



## A Review on Antimicrobial and Other Beneficial Effects of Flavonoids

Edewor-Kuponiya, Theresa Ibibia\*

Ladoke Akintola University of Technology, Ogbomosho, Nigeria.

\*Corresponding author's E-mail: [ibitheresa@yahoo.com](mailto:ibitheresa@yahoo.com)

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### ABSTRACT

Flavonoids constitute one of the most characteristic classes of natural phytochemicals present in higher plants. The study of flavonoids emerged as a result of search for new bioactive compounds. Different plant families have characteristic patterns of flavonoids and their conjugates. All these compounds play important biochemical and physiological roles. They are important components of human and animal diets. Due to their biological activities their regular consumption may have serious health consequences both positive and negative. This study is aimed to undertake a literature review of flavonoids covering the period 1983-2012. The objective was to contribute to a better knowledge of the beneficial effects of flavonoids. As such, the compilation of the accumulated knowledge concerning flavonoids will aid in the evaluation of its pharmacological values.

**Keywords:** Flavonoids, phytochemicals, antimicrobial, pharmacology.

### INTRODUCTION

Flavonoids are a group of phytochemicals found in different parts of plants. They are known to be responsible for colours of many flowers and fruits, and protection of plants against pathogens, insects and UV B radiation.<sup>1, 2</sup> They are also involved in photosensitization, energy transfer, the actions of plant hormones and regulators, control of respiration, photosynthesis, morphogenesis and sex determination<sup>3</sup>. The first set of flavonoids were discovered by Albert-Szent-Gyorgyi who called them vitamin P<sup>4</sup>. Some plants secrete bioflavonoids that inhibit the growth and germination of seeds of nearby plants of a different species<sup>5</sup>. The widespread distribution of flavonoids, their variety and their relatively low toxicity compared to other active plant compounds (for instance alkaloids) mean that many animals, including humans, ingest significant quantities of flavonoids in their diet. Several preclinicals and some clinical studies have shown that people who take diets rich in foods with flavonoids have reduced risk of developing cancer and cardiovascular disease<sup>6-11</sup>. Preclinical studies have been able to show some probable mechanisms by which flavonoids may confer cancer and cardiovascular protection<sup>12</sup>. Flavonoids have been referred to as "nature's biological response modifiers" because of strong experimental evidence of their inherent ability to modify the body's reaction to allergens, viruses, and carcinogens. The flavonoids comprise a large group of plant secondary metabolites which are characterized by a diphenylpropane structure (C<sub>6</sub>-C<sub>3</sub>-C<sub>6</sub>) (fig. 1). The two C<sub>6</sub> groups can be substituted or not while the C<sub>3</sub> is an aliphatic chain which may contain a pyran ring.

They can occur as O- or C- glycosides or in the free state as aglycones with methoxy or hydroxyl groups present on the aglycone<sup>13</sup>. They are divided into 7 types; flavones, neoflavonoids, flavanones, chalcones, xanthones, isoflavones and biflavones<sup>14</sup>; but some authors have

classified them according to their biosynthetic origin. For e.g. compounds such as chalcones, flavanones, flavan-3-ols and flavan-3, 4- diols are known to be intermediates as well as end products in biosynthesis. Other classes of compounds which are only end products of biosynthesis are anthocyanidins, proanthocyanidins, flavones and flavonols, isoflavonoids, and neoflavonoids. The structures of the different types of flavonoid are shown in fig 2.

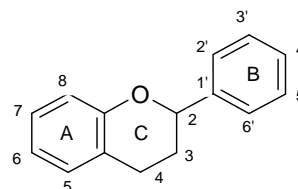


Fig. 1: Basic structural feature of flavonoids

Treatment of diseases with pure pharmaceutical agents is gradually losing ground and micro-organisms are developing resistance to these drugs. People are turning to nature for their healthcare. More research work is on going to determine which plants and plant parts can be used for the treatment of ailments. Flavonoids have been found to possess a variety of biological functions and therefore have been the subject of medical research. These functions include antimicrobial, anti-inflammatory, estrogenic activity, enzyme inhibition, antiallergic activity, antioxidant activity<sup>15</sup>, antitumour activity, vascular activity and antimalaria activity. They have also been used for the treatment of diabetes mellitus and skin infection.

Consumers and food manufacturers have become interested in flavonoids for their medicinal properties, especially their potential role in the prevention of cancer and cardiovascular diseases. The beneficial effects of fruits, vegetables, and tea or even red wine have been attributed to flavonoid compounds rather than to known nutrients and vitamins. This article focused on those

flavonoids with antiplasmodial, antimicrobial, antioxidant and anti-inflammatory activities that are most often encountered in nature and for which an analysis of possible structure-activity relationship exist.

## METHODOLOGY

An extensive bibliographic search was undertaken to identify works on medicinal plants that contain flavonoids

published in data banks, periodicals, monographs and rare or current texts stored in public and private libraries during the period between 1983 and 2012, Chemical Abstracts; ICBN - International Code of Botanical Nomenclature; FDA - Food & Drugs Administration (USA), and similar sources. In addition, proceedings of scientific congresses and websites were also consulted.

