An ethnopharmacological review on the therapeutical properties of flavonoids and their mechanisms of actions: A comprehensive review based on up to date knowledge

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ABSTRACT
Flavonoids - a class of low molecular weight secondary metabolites - are ubiquitous and cornucopia throughout the plant kingdom. Structurally, the main structure consists of C6-C3-C6 rings with different substitution patterns so that many sub-classes are obtained, for example: flavonols, flavonolignans, flavonoid glycosides, flavans, anthocyanidins, aurones, anthocyanidins, flavones, neoflavonoids, chalcones, isoflavones, flavones and flavanones. Flavonoids are evaluated to have drug like nature since they possess different therapeutic activities, and can act as cardioprotective, antiviral, anti-diabetic, anti-inflammatory, antibacterial, anticancer, and also work against Alzheimer’s disease and others. However, information on the relationship between their structure and biological activity is scarce. Therefore, the present review tries to summarize all the therapeutic activities of flavonoids, their mechanisms of action and the structure activity relationship.

1. Introduction
Recent studies suggest the rational development of more potent, less toxic compounds that can be used clinically to treat of patients suffering from chronic diseases that cause oxidative stress. Phytochemicals are plant-based molecules that protect people from many chronic diseases. Flavonoids are one of the most exciting types of phenolic compounds. They are found in a wide variety of plants. Studies in the chemistry of natural products are very common in leaves, flower tissues, pollen and fruits. This phytocompound is also abundant in stem and bark, and represents an integral part of human healthy lifestyle. Flavonoids are existed broadly in nature. Concerns about their extensive profitable bioactive benefits, including anti-inflammatory, antioxidant, anti-viral, antifungal, antibacterial, antihypertensive, cardioprotective, anti-ulcer, anti-diabetic, anti-Alzheimer, anti-depression, and anti-cancer effects have been receiving great attention and support by numerous studies. Till now, more than 9000 flavonoids have been reported, and their daily intake varies between 20 mg and 500 mg, mainly from dietary supplements including apples, grapes, berries, tea, tomatoes and onions.

Notably, despite their broad benefits and wide distribution, flavonoids have poor bioavailability, which can significantly influence their nutritional value. Besides, information on their pharmacokinetics is limited. How the problem can be fixed is far from being resolved. This review attempts to summarize all the data about structure and activity of flavonoids, with particular emphasis on their mechanism of action.

2. Structure of flavonoids
Flavonoids are divided into several classes. They have a C6-C3-C6 structure consisting of two aromatic rings together with a heterocyclic oxygenated benzopyran ring (Fig. 1).

3. Therapeutical potential of flavonoids
Flavonoids (phenolic compounds) are of the prevalent secondary metabolites in plants with about 9000 different compounds [280] being biologically active (Fig. 2). Due to differences in the structure, distribution, metabolism and bioavailability of flavonoids, different flavonoids can have different effects on human health [10,101,102,184,230,3–66–68,7]. In order to delineate the therapeutic activities of flavonoids more in depth, mode of flavonoids action and structure activity relationship were comprehensively reviewed.

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3.1. Potential against Alzheimer’s disease

Flavonoids are reported to have strong therapeutic activity in the treatment of Alzheimer’s disease and are considered future drug candidates. The report included in this comprehensive review suggests that the main mechanism of action in the treatment of Alzheimer’s disease is decreased due to the production of Reactive Oxygen Species (ROS) and beta amyloid protein. About 127 flavonoids were tested for anti-Alzheimer activity and showed acetyl and butylcholinesterase inhibitors were responsible for their activity.

3.1.1. Anti-Alzheimer mechanism of action

Flavonoids can reduce Aβ plaque either by increasing the activity of α-secretase or by inhibiting β-secretase activity. They can interfere with fibrillation, inhibit beta amyloid protein aggregation through metal chelating activity, increase cerebral vascular blood flow, decrease beta amyloid protein levels, or inhibit the factors involved in nerve damage, for example: ROS, Nitric Oxide (NO), beta amyloid protein, phosphorylation of tau and Acetyl Choline Esterase (AChE) as summarized in Fig. 3 and Table 1.

3.1.2. Structure activity relationship for anti-Alzheimer activity

Central Nervous System drugs require greater liposolubility that can be enhanced by non-polar fragments (ex: aliphatic rings, alkyls and halogen atoms) in the molecules. At the same time, topological polarity surface area can affect the cellular drug molecules penetration. Previous studies have shown that flavonoids contain lower topological polarity surface area and higher water-lipid partition coefficient that can bypass blood brain barrier with potential activity.

Xie et al. [284] examined the structural aspects of the AChE pathway...
inhibitory potential of flavonoids and found that the OH group in the A ring [122] (Fale et al., 2012) and hydrogen bonding play a role in increasing affinity for AChE. AChE inhibition generally increases by flavones and flavonols. Whereas methoxylation, glycosylation and hydrogenation of the C2-C3 double bond decrease (Fig. 4). AChE inhibition depends on conjunction site, flavonoid class and sugar moiety.

3.2. Potential against depression

Flavonoids have been reported to have antidepressant activity [25, 124]. Updated reports suggest that apigenin exhibits antidepressant activity via dopaminergic mechanism [292], whilst luteolin reduces stress on endoplasmic reticulum [107]. Other studies indicate that icarin inhibits the NF-κB receptor and activation of the 3-inflammatory / caspase-1 / IL-1β axis in the hippocampus [153], whereas antidepressant activity of rutin is displayed by increasing monoamines in synaptic clefts (Noldner and, 2002) (Fig. 5, Table 2).

3.2.1. Structure-activity relationship

In flavonoids, the position of the OH group on ring A affects the antidepressant activity where compounds with the OH group at the 2,4 positions show high activity well as the C-glucoside flavones [77]. It has been reported that the sequence of antidepressant activity of flavonoids as follow: flavones > flavonols > flavonoids glycosides > flavanones [85].

3.2.2. Anti-depressant mechanism of action

The antidepressive mechanism of flavonoids include a) restoring monoamine levels, b) increasing neural survival and maturation, c) increasing neurogenesis and neuroplasticity, d) increasing BDNF, e) decreasing neurotransmitters reuptake through receptor interaction.

1. Flavonoids increase biogenic amines

Flavonoids can increase levels of the monoamine neurotransmitter in neuronal synaptosomes, which leads to a reduction in clinical symptoms of depression [303,304].

2. Inhibition of bioamine reuptake

Flavonoids can re-absorb 5-HT prevention by decreasing the number of 5-HT receptors and by inhibiting catechic acid transmethylase activity using synaptosomes [299]. This effect in turn
induces the expression of neuroamine transmission in the brain [275].

