **2012**, *52*, 85–101. [CrossRef]
199. Xiao, J.; Cao, H.; Wang, Y.; Zhao, J.; Wei, X. Glycosylation of Dietary Flavonoids Decreases the Affinities for Plasma Protein. *J. Agric. Food Chem.* **2009**, *57*, 6642–6648. [CrossRef]