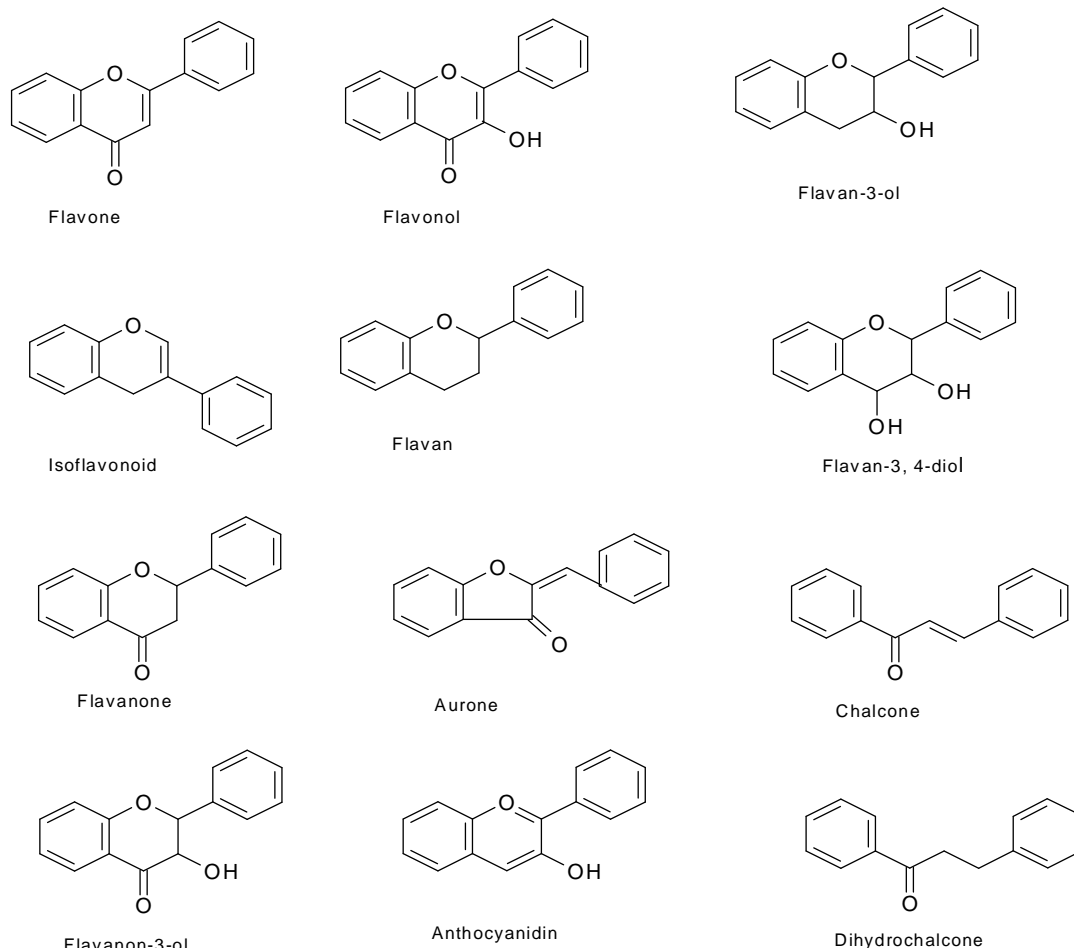


Fig. 2: Different types of flavonoids

## DISCUSSION

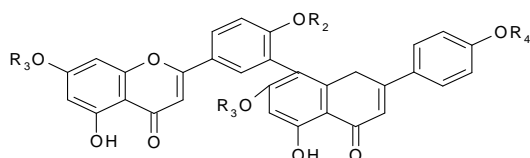
### Antiplasmodial activity

Malaria is known as the most dangerous infection in many subtropical and tropical regions of the world<sup>16</sup>. The malaria parasite is exhibiting increased resistance against the available antimalarial drugs. Natural products have been known to be useful medicinal agent for the treatment of human diseases. Scientists are currently working towards obtaining new antimalarial leads from subtropical and tropical plants. Discussed here are flavonoids that have been shown to exhibit significant antiplasmodial activity against the malaria parasite, *Plasmodium falciparum*.

Morelloflavone and volkensiflavone isolated from *Endodesmia calophylloides* (Guttiferae) were found to be

active against the W2 chloroquine- resistant strain of *falciparum* with  $IC_{50}$  7.40  $\mu$ g/ml and 7.60  $\mu$ g/ml<sup>17</sup>. The flavonoids citflavanone, ionchocarpol A and 8-prenylldaizein obtained from the stem bark of *Erythrina fusca* Lour exhibited in-vitro antiplasmodial activity at a concentration less than 12.5  $\mu$ g/ml. It was observed that the diprenylated flavanone with  $IC_{50}$  = 3.9  $\mu$ M was potent; while other flavonoids such as lupinifolin and rythrisenegalone which were also isolated from the same plant part were observed to be inactive<sup>18</sup>. This shows that the position of the prenyl groups in the flavonoid is important for it to exhibit anti-plasmodial activity. The flavonoids (deguelin,  $\beta$ -hydroxydihydrochalcone and obovatin isolated from *Tephrosia elata* (fabaceae) were observed to exhibit antiplasmodial activity against chloroquine-sensitive Sierra Leone I (D6) and chloroquine

resistant Indochina I (W2) strains of *P. falciparum*. They were found to have  $IC_{50}$  values up to  $27.60 \mu M$  against these strains while  $\beta$ -hydroxydihydrochalcone exhibited activity with  $IC_{50}$  value of  $8.2 \pm 0.80$  and  $16.30 \pm 0.90 \mu M$  against D6 and W2 strains respectively<sup>19</sup>. From a series of 12 biflavonoids isolated from the Indian medicinal plant *Selaginella bryopteris*, two of the biflavones (fig. 3) exhibited antiplasmodial activity with  $IC_{50}$  value of 0.30 and 0.26  $\mu M$  respectively.



Compound 1 -  $R_1 = H$ ;  $R_2 = CH_3$ ;  $R_3 = R_4 = H$   
Compound 2 -  $R_1 = CH_3$ ;  $R_2 = H$ ;  $R_3 = R_4 = CH_3$

Fig. 3: Biflavones from *Selaginella bryopteris*

A series of flavone derivatives magiferin and three of its derivatives (fig. 4) were isolated from the methanolic extract of the leaves of *Arrabidaea patellifera* (Bignoniaceae), a plant that grows in Panama. These compounds were found to exhibit moderate antiplasmodial activity against chloroquine-sensitive *P. falciparum* 3D7 clone with an  $IC_{50}$  value of 23.80, 26.50, 18.10 and greater than 38.20  $\mu M$ , respectively<sup>20</sup>. *Piptadenia perillei* Varke (Fabaceae) was one of the plants screened in Madagascar for antimalarial activity. Fractionation of the ethyl acetate extract of the leaves led to the isolation of (+)-catechin, (+)-catechin 5-gallate and ethyl gallate. (+)-catechin-3- and (+)-catechin-5-gallate exhibited antiplasmodial activity against chloroquine-resistant strain FcB1 of *P. falciparum* with  $IC_{50}$  values of 1.2  $\mu M$  and 1.0  $\mu M$  respectively, while (+)-catechin did not have any significant activity. The researchers observed that the activity of these compounds was associated with the presence of gallate ester. Luteolin which was among a series of common dietary flavonoids screened for antiplasmodial activity against the growth of 2 strains of *P. falciparum* was observed to be the most potent with an  $IC_{50}$  values of  $11.0 \pm 1.0$  and  $12.0 \pm 1.0 \mu M$  for chloroquine-sensitive (3D7) and chloroquine-resistant (7G8) respectively. It was found to prevent the progression of growth of the parasite beyond the young trophozoite stage but did not affect the parasite's susceptibility to the malarial drugs chloroquine and artemisinin<sup>21</sup>.

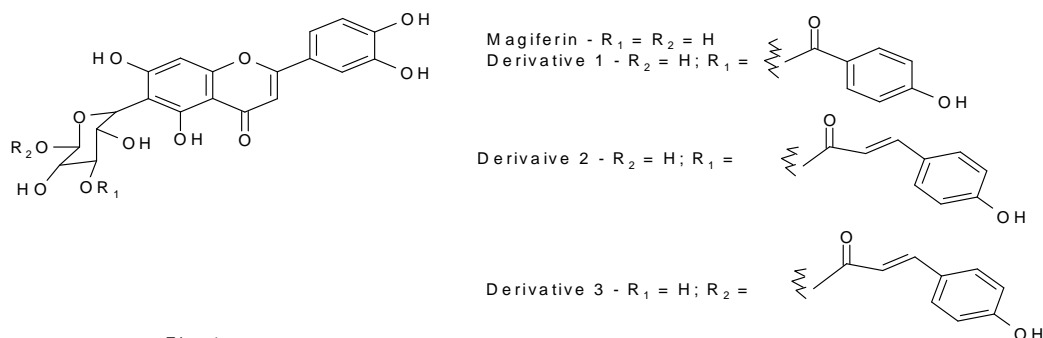


Fig. 4: Magiferin and its derivatives

## Cytotoxicity

Cytotoxicity is a degree of specificity to which an agent can destroy a particular cell. Cells treated with the cytotoxic agent may undergo necrosis in which they lose membrane integrity and die rapidly as a result of cell lysis. The active growth and division of the cells can stop or the cells can activate a genetic program to control the death of cells. Compounds that have cytotoxic effects often compromise cell membrane integrity<sup>1</sup>.