3. Effects of flavonoids on the neuroendocrine system

Flavonoids can enhance 5-HT neurological function and the action of adenylyl cyclase and neurotrophic factor 5-HT receptor mediated (Butterweck et al., 2000). The increase in phosphorylated BDNF and cAMP response element binding protein (CREB) was caused by hippocampal nerve synthesis (Knorr et al., 2017). In addition, increase the hippocampal nerve synthesis and BDNF expression (An et al., 2011). Flavonoids also inhibit stress hormone levels and increase the expression of glucocorticoid receptors in the hippocampus and prevent PC12 nerve cell damage (Patil et al., 2014) as well as its ability for restoration of IL-6 and TNF-α in serum (Pan 2006).

Flavonoids can inhibit ACh and triphosadenine, and limit ATP and α-amino-3-OH-5-methanoic acid [36]. One possible associated mechanism includes restoration of the activity of COX-2 (Li et al., 2013a, 2013b). Additionally, flavonoids can decrease levels of corticosterone and adrenal corticotropic hormones and can regulate corticotropin-releasing factor mRNA expression because they can modulate the DNA binding activity of glucocorticoid and cAMP receptors as well as the phosphorylation of extracellular kinase signal in the hypothalamic region.

3.3. Antioxidant potential

Oxidative stress refers to the excessive production of free radicals and other highly active enzymes causing imbalance of intracellular antioxidant capacity, which lead to lipid peroxidation, protein denaturation, and DNA damage. Oxidative stress is one of the main signs of inflammation. However, prolonged oxidative stress can damage the surrounding molecules. Recent clinical studies have shown that oxidative stress plays a crucial role in the development of many dangerous diseases such as cardiovascular disease [218,282], Alzheimer [234,301,41], cancer [189,87,9], diabetes [18]. The antioxidant potential of flavonoids has been well described in many studies (Havsteen 2002) [210].

3.3.1. Mechanism of antioxidant action

The antioxidant capacities of flavonoids are much powerful than those of VitC and VitE [209] by the following mechanisms:

| Flavonoids | Mechanism of action | References |
|------------|---------------------|------------|
| Hesperidin | Promotes neural differentiation Decrease β-amyloid plaques Inhibit AChE | [7] |
| Anthocyanin | Decrease β-amyloid protein | Vepalane et al., 2013 |
| Nariginin | Suppress neuronal death | Hernandez-Mantes et al., 2006 |
| Silbinin | Suppress inflammatory response Decrease in ROS production | [246] |
| Quercetin | Suppress apoptosis Increase AMPK activity Down regulation of tau phosphorylation | Lee et al., 2003 |
| Baicalein | Increase dopaminergic level | [105] |
| Resveratrol | Increase BDNF production Inhibit AChE | [281] |
| Luteolin | Decrease Aβ plaque formation | Rezai-zadeh et al., 2009 |
| Genistein | Increase neural survival Decrease apoptosis Decrease Aβ plaque formation | Weinreb et al., 2009 |
| Myrecetin | Inhibit butylycholinesterase activity | Leclerc et al., 2001 |

Table 1
List of flavonoids with anti-Alzheimer effect and their mechanism of action.

Fig. 3. Flavonoid mechanism of anti-Alzheimer activity.

Fig. 4. Summary of anti-Alzheimer structure activity relationships of flavonoids.
Mitigation of oxidation caused by NO [262]. b) Metal chelating activity [70]. c) Inhibit oxidases [52]. d) Activate antioxidant enzymes [187]. e) Reduce α-tocopheryl radicals [89,92]. f) Scavenge of ROS [187]. g) Increase in antioxidant properties of low molecular antioxidants [288]. h) Increase in uric acid levels [157].

The antioxidant effects of flavonoids also include a) inhibiting ROS production, either by chelating the trace elements or by inhibiting enzymes involved in ROS production; b) and improving regulation and protection of antioxidants. Flavonoids also inhibit ROS production enzymes, including monoxygenase, mitochondrial succinic oxidase, glutathione S-transferase, and NADH oxidase. The antioxidant mechanisms of flavonoids are listed in Table 3.

### 3.3.2. Structure activity relationship for antioxidant activity

Flavonoids are known to have high antioxidant activity. Many studies have shown significant differences in the antioxidant activity of the different flavonoid subgroups due to the many substitution patterns in their structures. Other studies discussed the structural effect on the antioxidant activity of flavonoids (Sichel et al., 1991; Rice-Evans et al., 1997). From these studies, the three main structural targets are summarized as follows (Fig. 6):

a) The 3′- and 4′-OH groups connected to the B-ring in an ortho position appear to stabilize their radical form. This site is believed to be responsible for metal chelation.

b) The 2,3 double bond on the C-ring plays a decisive role in junction with the 4-oxo group and facilitates the electronic delocalization of the B-ring. In addition, the ketol structure of 4-keto and 3-OH or 5-OH appears to be another chelation site for metals.

c) OH groups attached to rings A and C at positions 3, 5, and 7 seem to increase the antioxidant capacity together with the 4-oxo groups.

### 3.4. Potential against inflammation

Inflammation is responsible for chronic systemic damage which can lead to many dangerous diseases. There is currently a growing interest in the therapeutic potential of flavonoids as anti-inflammatory agents.
understanding of the effects of diet on inflammatory diseases. Therefore, the effects of flavonoids as an essential part of a healthy diet have received more attention because of their anti-inflammatory effects [90].

Flavonoids exhibit pleiotropic effects and can modulate inflammatory regulatory nodes (Fig. 7). The anti-inflammatory effect of flavonoids can be mediated in many ways; a) antioxidant effects, b) inhibition of inflammation-related gene expression, c) interactions with signaling pathways, d) interactions with inflammation-inducing proteins.

3.4.1. Anti-inflammatory mechanism of action

Flavonoids have anti-inflammatory activity through many actions including a) inhibition of transcription factors and regulatory enzymes that have a crucial role in the control of mediators involved in inflammation, b) additionally they are able to scavenge ROS and to enhance immune mechanisms and cells, c) modulation of secretory process, d) their effect on the arachidonic acid enzymes by inhibiting of lipooxygenase activity, e) modulation of signal transduction, f) inhibition of leukotriene synthesis, g) inhibition of cytokines production (Prostaglandins, No synthase, IL, TNF-alpha), h) modulation of enzymatic activity, i) inhibit COX-2 (Fig. 7). (Table 4).

3.4.2. Structure activity relationship for anti-inflammatory

Typically, the structural activity of flavonoids as anti-inflammatory agents is examined as follows: a) \(-C=O\) groups at C-4 b) position and number of OH groups c) non-glycosylated d) methoxylated e) glycosides with high lipophilicity f) and ring unsaturation [91] (Fig. 8, Table 5).

The most important sites in flavonoids as anti-inflammatory are the C2 and C3 double bonds, 3’, 4’ OH in the B-ring and 5, 7 OH in ring A. The OH group is important for anti-inflammatory activity because of its interaction with C4 carbonyl group (-C = O), which forms intramolecular hydrogen bonds
Table 4
List of flavonoids with anti-inflammatory effect and their mechanism of action.

| Flavonoids | Mechanism of action | Reference |
|------------|---------------------|-----------|
| Quercetin  | Suppression of IgE  | [208]     |
|            | Reduction of histamine | [27] |
|            | Reduction in oxidative stress | [27] |
| Kaempferol | Inhibit chemokines production | [62] |
| Baicalein  | Activation of regulatory T cells | [22] |
| Chrysin    | Inhibit platelet function | [222] |
| Isoflavone | Inhibit thrombus formation and platelets function | [221] |
| Genistein  | Inhibit Pro-inflammatory cytokines | [127] |
| Purarin    | Decrease in inflammatory responses | [115] |
| Ruthenium-conjugated chrysin | Decrease NF-kB activity | [222] |
| Anthocyanidin | Decrease adhesion between monocyte and endothelial cells | [51] |
| Luteolin   | Decrease of prostaglandins and histamine release | [130] |

Fig. 8. Summary of anti-inflammatory structure-activity relationships of flavonoids.

Table 5
Summary of anti-inflammatory structure-activity relationships of flavonoids.

| Responsible structural | Mechanism of action | References |
|------------------------|---------------------|-----------|
| 2,3-double bond        | Inhibit phospholipase A2 | [128] |
| 2,3-double bond        | Inhibit COX-1 | [128] |
| 3′,4′-OH groups        | Inhibition of inflammation-related gene expression | [53] |
| 4- C=O group           | Inhibit lipoxigenase | [128] |
| 2,3-double bond        | Inhibit COX-2 | [128] |
| 3-OH group             | Anti-inflammatory action | [53] |
| 2,3-double bond        | Galloyl moiety | |
| 3′,4′-OH or OCH3 groups | Anti-inflammatory action | [53] |
| 2,3-double bond        | | |

and increases its activity, whereas substitution causes decreased activity. Likewise, the C3 or C4 OH groups are important for increasing activity, and their replacement decreases activity. The introduction of substituents at C6 leads to a slight decrease in activity [138]. The presence of the OCH3 group increases the inhibition of lipoxigenase activity because it increases the lipophilicity and bioavailability of flavonoids and changes the pharmacokinetic behavior [126].

3.5. Hepatoprotective activity

Flavonoids have apparently hepatoprotective effects (Tapas et al., 2008; ElGengaihi et al., 2016a, 2016b; Mossa et al., 2016) by inhibiting oxidative stress with increasing superoxide dismutase (SOD), catalase (CAT), and reducing malondialdehyde (MDA), nitric oxide synthase (NOS). They reduce the levels of aspartate and alanine aminotransferase (AST and ALT, respectively) and pro-inflammatory cytokines in the serum and prevent the phosphorylation of NF-κB/p65, IKK, and IκBα in the NF-κB signaling pathway. Besides, flavonoids can inhibit hepatocyte apoptosis through suppressing caspase proteins and increasing Bcl-2 / Bax ratio [88]. Treatment with cyanidin-3-O-β-glucoside inhibits the release of inflammatory cytokines, reduces liver peroxidation, and prevents the development of hepatic steatosis (Zhu et al., 2012).

3.5.1. Hepatoprotective mechanism of action

Flavonoids have hepatoprotective activity through many actions like maintaining normal fluidity and stability of cell membrane, reversible inhibition of cytochrome P-450, ribosomal RNA synthesis, reduction of lipid peroxidation level, reduction of DNA damage, and decrease of protein carbonylation (ElGengaihi et al., 2016b) (Fig. 9, Table 6).

It has been reported that silymarin increases the enzymatic activity of DNA-dependent RNA polymerase 1 and subsequently RNA, DNA and protein biosynthesis, that leads to cell proliferation, leading to regeneration of liver cells (Sonnenbichler et al., 1986). The therapeutic properties of silymarin include scavenging of ROS, collagen production, regulation of cell membrane integrity and permeability, inhibition of NF-κB activity, and inhibition of leukotrienes and kinase depression (He et al., 2004).

3.5.2. Structure activity relationship for hepatoprotective activity

The double bond at the C2 and C3 in ring A and the OH groups of C3′ or C4′ in ring B increases the protective activity, but the hydroxymethylation effect at C3′ and C4′ is reversed (Fig. 10). In addition, apigenin has good hepatoprotective activity and good potential as promising therapeutic anti-inflammatory agent [88].

3.6. Potential against hypertension

Mechanically, flavonoids mediate antihypertensive effects [230] by increasing the bioavailability of NO, modulating vascular ion channel activity and decreasing oxidative stress in endothelial cells. At the endothelial level, flavonoids exert a vasorelaxant effect mainly by elevating NO levels through various mechanisms such as increasing the bioavailability of NO, increasing eNOS activation via the PI3K / Akt / eNOS cascade and increasing Ca levels.

3.6.1. Antihypertensive mechanism of action

Mechanistically, antihypertensive effect of flavonoids is mediated by increasing NO bioavailability, modulation of vascular ion channel activity or reduction of oxidative stress in endothelial cells (Fig. 11, Table 7).

3.6.2. Structure activity relationship

In general, there are two speculations that could be responsible for the high vasorelaxant effect of flavonoids: a) those with a planar structure, the same flavonoid basic skeleton and the C-O group attached to the C3′ position of the C ring, b) those with the same substituent attached to the C3′ position of A ring and the C3′ and C4′ positions of ring B (Fig. 12).