Damage from reactive oxygen species was proposed as being responsible for carcinogenesis. Damage of the DNA and division of cells with unrepaired or mis-repaired damaged cells can lead to mutation and possibly increase the exposure of DNA Mutagens. Stefani et al showed that flavonoids can inhibit carcinogenesis. Fotsis et al stated that flavonoids such as luteolin, apigenin and Fisetin are potent cell proliferation inhibitors. Researchers who carried out clinical study to determine the relation between flavonoid (quercetin) intake and incidence of lung cancer suggested an inverse association between them<sup>24</sup>. Caltagirone et al showed that quercetin and apigenin inhibited the growth of melanoma and also influenced the invasive and metastatic potential in mice. Meanwhile the flavonoids (kaempferol, 3-O-3'', 6''-di-O-p-hydroxy cinnamoyl- $\beta$ -galacto-pyranosyl kaempferol, 6''-O-p-hydroxy cinnamoyl- $\beta$ -galactopyranosyl kaempferol) were shown to exhibit significant anti-proliferative action when compared to quercetin. These flavonoids showed inhibitory and non-selective effects on DNA-topoisomerase I and II<sup>26</sup>.

The following prenylated flavonoids were obtained from the root bark of *Berchemia discolor* obtained from Tanzania: (6aS, 11aS)-2-hydroxyeleocarpin, discoloranone A (5, 2'-dihydroxy-3', 4'-methylenedioxy-3'', 3''-dimethylpyrano [7, 8] isoflavanone), isodiscoloranone A ((3S)-5, 2'-dihydroxy-3', 4'-methylenedioxy-3'', 3''-dimethylpyrano [6, 7] isoflavone), discoloranone B ((3S), 5, 2', 3' -trihydroxy-4'-methoxy-3''-methyl-3''-(4-methylpent-3-enyl)pyrano [7, 8] isoflavanone), isodiscoloranone B ((3S)-5, 2', 3'-trihydroxy-4'-methoxy-3''-methyl-3''-(4-methylpent-3-enyl) pyrano [6, 7] isoflavanone); alongside with nitidulin, amorphigenin and dabinol, but only discoloranone B, nitidulin and dabinol exhibited cytotoxic activity ( $ED_{50} = 5 \mu g/mL$ ) for one or more cell lines while nitidulin was active in 3 human cancer cell lines.

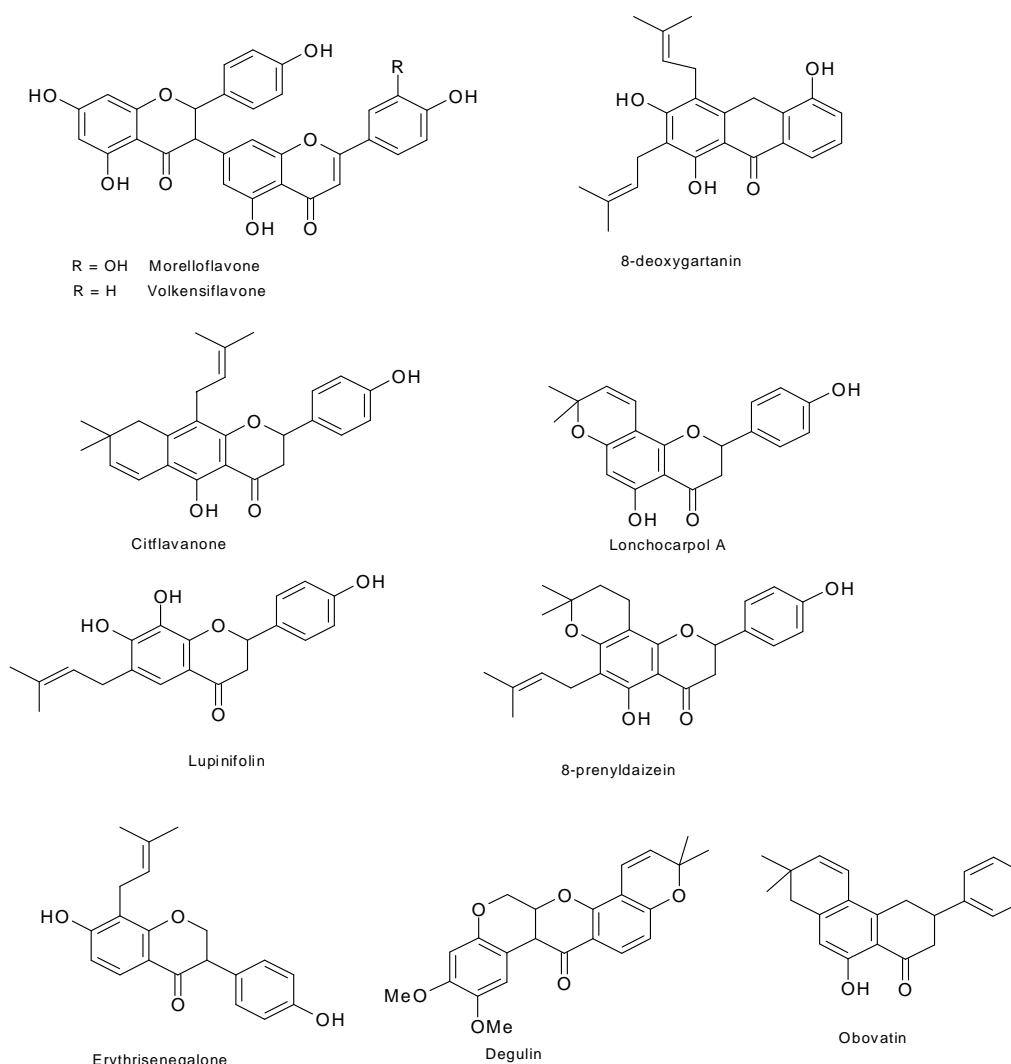


Fig. 5: Some antiplasmodial flavonoids

Nitidulin, dabinol and amorphigenin exhibited cytotoxicity when evaluated against small panel of human cancer cells. Nitidulin was found to be active against LNCaP (human hormone-dependent prostate cancer) cells implanted intraperitoneally at doses of 10, 20 and 40 mg/Kg<sup>5</sup>.