3.7. Potential against cardiovascular disease

Currently, flavonoids are attracting a lot of attention in the prevention of cardiovascular diseases (CVD). Foods rich in flavonoids have a positive effect on CVD. Evidence for the activity of metabolized and unmetabolized flavonoids in the three defense pathways in heart diseases is highlighted: NO bioavailability, induction of antioxidant enzymes, and anti-inflammatory processes.
3.7.1. Cardioprotective mechanism of action
Flavonoids have a positive effect on the cardiovascular system through various mechanisms. Although the direct mechanism is not understood, the effects of flavonoids appear to be diverse and dependent on many processes. The main pathways include anti-inflammatory and antioxidant activity, anti-platelet effect, anti-ischemic, anti-obesity, anti-atherosclerosis, dyslipidemia, anti-hypertensive, anti-diabetic, prevent endothelial dysfunction, prevent heart hypertrophy, inhibit adhesion molecule production, regulating blood pressure, lowering cholesterol, and protecting LDL from oxidation (Fig. 13, Table 8). Flavonoids can reduce the inflammatory process via a variety of mechanisms, including NO inactivation, and inhibition of the entry of leukocytes into inflammatory sites [166]. In addition, flavonoids improve vascular function and modulate vascular endothelial inflammation [82]. Besides, flavonoids decrease the activity of enzymes that produce ROS, lipooxygenase, NADPH oxidase, and xanthine oxidase [165]. Flavonoids increase adenosine monophosphate kinase activity leading to inhibition of the rate-limiting enzyme for cholesterol synthesis [268]. Inhibition of COX and lipooxygenase by flavonoids leads to reduction in thromboxane and leukotriene synthesis and thereby leads to decrease in vasoconstriction [98]. Flavonoids showed decreased vascular cell adhesion molecules and C-reactive protein [163]. Flavonoids’ inhibitory action of platelet aggregation is associated with the inhibition of the compounds that impair endothelial function and the formation of NO in the vascular endothelium [260].

3.7.2. Structure activity relationship for cardioprotective activity
The sequence of effectiveness of cardioprotective flavonoids is as follows descendingly; apigenin and luteolin, and kaempferol and quercetin followed by genistein and daidzein, then naringenin, then fleoorin and finally catechins then epicatechins. Analysis of the relationship between structural activities revealed that 5-OH, 7-OH, 4’-OH are essential for good cardioprotective activity. While, the presence of a glycosylated group significantly reduces cardioprotective activity. In addition, molecular volume and total energy predict the cardioprotective activity of flavonoids.

3.8. Potential against ulcers
Flavonoids are one of the most important types of phytocompounds...
used in ulcer therapy especially to combat *Helicobacter pylori* (*H. pylori*) [5]. Rutin was investigated for its anti-ulcer effect against gastric lesions due to its anti-liperoxidation effect in addition to its antioxidant potential, which reduces gastric MPO activity, increases nitrite / nitrate, exhibits NO production and increases GSH activity [83]. The various flavonoids of *Oroxylum indicum* have been used for centuries to treat various gastric ailments [249]. It was also found that several substituted flavones showed good gastroprotective activity. Flavonoid glycosides exhibit gastroprotective properties in mice exposed to multiple ulcer causes. It has been demonstrated that 5-methoxy-49-fluoroflavone is very effective as anti-ulcer agent [16].

**3.8.1. Antiulcer mechanism of action**

Flavonoids provide a cytoprotective effect by increasing levels of endogenous prostaglandins, increase mucus, reduce gastric PH, release myeloperoxidase reducing histamine secretion, inhibiting *H. pylori*, scavenging ROS and antisecretory mechanisms (Fig. 14, Table 9) [51, 191]. The gastroprotective effect of resveratrol is sufficiently based on its potential to inhibit the production of important inflammatory mediators, to inhibit the expression of NF-κB and intracellular transcription enzymes (MAPKs) [110] and to decrease gastric MPO activity, decrease MDA, increase the collagen content and restore depleted GSH. Flavonoids play an important role in its therapeutic function in gastric tissue by inhibiting TNF-α. These polyphenols also reduce the elevated levels of lucigenin and luminol chemiluminescence, which indicate a
significant inhibition of intracellular and extracellular oxidative events in the gastric mucosa.

3.8.2. Structure activity relationship

The presence of an OCH3 group at the position C-7 appears to enhance gastroprotection. The presence of OH groups in C7 and C5 in flavones reduces their gastroprotective activity. The double bonds in the intact C-2 and C-3 and C-ring appear to be required for the strong activity [180]. Replacing the aromatic B ring with either alkyl group or heterocyclic ring or indole does not alter the gastroprotective properties [30].

3.9. Potential against diabetes

Flavonoids, which have strong antioxidant activity, are believed to be beneficial for treating diabetes [100]. The potential of antioxidants to protect against harmful effects of hyperglycemia, as well as to improve the metabolism and absorption of glucose, should be viewed as a major alternative in diabetes treatment [181]. In addition to their antioxidant effects, flavonoids can act on α-glycosidase which is considered as one of the biological targets involved in diabetes type 2. As free radical scavengers, flavonoids can effectively prevent and / or treat diabetes type 2.
3.9.1. Antidiabetes mechanism of action

Flavonoids have a beneficial effect on diabetes through many pathways such as a) decrease cholesterol synthesis and TG levels, increase functional availability of antioxidants, increase insulin sensitivity glucose utilization, improve cell function and insulin action, reduce carbohydrate metabolism (Fig. 15), they interact with various signaling and metabolic pathways in pancreatic β cells, skeletal muscle, adipose tissue, and liver. Flavonoids increase glucose absorption by white adipose tissue and skeletal muscle. They affect β cell function, mass, insulin sensitivity, energy metabolism and stimulate protein kinases, which are essential for maximum glucose uptake stimulation [21].

3.9.2. Structure activity relationship for Antidiabetes

A study Xu (2010) reported that the di-OH groups at the C3′ and C4′ positions were effectively conjugated to α-glucosidase. The lack of C2-C3 double bonds and ketone groups on C4 in the C ring reduces the inhibitory activity of α-glucosidase and xanthine oxidase. In addition, the presence of a catecholic system in B ring in the absence of the C2-C3 double bond and the ketone group at the C4 position is not significant enough to demonstrate antidiabetic effects. In addition, the acetylation or alkylation of the OH groups in ring A decreases flavonoids bioactivity, demonstrating their inability to interact with enzyme binding sites and scavenging ROS.

In summary, the results of the antidiabetic analysis indicate that the chemical criteria for the flavonoids bioactivity are very important (Fig. 16). The alkyl substitution is important determinant of antidiabetic activity when compared to spine alone. Both the configuration and the number of OH groups have a significant influence on the radical scavenging mechanism [253] and the antidiabetic effect. Therefore, the hydroxyl-configuration, number of OH groups, C2-C3 double bonds and functional C4 ketone groups are the main structure features of flavonoid bioactivities, especially with regard to the antidiabetic effect.

3.10. Potential against fungal infections

Fungal infections cause high mortality rates worldwide. The incidence of increasing drug resistance in fungal diseases continues to increase. The scenario for the existing antifungal drugs and their complications is critical. Antifungal drugs have limitations: high toxicity, renal failure, and low performance. Therefore, it is important to seek new treatments, such as alternative therapies, that may be more active against most fungal diseases. Plants and herbs that contain flavonoids are known for their many therapeutic activities. Various flavonoids have been studied for their antifungal activity and are perhaps the promising, and most potent agents for inhibiting fungal infection [104,12,197,231]. They often inhibit fungal growth in various mechanisms of actions and increase plasma membrane damage and mitochondrial dysfunction, and inhibit cell wall formation, cell division, protein synthesis and the pumping system. These flavonoids are capable and effective in synergistic combination therapy with conventional drugs, which may be more suitable and supportive in finding new drug therapies to fight fungal pathogens ([205]; Jin, Y.S., 2019).