### Antioxidation

Antioxidants are compounds that protect cells against the damaging effects of reactive oxygen species, such as singlet oxygen, superoxide, peroxy radicals, hydroxyl radicals and peroxynitrite. An imbalance between antioxidants and reactive oxygen species results in oxidative stress, leading to cellular damage. These species are produced in an organism during oxygen metabolic reactions or are induced by exogenous damage<sup>27</sup> that contributes to the development and maintenance of cellular life<sup>28</sup>. Body cells and tissues are continuously threatened by the damage caused by these free radicals due to reaction with endogenous molecules such as DNA, proteins and lipids. Flavonoids have been found to have an additive effect to endogenous scavenging compounds and can interfere with three or more different free radical producing systems<sup>29</sup>. Korina and Afanas'ev observed that

flavonoids can prevent injuries caused by free radical by reacting with the reactive compound of the radical. This could be achieved due to the high reactivity of the hydroxyl groups on the flavonoids<sup>30</sup>. By directly scavenging radicals flavonoids can inhibit LDL oxidation in-vitro thereby protecting the LDL particles which could result in the prevention of atherosclerosis<sup>31</sup>. Several flavonoids have been reported to interfere with inducible nitric oxide synthase activity; in that a high concentration of nitric oxide produced by inducible nitric oxide synthase in macrophages can result in oxidative damage<sup>32, 33</sup>. Xanthine oxidase is another pathway to the oxidative injury of tissues, especially after ischaemia reperfusion<sup>34</sup>. Flavonoids such as quercetin, luteolin and silibin have been found to inhibit xanthine oxidase activity, resulting in a decrease in oxidative injury<sup>37</sup>. Apart from these compounds other flavonoids such as apigenin 6-C-(2''-O-galloyl)- $\beta$ -D-glucopyranoside, apigenin 8-C-(2''-O-galloyl)- $\beta$ -D-glucopyranoside isolated from *Terminalia catappa* (Combretaceae) showed significant antioxidative effects with IC<sub>50</sub> values of 2.1 and 4.5  $\mu$ M respectively<sup>38</sup>. 3, 5, 7, 4'-tetrahydroxy-2'-methoxyflavone was also shown to possess an antioxidative effect<sup>39</sup>.

### Antifungal activity

Fungi are eukaryotic organisms. Despite the fact that they include some of the most important organisms both in terms of their ecological and economic roles; they also cause a number of plant and animal diseases. Several of these diseases may be fatal if not treated. Antifungals are agents that preferential destroy the fungi cells without any adverse effect on the host. The following flavonoids have been shown to possess the ability to destroy fungal cells without any dangerous effect on the host. The flavonoids 4'-methoxykaempferol-7-(acetyloxy-3, 5-O- $\alpha$ -L-rhamnoside, apigenin 7-O-methoxyquercetin and quercetin were isolated from the leaf extract of *Chiococca braquita* (Rubaceae). The pure flavonol exhibited weak activity on *C. cladosporioides*. It was noted that a combination of the isolated compounds gave an enhanced activity against the fungus, but the activity was lost when apigenin 7-O-methoxyquercetin was absent from the mixture<sup>40</sup>. A prenylated flavanone identified as 5, 7, 4'-trihydroxy-8-methyl-6-(3-methyl-2-butenyl)-(2S)-flavanone isolated from *Eysenhardtia toxana* showed ability to inhibit *Candida albicans*<sup>41</sup>. The flavan 7-hydroxy-3', 4'-(methylenedioxy) flavan isolated from *Terminalia belleria* fruit rind was also active against *Candida albicans*<sup>42</sup>. Three flavones (6, 7, 4'-trihydroxy-3', 5'-dimethoxy flavone; 5, 5'-dihydroxy-8, 2', 4'-trimethoxyflavone and 5, 7, 4'-trihydroxy-3', 5'-dimethoxy flavone) were reported as being potent against *Aspergillus flavus*<sup>43</sup>. The flavonol, galangin was reported to have inhibitory activity against *Aspergillus tamari*, *Aspergillus flavus*, *Cladosporium sphaerospermum*, *Penicillium digitatum* and *Penicillium italicum*<sup>44, 45</sup>.

### Anti-inflammatory activity

Inflammation is a fundamental contributor to diseases such as cancer, e.t.c. it is a last resort response to injury of tissue Ischemia, anti immune response or infectious agents. For a compound to possess an anti-inflammatory activity, it must have the ability to inhibit the increase in the number of fibro-blast during granular tissue formation. Lipoxygenase and cyclooxygenase are known inflammatory mediators which are involved in the release of arachidonic acid. Neutrophils containing lipoxygenase provoke the release of cytokines and produce chemotactic compounds from arachidonic acid. Some researchers have shown that some flavonoid compounds (quercetin in particular) can inhibit both the 5-lipoxygenase and cyclooxygenase pathways<sup>24, 46, 47</sup>, thereby reducing the release of arachidonic acid<sup>48, 49</sup>. They can also inhibit neutrophils degranulations which is a direct way of reducing the release of arachidonic acid. Tyrosine-3-monooxygenase kinase is an integral membrane protein which is involved in enzyme catalysis, transduction of signals that function as receptors of hormones and growth factors, energy transfer in ATP synthesis and transport across membranes. It was observed that some flavonoids have the ability to inhibit

these proteins resulting in the inhibition of uncontrolled cell grow and proliferation<sup>50</sup>.

Another anti-inflammatory effect of flavonoids is their ability to inhibit both cytosolic and eicosanoid synthesis which are end products of cyclo-oxygenase and lipoxygenase pathways and are involved in several immunologic responses<sup>51</sup>. Apart from quercetin, flavonoids such as 5-hydroxy-7-methoxy -2-methyl chromone and apigenin-7-O- $\beta$ -D-glucuronide isolated from the leaves of *Marchantia convoluta* (Marchantiaceae)<sup>52</sup> and 4' -kaempferol -7-(acetyloxy-3-5-O- $\alpha$ -L-rhamnoside, apigenin 7-O-methoxy quercetin and quercetin isolated from *Chiococca braquata* (Rubiaceae) were shown to exhibit anti-inflammatory effects<sup>40</sup>.

Morusin, Kuwanon C, sanggenon B, sanggenon D and kazinol B were shown to exhibit moderate inhibitory activity on COX-2. Their IC<sub>50</sub> values were greater than 73.0  $\mu$ M. The prenylated flavonoids lonchocarpol A was shown to act as mixed inhibitor of COX-1/COX-2. It exhibited some selective inhibition alongside with tomentosanol against COX-2 over COX-1<sup>53, 54</sup>. So far only wogonin has been shown to selectively inhibit COX-2 over COX-1<sup>55</sup>.

Kaempferol, quercetin and myricetin were found to inhibit 5-LOX more than 12-LOX. But their inhibitory power was observed to be higher than that of flavones except for that of cirsiol<sup>47</sup> and its analogues. Quercetin, hibifolin and quercetagenin-7-O-glucoside were found to inhibit 12-LOX strongly; also did flavones such as 5, 6, 7-trihydroxyflavone (baicalein), hypolaetin and sideritoflavone. However, the flavanone such as naringenin did not inhibit both 5- and 12-LOXs indicating the importance of C-2, 3 double bond. The flavonoids, quercetin, fisetin and kaempferol were observed to strongly inhibit 12-LOX from mouse epidermis<sup>56</sup>. The artonins were observed to be the most potent inhibitors of 5-LOX purified from porcine leukocytes with IC<sub>50</sub> in the range of 0.36-4.3  $\mu$ M but showed less inhibitory activity on 12-LOX<sup>57</sup>. The flavonoids sophoraflavanone G and kenusanone A significantly inhibited 5-LOX with IC<sub>50</sub> values ranging from 0.09-0.25 and 0.5-0.9  $\mu$ M respectively; while the flavanols kuraridin, papyriflavonol A, sanggenon B and sanggenon D showed moderate inhibition. The prenylated flavonoids, sophraflavanone G, kuwanon C and papyriflavonol A showed moderate inhibition against 12-LOX with IC<sub>50</sub> values of 20, 19 and 29  $\mu$ M respectively<sup>58</sup>.