3.10.1. Antifungal mechanism of action

Flavonoids have been widely used for centuries to inhibit fungal growth through various mechanisms (Fig. 17, Table 10). The way flavonoids work as antifungal agents is based on the induction of apoptosis, DNA fragmentation, mitochondrial damage, accumulation of ROS, etc.

3.10.2. Structure activity relationship for antifungal activity

The three main molecular properties that affect the antifungal activity (Fig. 18) are as follows:

Table 8

| Flavonoids          | Mechanism of action                                      | References  |
|---------------------|----------------------------------------------------------|-------------|
| Cyanidin            | Increase eNOS                                             | Xu et al., 2007 |
| Quercetin           | Increase Thioredoxin                                      | Shen et al., 2012 |
| Increase eNOS activity | Increase Phosphorylation of eNOS                           |             |
| Increase NO production | Decrease HOCl-induced endothelial dysfunction              | Qian et al., 2017 |
| Resveratrol         | Increase eNOS                                             | Edwards, et al., 2015 |
| Cyanidin-3-glucoside| Enhance relative coronary flow                             | [24]        |
| Luteolin            | Induce vasorelaxion                                        | [117]       |
|                    | Reducing oxidative stress                                 | [31]        |
|                    | Prevent ischemia-reperfusion injury                       |             |
|                    | Regulate potassium and calcium channels                  |             |

Fig. 14. Flavonoid mechanism of gastroprotective activity.
3.11. Potential against cancer

Cancer is a terrible disease all over the world and one of the biggest problems for human health. New techniques are needed for successful treatment. Many limitations have been noted with conventional

#### Table 9
List of flavonoids with gastroprotective effect and their mechanism of action.

| Flavonoids | Mechanism of action | Ref |
|------------|---------------------|-----|
| Flavones and flavonols | Inhibit H. pylori | [164] |
| Artemisin | Bactericidal kinetics | [42] |
| | Morphological degeneration | |
| Pinostrobin | Decrease gastric motility | [2] |
| Catechin | Urease inhibitor | [171] |
| | Anti-inflammatory | [251] |
| | | [226] |
| Isoflavonoids | Inhibit ulcer | [289] |
| | Eradicate H. pylori | [259] |
| Curcumin | Inhibit proton potassium ATPase | [294] |
| | Chemo-preventive | [112] |
| 4-methoxy quercetin-7-O-glucoside | Chemopreventive | [220] |
| | | [103] |
| Glabridin | Anti-adhesive activity | [17,279] |
| | Inhibit dihydrofolate reductase | |
| | Inhibit DNA gyrase | |
| Licoicidin | Chemopreventive agents | [71] |
| | | [11] |
| Leucocyanidin | Increase mucus | [145] |
| | | [113] |
| Baicalein and chrysine | Inhibit NADH oxidation | [190] |
| | | [11] |
| Vitexin | Release myeloperoxidase | [249] |
| | Inhibit H + ,K + ATPase activity | [215] |
| Quercetin | Acetylation | |
| | Anti-inflammatory | |
| | Antiulcer invivo | |
| | Analgesic | |
| Emodin | Damage DNA H. Pylori | [271] |
| Kampferol | Reduce gastric PH | [169] |
| | Participate No and SH | |
| Rutin | ulcer-protecting effects against gastric lesions | [136] |
| Resveratrol | Chemo-preventative | [204] |
| | Antioxidant | |
| 7-carboxymethyloxy-3,9,49,5-trimethoxyflavone | suppresses the H. pylori-induced IBD by targeting NF-kB and ERK | [267] |
| | | [109] |

Fig. 15. Flavonoid mechanism of antidiabetic activity.
treatments, including the high cost and high toxicity of current cancer drugs. Such a situation poses great challenges for all scientists and requires the development of new drugs that are environmentally friendly and have a more financially sound methodology. In this context, the high biodegradability and biocompatibility of phytocombinants increase their effectiveness in treating cancer [1]. In this sense, special attention is paid to improve cancer drugs using plant phytocompounds. Their potential, availability and low cost compared to modern therapeutic drugs for the treatment of dangerous diseases make them more attractive [184] (El Gengaihi et al., 2016a, 2016b).

3.11.1. Anticancer mechanism of action
So far, various mechanisms have highlighted the role of flavonoids in cancer therapy (Fig. 19, Table 11), including inhibition of proteasomes, induction of apoptosis, differentiation and cell cycle arrest [132,133, 243], inhibition of nuclear factor signaling [13], and receptor interaction [96]. In addition, flavonoids may exhibit specific cytotoxicity for cancer cells, which is drawing much attention to flavonoid cytostatics as anticancer prodrugs [296].

Fig. 16. Summary of antioxidant structure-activity relationships of flavonoids.

Fig. 17. Flavonoid mechanism of antifungal activity.
Table 10
List of flavonoids with antifungal effect and their mechanism of action.