Three types of NO have been identified (endothelial NOS (eNOS), neuronal NOS (nNOS) and inducible NOS (iNOS)). Quercetin was found to exhibit weak inhibitory activity on eNOS at high concentration (IC<sub>50</sub> = 220  $\mu$ M)<sup>59</sup> but did not show any significant inhibition against nNOS and iNOS; while rutin, hesperidin, catechin and tricin did not inhibit any of the isoforms of NOS; but echinoisosphoranone significantly inhibited iNOS at reasonable concentrations.<sup>60</sup>



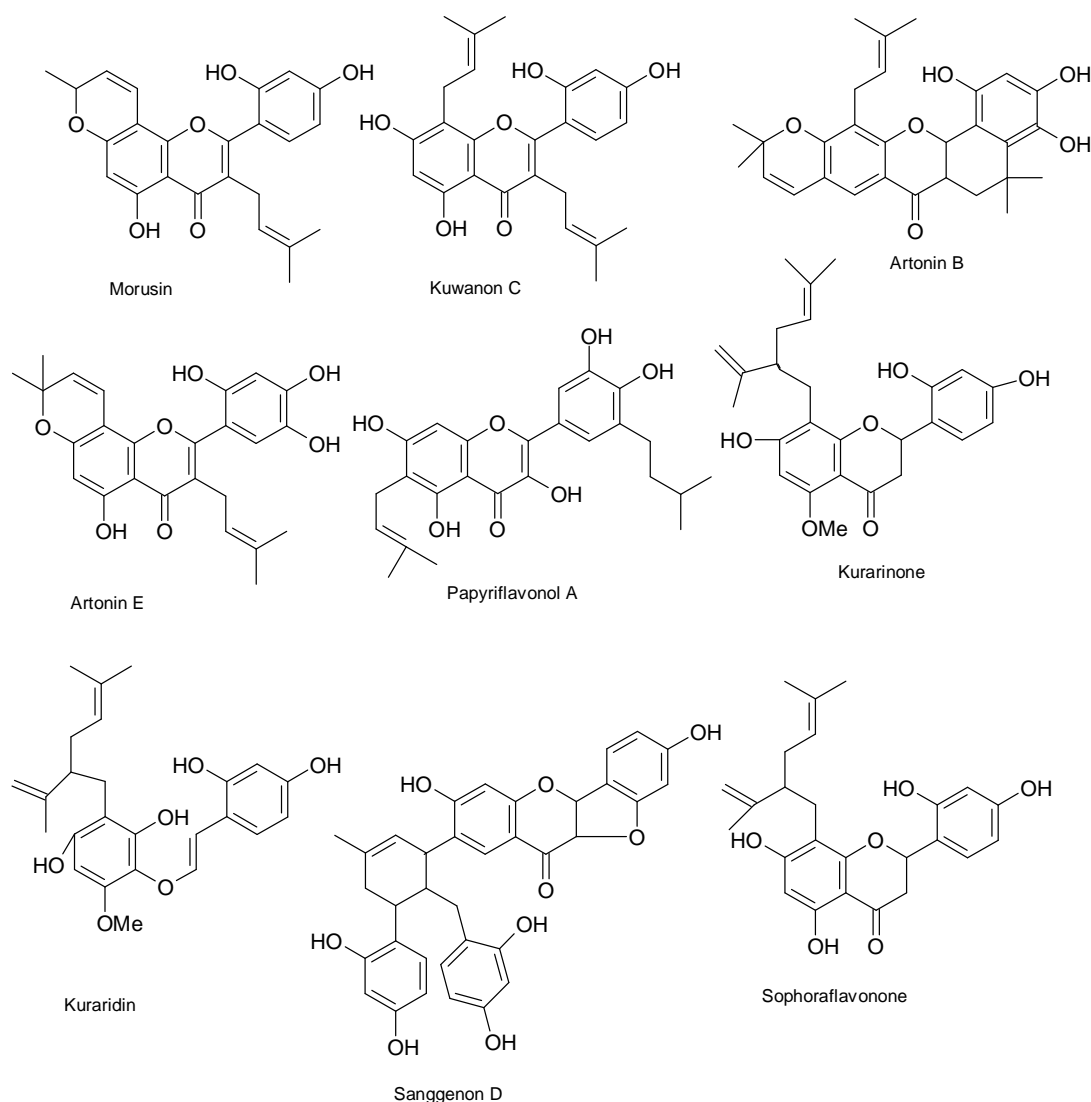


Fig.6 : Some antiinflammatory prenylated flavonoids

Genistein was shown to inhibit LPS-induced NO production in microphages<sup>61</sup>, but apigenin, quercetin and morin were shown to inhibit NO production from LPS/interferon (IFN)- $\gamma$ -activated C6 astrocytes<sup>62</sup>. However, it was observed that catechins and flavones were not active up to a concentration of 100  $\mu$ M. On the other hand, flavonoid glycosides such as vitexin did not give any significant inhibition on NO production up to 100  $\mu$ M. It was shown that flavones exhibited a stronger inhibition of NO production than flavonols. This shows that the C-2, 3 double bond is important for the inhibition of NO production. The hydroxyl substitutions on rings A and B also have significant influence on the inhibitory activity. It was also observed that the ring A, 5,-/7- and ring B 3'-/4' hydroxylations gave favourable results while C-3 hydroxylation in the flavonol did not. It was also demonstrated that these flavonoids did not actually inhibit iNOS activity but strongly suppressed its expression<sup>63</sup>. From the dichloromethane extract of *T. microphyllum* aerial parts were isolated 5, 7, 3', tri hydroxy-3, 6, 4'-trimethoxy flavone and 5, 3'-dihydroxy-4'-methoxy-7-carbmethoxy flavanol. Both compounds

were shown to exhibit anti-inflammatory activity<sup>64, 65</sup>. The anti-inflammatory activity of hypolaetin-8-O- $\beta$ -D-glucoside and sidevitoflavone from Spanish *Sidevitis gossypin* and hibifolin from Indian medicinal plants were reported<sup>46</sup>. Quercetin was found to inhibit PLA<sub>2</sub> obtained from rabbit peritoneal neutrophils with an IC<sub>50</sub> range 57-100  $\mu$ M and selectively inhibited group II SPLA<sub>2</sub> from *Vipera russelli* with less inhibition of PLA<sub>2</sub> from porcine pancreas, PLA<sub>2</sub>I-B. The flavanones – hesperatin, narigenin and flavanone showed a lesser inhibition on snake venom PLA<sub>2</sub> than the flavonols such as kaempferol, quercetin and myricetin. This shows that the presence of C-ring-2, 3 double bond is important<sup>66</sup>. Several biflavonoids such as ochnaflavone, aminoflavone, ginkgetin and isoginkgetin exhibited inhibitory activity against sPLA<sub>2</sub> –II A from rat platelets at micromolar concentrations with some selectivity over PLA<sub>2</sub>-IB, with IC<sub>50</sub> values within 10  $\mu$ M<sup>67</sup>. Ochnaflavone<sup>68-70</sup>, was observed to inhibit sPLA<sub>2</sub>-IIA non competitively. Also morelloflavone was shown to possess inhibitory activity against sPLA<sub>2</sub><sup>71</sup>. A prenylated flavonoid, papyriflavonol A isolated from *Broussoneta papyrifera* was shown to selectively inhibit PLA<sub>2</sub> –IIA but less active