| Flavonoids          | Mechanism of action                                      | References |
|---------------------|----------------------------------------------------------|------------|
| Baicalein           | Disrupt plasma membrane                                  | [120]      |
|                     | induce apoptosis                                          | [241]      |
|                     | Elevates ROS                                             | Tsang et al., 2010 |
| Catechin            | Activate phosphatidylserine                              | [57]       |
|                     | Inhibit fatty acid synthase                              |            |
|                     | Increase ROS                                             |            |
|                     | Induce apoptosis                                          |            |
|                     | Mitochondrial depolarization                             |            |
|                     | DNA fragmentation                                         |            |
| Glabridin           | Decrease cell size                                       | [179]      |
|                     | Increase membrane permeability                           |            |
|                     | DNA fragmentation                                         |            |
|                     | Chromatin condensation                                   |            |
| Wogonin             | Accumulate ROS in mitochondria                           | [58]       |
|                     | Decrease membrane potential                              |            |
|                     | Reduce ATP synthesis                                     |            |
| Resveratrol, curcumin and quercetin | Inhibit oxidative phosphorylation of mitochondrial proteins | [192,193] |
|                     | Increase ROS in mitochondria after MODULATION            | [79]       |
|                     | Control mitochondrial proteins’ expression               |            |
|                     | Exhibit proapoptotic functions                           |            |
|                     | Upregulate Bcl-2 expressions                             |            |
|                     | Downregulate anti-apoptotic proteins                     |            |
| Apigenin            | Disrupt plasma membrane                                  | [142]      |
| Chrysinarin         | Inhibit cell cycle                                       | [167]      |
| Alizarin            | Inhibit hyphal formation                                 |            |
| Honokiol            | Inhibit effects on the cell cycle and biofilm formation  | [250]      |
| Magnolol            | Inhibit cell division                                    | [270]      |
| Daphnegravone D     | Arrest G0/G1 phase                                       |            |
|                     | Induce apoptosis                                          |            |
|                     | Reduce CDK2, CDK4 and cyclin E1, E1 expression           |            |
|                     | Increase caspase 3 and PARP                              |            |
| Baicalein           | Inhibit lipooxygenase                                    | [97]       |
| diocerin D          | Inhibit efflux pump                                      | [148]      |
|                     | Decrease Cde1 expression                                 |            |
| Apigenin, luteolin, wogonin, tangerin, baicalein scutellaren, chrysin, sedonan A | Inhibit efflux pumps | [293] |
|                     | Inhibit cell death                                       | [241]      |
|                     | Increase membrane permeability                           | [238]      |
| Dorsmanin           | Inhibit efflux pumps                                     | [29]       |
| 5-flurocytosine     | Inhibit efflux pumps                                     |            |
|                     | Formation of fluorinated pyrimidine metabolites, deficit of cytosine deaminase | [174] |
|                     | Deregulate pyridine biosynthesis                         |            |
| Catechin            | Inhibit nucleic acid synthethsis                         | [229]      |
|                     | Reduce the hypha-specific gene expression                |            |
|                     | Inhibit FCS-induced hyphal formation                     |            |
| Myricetin, kaempferol, fisetin, luteolin narigenin genistein | Inhibit filamentous fungus | [40] |
|                     | Inhibit nucleic acid synthethsis                         |            |
|                     | Cochliobolus lunatus                                     | [213]      |
| Apigenin            | Interfere with the translational activity of fungal foot-and-mouth disease | [285] |
| Carvacrol           | Inhibit nucleic acid synthethsis                         | [305]      |
|                     | Disrupt the cellular cytoplasmic membrane                |            |
|                     | Induce apoptosis                                          |            |
| Lico A              |                                                          | [37]       |

Table 10 (continued)

| Flavonoids          | Mechanism of action                                      | References |
|---------------------|----------------------------------------------------------|------------|
|                     | Biofilm formation                                        |            |
|                     | Inhibit glucan synthase, ergasterol synthesis and efflux pumps |            |
|                     | Induce apoptosis                                          | [129]      |
| Fisetin             | Inhibit ergasterol biosynthesis                          | [223]      |
| Isoquercetin        | Bind to ergasterol and disrupt cell membrane             | [129]      |
| Baicalein           | Biofilm formation                                        | [38]       |
|                     |                                                          | [135]      |
| Glabridin           | Inhibit nucleic acid synthethsis                         | [44]       |
| Apigenin            | Inhibit glyoxylase cycle                                 | [142]      |
| Silymarine          | Disrupt membrane                                         |            |
|                     | Increase membrane permeability                           |            |
|                     | Decrease membrane fluidity                               |            |
|                     | Membrane depolarization and K+ leakage                  |            |

3.11.2. Structure activity relationship for anticancer activity

The important role of the C2=C3 double bond is essential for strong tumor inhibition [132,133,96]. In addition, greater inhibition will occur if the two hydroxyl groups of ring B exist side by side and C2=C3 is unsaturated [96]. It should be noted that many reports provide evidence of the effect of hydroxylation on tumor modulation. Specific hydroxylated flavonoids have a stronger inhibitory effect on cancer cells than permethoxylation analogs. It is proposed to replace the B ring as a catechol part with vital influence. Meanwhile, the additional substitution of hydroxyl groups on ring B does not change the activity [132,133]. In the case of the C ring, 3-hydroxylation is seen as a very important component in enhancing the biological effect [13]. The flavonoid derivatives of O-methylation contribute to increased biological activity, which is often associated with ring A polymethylation. According to previous studies, glycosylation does not contribute to the induction of cell differentiation [132,133] (Fig. 20).

3.12. Potential against bacterial infection

The development of antibiotic resistance in bacteria is a global problem that requires the search for more potent phytocompounds derived from nature to overcome this problem. Flavonoids are phyto-compositions with antibacterial, antioxidant and anti-inflammatory potential. In this way, flavonoids can be developed into new antimicrobial agents in food and therapeutical products.

3.12.1. Antibacterial mechanism of action

The proposed flavonoid antibacterial mechanisms (Fig. 21, Table 12) are mainly as follows: Inhibition of energy metabolism, inhibition of cell proliferation, inhibition of nucleic acid synthesis, reduction of biofilm formation and cell adhesion, attenuation of pathogenicity [54] and damage to membranes possibly by producing hydrogen peroxide (Cushnie and Lamb, 2005).

3.12.2. Structure activity relationship for antibacterial activity

The amphipathic properties of flavonoids play an important role in their antibacterial properties [65]. Hydrophobic substituents like alkyl chains, alkylamino chains, prenyl groups and heterocyclic units containing oxygen or nitrogen usually increase flavonoids antibacterial activity [285]. The number and position of the prenyl groups in ring A increased activity, but the addition of the prenyl groups to another ring decreased activity. In addition, it has been reported that the presence of OH groups at different positions on rings A and B increases antibacterial activity [172,173,194,195]. The number of glycosyl groups instead of OH groups at different positions on rings A and B increases antibacterial activity [172,173,194,195].
methoxylation of position 3 [20].

3.13. Potential against viral infection

Viral infections are very difficult to control than bacterial infections, while antiviral agents are the least available. Natural phytocompounds provide a powerful resource for antiviral agents. Flavonoids exhibited potent antiviral activity (Table 13) [295]. Flavonoids stop HIV cell by the phosphorylation of proteins and inhibition of cytokines [147,150,19,201].

3.13.1. Flavonoids potentiality against CoVs

Coronavirus is responsible for the increasing severity of death causing COVID-19 disease. However, there is still a lack of antiviral drugs that are effective against the coronavirus. In short, there is a worldwide need for concerted efforts to combat such disease in the future. Most of the publications focus on polar compounds. Compounds that show promise in inhibiting coronavirus are scotelarein, silvestrol, tryptanthrin, saicozaponin B2, myricitin, quercetin, caffeic acid, isabavacalcone, and psoralidin. The most promising small molecule identified as a coronavirus inhibitor has been found to contain a conjugated fused ring structure, most of which are classified as flavonoids. An important area of research is the inhibitory effect of flavonoids on the coronavirus. Flavonoids existing naturally offer a large amount of biological diversity, including antiviral activity, and therefore may be useful as therapy against coronavirus infection. Flavonoids can prevent or modulate SARS-CoV-2 infection by many mechanisms (Fig. 23, Table 14) such as inhibiting spike glycoprotein, N protein, TMPRSS2 replication protein, ACE-2 entry receptor, protease, helicase, RNA-dependent RNA polymerase, activating Nrf2, and stimulating innate immunity ([295]; Antonio et al., 2020; Fuzimoto and Isidoro et al., 2020; [50,227,264,265,283]).