against PLA<sub>2</sub> –IB<sup>72</sup>. Ginkgetin and bilobetin were found to repeatedly inhibit group II sPLA<sub>2</sub> from several sources<sup>73</sup>. Polyhydroxylated flavonoids such as quercetagenin, kaempferol-3-galactoside and scutellarin were shown to strongly inhibit group II human recombination PLA<sub>2</sub> with less inhibition against *Naja Naja* PLA<sub>2</sub> and PLA<sub>2</sub>-IIB. Their IC<sub>50</sub> values range from 10-30 µM<sup>74</sup>.

Flavone with several of its derivatives such as apigenin were found to be COX inhibitors while some flavonol derivatives such as quercetin and myricetin were found to preferentially inhibit LOX. It was observed that the reduction of C-2, 3 double bond and glycosylation reduced the inhibitory effect. The flavonoids such as quercetin and xanthomicrol were found to inhibit sheep platelet COX-1. Also the flavones such as cirsiolol, hypolaetin and diosmetin were shown to inhibit sheep platelet COX-1 with IC<sub>50</sub> value more than 100µM<sup>75</sup>. The isoflavone, tectorigenin showed weak inhibitory activity against COX-1<sup>76</sup>. Chalcones having a 3, 4-dihydroxycinnamoyl moiety were reported to inhibit COX but were more active in LOX<sup>56</sup>. Prenylated flavonoids such as morusin and kuwanon C showed strong inhibition on COX from rat platelets<sup>77</sup>. Also sanggenin D inhibited COX<sup>78</sup>. Other prenylated flavonoids such as cycloheterophyllin, brousochalcone A, brousoaurone A and brousoflavonol F inhibited platelet aggregation and COX from ram seminal vesicle with an IC<sub>50</sub> ranging from 17.5-26.1 µg/ml<sup>79</sup>. The prenylated flavonoids kuranidin, kurarinone and sophraflavanone G were found to possess potent COX-1 inhibitory activity from bovine platelets homogenate (IC<sub>50</sub> = 0.1-1.0 µM). Amentiflavone which is a biflavone gave a strong inhibition against COX-1 guinea-pig epidermis with an IC<sub>50</sub> value of 3.0 µM while ginkgetin did not show any significant inhibitory activity against COX and LOX<sup>49</sup>. Several flavan-3-ols such as catechin and 4'-methylgallo catechin exhibited weak activity at high concentrations (>100 µM) on COX-2.<sup>80</sup> Quercetin showed moderate inhibitory activity on COX-2 and exhibited low selectivity over COX-1.<sup>81</sup>

Kong et al in their determination of structure-activity relationship of some flavonoids noted that the number of hydroxyl groups in the A and B rings might promote the activity of the flavonoid while loss of C-2 – C-3 double bond might reduce activity. The flavones (Chrysin, apigenin, luteolin, diosmetrin, baicalein, baicalin and tangeretin), flavonols (kaempferol, quercetin, myricetin, and quercetagenin), a flavanone (naringenin), an isoflavone (genestein), a flavanodiol (taxifolin) and other analogues (quercetin-3-β-D-glucoside, guguetin and casticin) were used for the analysis. For the flavones, luteolin exhibited the highest activity. Correlating their activities with their chemical structures showed that the activity is increased as the number of the hydroxyl groups in ring B increased. For the flavonols, the number of hydroxyl groups in both rings A and B gave a positive effect on their activity. But the existence of OH groups in ring C might not increase the activity. Also it was observed that glucosidation at C-3 might decrease

potency. With the flavanone the loss of C2-C3 double bond might decrease the inhibiting potency. Also, the presence of a hydroxyl group might be a must for a PI3ka inhibitory activity of flavonoids. Rao et al showed that ternatin, a tetramethoxyflavone isolated from the Brazilian medicinal plant *Egletes Viscosa* L. possess anti-inflammatory activity. Ueda et al investigated the effect of flavones (luteolin, apigenin and chrysin), flavonol (quercetin and myricetin), flavanonol (taxifolin) and anthocyanidin (cyanidin chloride) in-vitro on several inflammatory models. Their results showed that oral administration of luteolin was the most suitable and that the introduction or removal of a hydroxyl group may cause loss of efficacy. Investigation of *Viscum album* L. led to the isolation of five flavonoids (5, 7-dimethoxyflavanone 4'-O-β-D-glucopyranoside; 2'-hydroxy-4', 6'-dimethoxy chalcone-4-O-β-D-glucopyranoside; 5, 7-methoxy-flavanone-4'-O-2''-O-(5'''-O-trans-cinnamoyl)-β-D-apio-furanosyl)-β-D-glucopyranoside; 2'-hydroxy-4'-β-di methoxychalcone-4-O-2''-O-(5'''-O-trans-cinnamoyl)-β-D-apio furanosyl-β-D-glucopyranoside and 5, 7-dimethoxyflavanone-4'-O-β-D-apiofuranosyl (1→2) β-D-glucopyranoside. The compounds 2'-hydroxy-4', 6'-dimethoxy chalcone-4-O-β-D-glucopyranoside and 5, 7-dimethoxyflavanone-4'-O-β-D-apiofuranosyl (1→2) β-D-glucopyranoside were shown to possess anti-inflammatory effects in a 30 mg/kg dose without any remarkable acute toxicity and gastric damage<sup>85</sup>. Hussain et al showed that flavonoids such as silymann inhibits the expression of pro-inflammatory molecules in animal models and human studies. They suggested that the modulation of pro-inflammatory mechanisms is one of the actions mechanisms that may explain the anti-inflammatory activity of flavonoids. Flavonoids have been found to inhibit transcription factors such as NF-KB and activate protein-1(AP-1), as well as activation of nuclear factor- erythroid 2- related factor 2 (Nrf2).<sup>87</sup> Zheu et al isolated trifolirhizin, a pterocarpal flavonoid from the roots of *Sophora flavonscens*. This flavonoid was found to dose-dependently inhibit LPS- induced expression of pro-inflammatory cytokines including tumor necrosis factor - (TNF-α) and inter-leukin-6(IL-6) and lipopolysaccharide induced expression of cyclooxygenase-2(COX-2).

The anti-inflammatory activity of flavonoid fraction obtained from the stem bark of *Butea monosperma* was attributed to the presence of the isoflavones genistein and prunetin. They were observed to modulate cyclooxygenase and lipoxygenase enzymes and augment anti-oxidant defense system in the inflammation bearing rat.<sup>89</sup>

In a wide variety of chronic human diseases such as Cardio-vascular diseases and Cancer, inflammation has been known to play a key role. It has been demonstrated that pro-inflammatory cytokines, cyclooxygenase -2(COX-2), and free radical species interact in a complex manner in an inflammation environment.