The sequence of effectiveness of anticovid-19 flavonoids is as follows kaempferol > quercetin > luteolin-7-glucoside > demethoxycurcumin > naringenin > apigenine-7-glucoside > oleanuropein > curcumin > catechin > epigallocatechin > zingerol > gingerol > allicin [123].

3.13.2. Structure activity relationship for antiviral activity

Structurally, the antiviral activity increases with the decrease in the number of OH groups in the B-ring. Meanwhile, the C2=C3 double bond present in the C ring is seen as an important element which is beneficial for antiviral activity. In addition, trifloroside belongs to the group of dihydrocarbons without a flavonol structure, which has very little antiviral activity. This may be due to the hydrogen bonding formed by the galloyl group with amino acid residues at the active site of the enzyme [43].

Flavonoids exhibited significant binding at the N3-binding site compared to the main CoV protease inhibitor currently used, darunavir. The flavonol basic structure and the presence of a routine unit at position 3 in ring C and the absence of OCH3 group on the B ring of the
### Table 11
List of flavonoids with anticancer effect and their mechanism of action.

| Flavonoids   | Mode of action                                                                 | References |
|--------------|--------------------------------------------------------------------------------|------------|
| Genistein    | Increases expression of Bax, P2, GTP, glutathione peroxidase                  | [168]      |
|              | Inhibit topoisomerase II and NF-kB                                            | [160]      |
| Apigenin     | Caspases activation, GSH, GST, GPx, GTP, STAT3                                | [28,240]   |
|              | Inhibit signal transducer                                                     |            |
|              | Block phosphorylation of JAK2 and STAT3                                      |            |
| Resveratrol  | Increase p53 and Bcl2 of X protein                                            | [33]       |
|              | Decrease PI3K, Akt, MMP, Bcl2                                                | [202]      |
|              | Reduce MAP kinase phosphorylation                                            | [263]      |
|              | Inhibit angiogenesis                                                          |            |
| Kaempferol   | Activation caspase 3, p53 Cdc2, CDK2, CDK4, inhibition                         | [139]      |
|              | G1, G2, M phase arrest                                                        | [80]       |
| Chrysin      | G1, G2, M phase arrest                                                        | [121]      |
|              | Induce apoptosis                                                              | [228]      |
| Flavopiridol | Inhibit cyclin dependent kinase                                               | [266]      |
|              | Inhibit Topoiso merase-1                                                      | [111]      |
|              | G1, G2, M phase arrest                                                        |            |
| Cyanidin     | Inhibition of COX-1 and II                                                   | [125]      |
|              | MMP-2 and 9 EnK, JNK, TNF alpha                                               |            |
| Silamarin    | Induce apoptotic factors                                                     | [140]      |
|              | Inhibition of anti-apoptotic factors                                          | [254]      |
|              | G1, G2, M phase arrest                                                        |            |
| Epigallocatechin Gallate   | Stimulate genes expression of tumor suppression                             | [183]      |
| Oroxylin A flavone | Decrease COX-2 and iNOS                                                        | [45]       |
|              | Block NF-kB                                                                   | [81]       |
| Quercetin    | Scavenge ROS                                                                  | [23]       |
|              | Cell proliferation signaling pathways                                          | [158]      |
|              | NF-kB, MAPK, STAT3, PI3K/Akt, mTOR                                             |            |
|              | Decrease growth factors                                                       |            |
|              | Induce apoptosis and cell cycle arrest                                        |            |
| Luteolin     | Induce cell cycle arrest                                                     | [106]      |
|              | Induce apoptosis                                                              |            |
|              | Cytoskeleton shrinkage                                                        |            |

**Fig. 20.** Structure activity relationship of cytisine-flavonoid conjugates as potent anti-breast cancer agent.
flavonol structure can increase the anti-COVID-19 activity [295].

Fig. 24 shows the interaction between phenyl group in kaempferol and corona virus catalytic center, which is the hydrophilic task of the corona virus through hydrogen bonding with Glu166. Another hydrogen bond is formed between the OH group and Asp142, Ile188, while the chromen-4-one backbone is at the hydrophobic S2 site [119].

4. Conclusion and future approaches

In order to summarize the ongoing review, some main points are to be highlighted. Flavonoids could be effective drugs against the most dangerous degenerative diseases in the future. Compared to other natural plant phytochemicals, flavonoids can significantly enrich the pathways of breast cancer, Huntington’s disease, Alzheimer’s disease, insulin resistance, and drug resistance. In this regard, its versatile therapeutic capabilities demonstrate the usefulness of flavonoids in producing drugs related to cancer and the nervous system.

Various physicochemical and structural properties of flavonoid can be attributed to differences in activity and can be found in physicochemical characteristics, including H bond donors, H bond acceptors, topological polarity surface area and water-lipid partition coefficients, because the proper solubility and water lipid partition coefficient play an important role in the effectiveness of the drug.

Since flavonoids contain the same skeleton, the functional differences are mainly related to the replacement groups. The relationship between the chemical constitution fragments and the biological effects

![Table 12](image)

**Table 12**
List of flavonoids with antimicrobial effect and their mechanism of action.

| Flavonoids    | Mode of action                                                                 | References |
|---------------|-------------------------------------------------------------------------------|------------|
| Silymarin     | Inhibit ATP synthase                                                          | [75]       |
| Chalcon       | Inhibit NADH-cytochrome c reductase activity                                  | [86]       |
| Quercetin     | Inhibit reflux pumps, Decrease lipid peroxide, Inhibit DNA gyrase and protein kinase, Disrupt cell membrane | [46], [242], [257] |
| Apigenin      | Inhibit peptidoglycan crosslinking, Inhibit dehydratase and protein kinases   | [242]      |
| Naringenin    | Disrupt membrane                                                              | [64]       |
| Epicatechin   | Inhibit nucleic acid synthesis, Inhibit dihydrofolate reductase, Inhibit quorum sensing | Cushnie et al., 2011 |
| Myricetin     | Inhibit helicase                                                              | [239]      |
| Luteolin      | Inhibit topoisomerase                                                        | [272], [79] |
| Kaempferol    | Inhibit bacterial virulence                                                    | [176]      |
| Taxifolin     | Inhibit peptidoglycan synthesis and fatty acid synthase                       | [76]       |
| Glabridin     | Inhibit DNA gyrase and dihydrofolate reductase                               | [17]       |
| Emodin        | DNA damage                                                                    | [63]       |
| Catechin      | Disrupt cell membrane                                                        | [217]      |
|               | Damage cytoplasmic membrane by perforation                                   |            |
suggests that significantly different side chains can influence flavonoid activity in the same target. Apart from general biological functions, the specific functions of the various subclasses of flavonoids were analyzed and demonstrated at the target and pathway levels. For example, flavones and isoflavones were significantly amplified in a pathway associated with more cancers than others, suggesting potential therapeutic benefits in treating cancer. Flavan-3-ols have also been found in cellular processing and lymphocyte regulation, flavones have a specific effect on cardiovascular activity, and isoflavones are closely related to cellular multisystem disorders.