The inhibition of these expressions and production of power mediators by anti-inflammatory components

might represent a possible preventive or therapeutic target, and may be used to develop anti-inflammatory nutraceuticals for health promotion and disease prevention.

### Antibacterial activity

Bacteria are a large group of prokaryotic microorganisms. These microorganisms were first discovered by Anloric van Lecuwenhoek in 1676<sup>14</sup>. Most of these bacteria that get into the body are rendered harmless by the body's immune system and a few of them have been shown to possess some beneficial properties. However a few species are pathogenic and are the major cause of human diseases that could be infectious and may result in human death<sup>163</sup>.

Bacteria have been classified into two groups based on the stain developed by the Danish physician Hans Christian Gram in 1884<sup>91</sup>. The Gram stain is important because bacteria have different susceptibility to antibiotics<sup>92</sup>. The Gram-positive possess a thick cell wall that contains many layers of peptidoglycan and teichoic acid while the Gram-negative bacteria have a relatively thin cell wall consisting of a few layers of peptidoglycan which is surrounded by a second lipid membrane containing lipopolysaccharides and lipoproteins<sup>75</sup>.

From the 20<sup>th</sup> century there was great advancement in the discovery, development and clinical use of antibiotics that resulted in a decrease of rate of mortality from bacterial infections. However there has been a decline in the introduction of new antibiotics probably due to the huge investment involved in developing and testing of new drugs. There is also the problem of increased resistance of bacteria to existing antibiotics<sup>2</sup>. A renewed effort is in place to determine and produce new antibacterial agents that are effective against pathogenic bacteria which are resistant to current antibiotics. A lot of research work has been documented concerning the antibacterial activity of flavonoids. Crude extracts from plants used in traditional folk medicine has been screened for antibacterial activity<sup>93-103</sup>. Some researchers took a step further to isolate and identify the specific flavonoids that are responsible for the exhibited antibacterial activity. Fang et al reported the isolation of the following prenylated flavanone glycosides from the rhizomes of *Cyclosorus acumintus* (Houtti) Nakai (Thelypteridaceae): (2S), 5, 7, 5'-trihydroxyflavanone 2'-O-β-D-glucopyranosyl-(1→3)-α-L-2-O-acetylramnopyranoside; (2S), 5, 7, 5'-trihydroxyflavanone 2'-O-β-D-6-O-glucopyranosyl-(1→3)-α-L-2-O-acetyl ramnopyranoside; (2S), 5, 7, 5'-trihydroxyflavanone 2'-O-β-D-2, 6-di-O-acetylglucopyranosyl-(1→3)-α-L-2-O-acetylramno pyranoside; (2S), 5, 7, 5'-trihydroxyflavanone 2'-O-β-D-3, 6-di-O-acetyl glucopyranosyl-(1→3)-α-L-2-O-acetylramnopyranoside; (2S), 5, 7, 5'-trihydroxyflavanone 2'-O-β-D-4,6-glucopyranosyl-(1→3)-α-L-2-O-acetylramno pyranoside and 3, 4, 6-tri-O-acetyl glucopyranosyl-(1→3)-α-L-2-O-acetyl ramnopyranoside. These compounds showed weak antibacterial activity against. *S. aureus*, *E. coli* and

moderate inhibitory activity against *Streptococcus pneumoniae* and *Hamophilus influenzae*. The flavonoid from *Marchantia convoluta* (Marchantiaceae) inhibited *Coli bacillus*, *typhoid bacillus*, *Staphylococcus aureus*, *Bacillus enteritidis*, hemolytic streptococci type B and *Diplococcus pneumoniae*. Pinocembrin isolated from *Cleistochlamys kirkii*<sup>105</sup> and *Mitrephora maingayi*<sup>106</sup> showed moderate inhibition against *S. aureus* at low concentration of 0.1 µg/ml<sup>107</sup>, but weak inhibition against *P. phaseolicola*. Other researchers have also determined the antibacterial activity of this compound<sup>108, 109</sup>. Apigenin was observed to inhibit *P. vulgaris*, *Ps. aeruginosa*, *E. coli*, *B. subtilis* and *K. pneumoniae* with MIC ranging from 54-219 µg/ml<sup>110-118</sup>. But Basile et al noted that apigenin acted selectively only toward certain Gram-negative bacilli: *Proteus vulgaris*, *Proteus mirabilis*, *Ps. aeruginosa*, *E. coli*, *Klebsiella pneumonia* and *eterobacter cloacae*. However they were not active against the Gram-positive cocci *S. aureus* and *Entrococcus faecalis*. Other compounds that were shown to exhibit similar activity were vitexin, saponarin, luteolin 2-O-glycoside and luteolin 7-O-glycoside. It was also reported that chrysin (a flavone) inhibited the growth of the negative bacilli *E. coli* and *Ps. aeruginosa* at a rate that was comparable to that of streptomycin. On the other hand, baicalein which possess an extra hydroxyl at C-6 did not inhibit the growth of Gram- negative bacteria. It was active against *Bacillus subtilis* and *Staphylococcus aureus*<sup>119</sup>. The flavanones: naringenin, taxifolin and dihydrokaempferide were evaluated for their antibacterial activity. It was observed that only naringenin showed inhibitory activity against *E. coli*, *S. aureus* and *E. facaecalis*<sup>120</sup>. Wachter et al showed that 5, 7, 4'-trihydroxy-6-methyl-8-isoprenylflavanone and 5, 7, 4'-trihydroxy-8-methyl-6-isoprenylflavanone can inhibit the growth of *S. aureus* at a concentration of 0.1mg/ml. Flavanones such as 5, 3'-dihydroxy-4'-methoxy-6'', 6''-dimethylchromeno-(7, 8, 2'', 3'') flavanone and 5, 7, 4'-trihydroxy-6, 8-di-(3-methylbut-2-enyl) flavanone were reported to be potent against both Gram-positive and Gram-negative bacteria<sup>121</sup>. A series of researchers carried out some test on quercetin and its derivatives and it was observed that quercetin-3-O-rhamnoside exhibited the strongest inhibitory activity against *Pseudomonas maltophilia* and *E. cloacae* and quercetin 3-arabinopyranoside-2''-gallate inhibited the growth of *E. coli*, while the other derivatives did not show any significant activity against the bacteria screened<sup>95, 110, 117, 122-129</sup>. The researchers who worked on isoflavanones showed that those with prenylated groups gave the highest inhibition activity against *S. aureus* and *B. subtilis* especially those that have the prenyl group at positions C-6 or C-8 in ring A and C-3' or C-5' in ring B<sup>130, 131</sup>. It was noted that among a series of acylated kaempferol-3-O-glucosides tested against the Gram-positive bacteria *Bacillus cereus*, *Staphylococcus epidermidis* and *Staphylococcus aureus*; that the most effective among them were those compounds that possess one or two cis-p-coumaroyl groups<sup>95, 110, 126, 132, 135</sup>. Mitrokosta et al showed that the acylated flavonols,