Cumulative structure activity relationship findings from previous pharmacological reports provide useful evidence for the role of different functional groups in nutritional benefits. Based on the description above, it can be concluded that the 4-carbonyl group, the C2=C3 double bond, and the hydroxylation pattern, especially the 3-OH and catechol residue in the B ring, are the main known factors of the therapeutical effects of flavonoids. For example, the beneficial effect of hydroxylation is achieved in terms of exclusive antiviral, antibacterial, cardioprotective, anti-diabetic and carcinogenic effects. O-methylation is useful for antiviral, antibacterial, anti-diabetic, but of lower benefit for

Fig. 22. Summary of antibacterial structure-activity relationships of A) chalcones, B) flavans, C) flavanols, D) flavonols and E) flavones.
### Table 13
Antiviral potentialities of some flavonoids and their mechanism of action.

| Flavonoid                          | Activity against virus                                      | References                        |
|-----------------------------------|-------------------------------------------------------------|-----------------------------------|
| Glabranine 7-O-methyl-glabranine  | Dengue virus                                                | [280]                             |
| 5-hydroxy-7,8-Dimethoxyflavone    | Anti-influenza viruses                                      | Wu et al., 2010                   |
| Vitexin                           | Para influenza type 3 virus                                 | Peterson 1991                     |
| Orientin                          | Para influenza type 3 virus                                 | Pang et al. 2013                  |
| Quercetin                         | HCV, polio, herpes simplex                                 | Chwil et al. 2014                 |
| Naringenin                        | HCV                                                         | Ashfaq and Idrees 2014            |
| Apigenin                          | Anti-influenza viruses, HCV, Enteovirus-71                 | Grienke et al. 2012               |
| Quercetin                         | Mayaro virus                                               | Santos et al. 2014                |
| 7-hydroxyisoflavone               | Enteovirus71                                                | Wang et al. 2013                  |
| Acacetin                          | Anti-influenza viruses                                     | Wu, Yu et al. 2010                |
| Liquiritigenin                    | HCV                                                         | Adianti et al. 2014               |
| Chrysospheneol C Pterocaulonsphacelatum | Polio virus                                                | Bhatti 1999                      |
| Eudraflavone B hydroperoxide      | Herpes simplex type 1 virus                                 | Rocha Martins et al. 2011         |
| Morbalanone                       | Herpes simplex type 1 virus                                 | Farmer et al., 2012               |
| Ladanein                          | HCV                                                         | Haid et al. 2012                  |
| Leachianone G                     | Herpes simplex type 1                                       | Zafar et al. 2013                 |
| Baicalin                          | HIV                                                         | [147]                             |
| Myricetin                         | HIV                                                         | [201]                             |
| Flavonol-7-O-glucoside herbacitin | HIV-1                                                       | [19]                              |

![Fig. 23. Different actions of flavonoid on CoV.](image-url)
Table 14
List of flavonoids inhibiting corona virus and their mechanism of action.

| Flavonoids               | Mechanism of action                      | References |
|--------------------------|------------------------------------------|------------|
| Quercetin                | Inhibit viral replication                 | Jo et al., 2019 |
|                          | Inhibit viral entry into the host cells  | (264,265)  |
|                          | Block interaction sites                   |            |
|                          | Stop viral spread                         |            |
| Theaflavin-3,3-digallate | Inhibit protease                          | [47]       |
| Resveratrol              | Suppress viral replication                | [146]      |
| Luteolin                 | Suppress viral replication by inhibiting N protein | Yi et al., 2004 |
| Bavachinin               | Inhibit protease                          | [127]      |
| Neohesperidin            | Inhibit protease                          | [48]       |
| Jatropha lactea          | Inhibit protease                          | [159]      |
| Juglanin                 | Blocks the 3a channel and inhibit virus release | Schwarz et al. 2014 |
| Myricetin scutellarein   | Inhibit helicase                          | Yu et al., 2012 |
| Kampferol                | Interact with coronavirus catalytic site  | [119]      |
| Emodin                   | Inhibit spike glycoprotein                | [237]      |
| Theaflavin               | Inhibit RNA-dependent RNA polymerase (replication enzyme) | [159]     |
| Hesperetin, hesperidin   | Inhibit ACE2, major receptor of corona virus | Cheng et al., 2020 |
| Naringin, naringenin     | Inhibit protease                          | [175]      |
| Herbacetin, rhoifolin, pectolinarin | Inhibit protease by forming H bonds in the active site | Kim et al., 2020 |
| 5,7,3’,4’tetrahydroxy-2’-C3,3’-dimethylallyl)isoflavone | Competitive inhibition of papain-like protease | [211,212] |
| Quercetin-3 galactoside  | Form H bond with protease receptors       |            |
| Tomentin                 | Inhibit protease                          | [49]       |
| Papyriflavonol A         | Inhibit protease                          | [199]      |
| Cynadin                  | Inhibit RNA polymerase                    | [264,265]  |
| Quercetin, phloretin, daidzein, arbutin, genistein, fisetin, myricetin, liquiritin, kaempferol, eriodictyol and chalconaringenin | Halting viral replication | [264,265] |
| Naringenin               | Inhibit spike protein and therefore inhibit viral spread | [258]     |
| Ponasinid                | Inhibit ACE2 receptor                     |            |
|                         | Inhibit replication                       |            |

Fig. 24. Interaction sites in kaempferol with CoV catalytic site by formation of hydrogen bond.

anti-inflammatory and anti-cancer effects. In general, glycosylation can reduce the associated activity as anti-Alzheimer’s disease, but on the contrary increases the antiviral and antibacterial effects.

However, future approaches and further research efforts at the clinical level and in the field of bioavailability will provide a deeper understanding of the therapeutic effects of flavonoids on human health in general.

Conflict of interests

The author declares that they do not have any conflict of interests.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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