tiliroside and plantanoside were active against the Gram-positive cocci *S. aureus*, *S. epidermidis* and Groups B and F streptococci. They were also active against the Gram-negative bacilli *E. coli*, *Ps. aeruginosa* and *K. pneumoniae*. The activity of tiliroside was stronger than that of plantanoside which was weakly active. A series of aglycones of flavones, isoflavones, flavonols, and flavanones were tested against *P. vulgaris* and *S. aureus*. The most active among them were myricetin, morin, quercetagenin, datiscetin and robinetin. Myricetin and robinetin exhibited the highest activity against *S. aureus* (MIC = 100mcg/ml) while myricetin was the only one active against *P. vulgaris*. The other flavonoids studied chrysin, luteolin, apigenin, apigenin 7, 4' dimethylether, kaempferol, eriodictyol, hesperidin and taxifolin did not inhibit the growth of the bacteria used. It was also reported that the lipophilic compound 7, 8-dihydroxyflavone exhibited weak activity against *S. aureus* and no activity against *P. vulgaris*. It was noted that the weak activity was as a result of the high lipid content of the cell wall of *P. vulgaris* which could have trapped the tested compound whereas the cell wall of *S. aureus* is penetrable due to lack of a lipid layer<sup>134</sup>. Other flavonoids have also been isolated that exhibit antibacterial activity. For example, apigenin<sup>118</sup>, galangin<sup>45, 131, 135, 137, 138</sup>, sophoraflavonone G and its derivatives, naringin and naringenin<sup>95, 122, 139-142</sup>, Epigallocatechin gallate and its derivatives<sup>143, 144</sup>, flavones and flavanones<sup>43, 95, 135, 145-148</sup> were active against MRSA. Epigallocatechin was also found to be active against *S. epidermidis* a skin bacterium<sup>149</sup>. Luteolin and its 7-glucoside derivative<sup>114, 118, 150</sup>, flavones glycosides<sup>142, 151, 152</sup>, isoflavones<sup>153, 154</sup>, isoflavanones<sup>131</sup>, isoflavans<sup>155</sup>, flavonols<sup>135, 156, 157</sup>, flavonol glycosides<sup>142, 158-160</sup>, and chalcones<sup>145, 154, 161</sup> are also flavonoids reported to possess antibacterial activity.

### Anti-viral activity

Viruses are microorganisms that cause a number of diseases in animals including humans. Once in contact with a host deposits its genetic material into the host. The infected cell then ceases from its usual function and starts producing more viral protein and genetic material. The new viruses can self assemble and burst out of the cell killing the cell and then infecting other nearby cells. Antiviral agents function by inhibiting the virus before it enters the cell, stop its reproduction or prevent it from leaving the infected cell. The anti-viral activity of flavonoids has been reported by researchers<sup>162-164</sup>. Some of the viruses reported to be affected by flavonoids are HIV, parainfluenza, herpes simplex virus, adenovirus, and respiratory syncytial virus. Flavonoids have shown great ability to interact with these viruses at different stages in the replication cycle of the virus. Some flavonoids have been shown to inhibit the intracellular replication of viruses while others inhibited the infection process of the viruses. It was also observed that flavonoids in their glycone form exhibited better potency in their inhibiting effect against rotavirus infectivity than those in their aglycone form<sup>165</sup>.

### Human immunodeficiency virus (HIV)

Research on flavonoids that can inhibit the human immunodeficiency virus (HIV) has increased of recent. In-vitro studies have shown that acacetin-7-O- $\beta$ -galactopyranoside and chrysin exhibit high anti HIV-1 activity with relatively low toxicity. It was observed that replacement of the methoxy group at C4' with the hydroxyl group significantly reduced the anti- HIV property of this compound while the addition of a second sugar moiety as in acacetin 7-O-(6''-rhamnopyranosyl)- $\beta$ -galactopyranoside completely destroyed the anti-HIV effect, meanwhile luteolin and its acetate derivatives were shown to exhibit similar anti-HIV activity but were found to be more toxic, a comparison of the activity of luteolin and quercetin showed that the addition of a hydroxyl group at C-3 significantly reduced their activity<sup>166</sup>. Baicalein have been shown to have the ability to inhibit HIV-1 reverse transcriptase while flavones-O-glycoside can antagonize it<sup>167</sup>. The inhibition by baicalein was observed to be specific which shows that it is less toxic to the DNA and RNA polymerases and therefore their interaction with HIV-1 enzyme is believed not to be specific<sup>168</sup>. Biflavonoids made up of two apigenin units such as robustaflavone, amentoflavone, agathis flavones and hinokiflavone demonstrated significant activity against HIV-1 reverse transcriptase with IC<sub>50</sub> values of 65, 119, 1000 and 62 mcg/ml respectively; while biflavonoids made up of flavanone and flavones such as Morelloflavone and volkseniflavone exhibited moderate to weak activity. Meanwhile, biflavonoids that linked C-3 to C-8 were moderately active, while those made up of 2 naringenin units linked through ring A (rhusflavanone and succedaneafavanone) were observed to be inactive. Apigenin exhibited inhibitory activity of IC<sub>50</sub> = 443mcg/ml while naringenin showed a moderate inhibition of HIV-1 transcriptase<sup>169</sup>. Knin et al reported that quercetin 3-O-(2', 6'-digalloyl)-galactoside and quercetin 3-O-(2'-galloyl)arabinoside inhibited HIV-1 integrase and affected its penetration into the host cell. This shows that the inhibition of integrase can prevent the replication of viruses and can be effective in the treatment of AIDS<sup>172</sup>. Ribinetin, myricetin, baicatin and quercetagenin were also active against HIV-I integrase<sup>173</sup>. But that of Myricetin and quercetagenin were observed to be non-specific<sup>174</sup>.

### Toxicity

Due to the fact that flavonoids are widely distributed in consumable plants, it has been suggested that they are likely to have minimal toxicity. It was discovered that high doses of quercetin over several years might result in the formation of tumor cells in mice. However, other long-term studies did not show any correlation between flavonoids and carcinogenicity<sup>175</sup>. Other researchers have shown that flavonoids have antimutagenic effect *in-vitro*<sup>176-177</sup>. These conflicting data on flavonoids show that there is need for individual flavonoids to be accessed for toxicity since the selectivity of flavonoids for eukaryotic enzymes appear to vary from compound to compound<sup>178</sup>.



## CONCLUSION

In recent years, the number of new synthetic drugs entering the market has been low probably due financial challenges in that respect in the pharmaceutical industries. Moreover synthetic drugs have been shown to be toxic and/or possess adverse side effects. In order to overcome these challenges scientists have shifted their attention to natural products such as flavonoids in order to meet up with health challenges. This class of phytochemicals has been found to possess potential health benefits. However, most of the research work has been on in-vitro studies which have minimal impact due to the non-physiological concentrations utilized. Also compounds with weak inhibitory effects can be structurally adjusted in order to increase its activity. This means that scientists should find a way of synthesizing these bioactive compounds and introduce other substituents which might increase the activity. It is believed that renewed scientific efforts using human trials with pure flavonoids and the appropriate placebo will go a long way to provide new insight into the beneficial effects of flavonoids and which might eventually lead to the development of new class of bioactive compounds.

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