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Flavonoids as the emerging therapeutic agents: A review of their bioactivity, chemoprevention and chemotherapy approach

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ABSTRACT

Background & Aim: The aim of the review is to study the bioactivity, chemoprevention and chemotherapy approach of flavonoids as the emerging therapeutic agents.

Results: The quickest way of managing health challenges in the developing world is by the uses of herbs. These medicinal plants are known to contain phytochemicals that conferred on them these pharmacological potentials. Among these chemical constituents are the flavonoids which become the emergent therapeutic agents because of their vast pharmacological properties. Among reported activities of plants derived phytochemicals, flavonoids have shown various pharmacological activities. Many flavonoids have shown significant anticancer, antibacterial, antifungal and antioxidant activities. Therefore, researches have focused on developing potent bioactive flavonoids. Recent researchers have focused on the development of potent drugs with minimal toxicity for cancer chemoprevention and chemotherapy. The antibacterial activities of flavonoids against a wide range of microorganisms and their radical-scavenging ability are well known and reported. Therefore, one can conclude that flavonoids have actually become emerging therapeutic agents.

Recommended applications/industries: In view of the pharmaceutical properties of various flavonoids such as anticancer, antibacterial, antifungal and antioxidant activities, they could be used in pharmaceutical industries.

1. Introduction

Flavonoids are phenolic constituents regarded as secondary metabolites found in plants. They represent a highly diverse class of polyphenolic secondary metabolites with known pharmacological activity. Dietary flavonoids are found in wines, cocoa, fruits, vegetables and teas. Both antioxidant and chelating properties of flavonoids have been reported in previous studies (Heim *et al.*, 2002). They have also being reported to show other useful pharmacological

properties such as anticancer, antiatherosclerotic, antioxidative, coronary heart prevention, antiviral, antifungal, hepatoprotective and anti-inflammatory activities (Górniak *et al.*, 2019). Because of the pharmacological importance of flavonoids, pharmaceutical companies have developed various products from them. Therefore, they have resulted in various indispensible pharmaceutical applications. These applications of flavonoids are attributed to their various reported pharmacological activities (Panche *et al.*, 2016).

Flavonoids are large class of metabolites as about 10,000 different flavonoids have been reported (Weston and Mathesius, 2013). Out of these numbers, more than 6500 of these flavonoids classifications are based upon 15 carbon skeleton (Corradini *et al.*, 2011). Thus, they are classified as flavonols, flavones, flavanones, isoflavones, anthocyanidins, chalcones, aurones, flavanols (Mierziak *et al.*, 2014). Biosynthetically, they are all derivative from 2-phenyl-benzo-γ-pyrone. The carbon atomsarrangements in flavonoid molecules are based on two benzene rings denoted as A and B. These rings are connected to ring C which is the pyrene ring containing oxygen. The carbon skeleton of flavonoids are based on flavan system (C6-C3-C6) (Figure 1) (Małgorzata Brodowska, 2017).

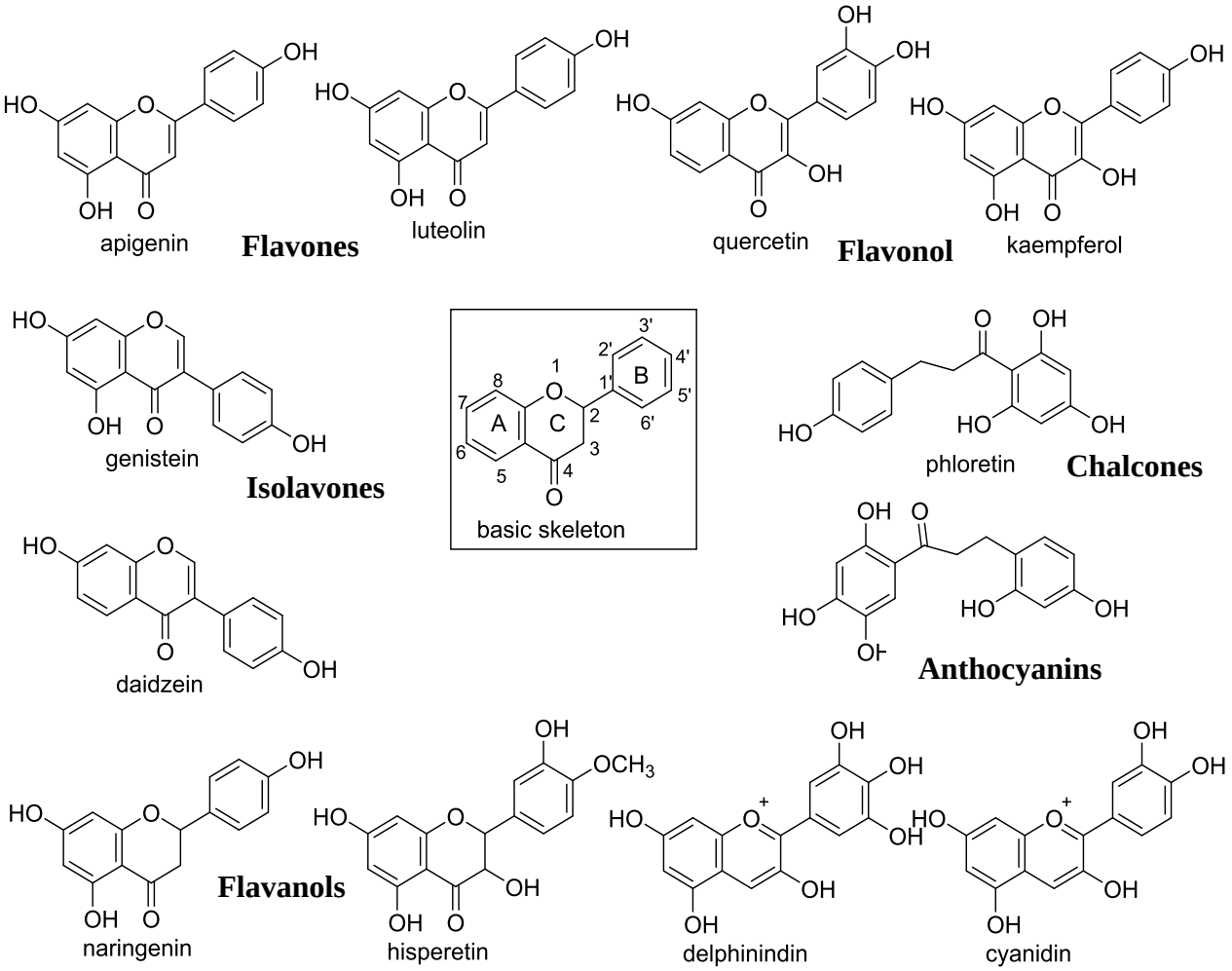

Figure 1. Basic skeleton of flavonoids and its various classes (Panche *et al.*, 2016)

2. Anticancer activity of flavonoids

Cancer is a disease where the cells grow abnormally, out of control or in a wrong place. The term cancer describes the disease that results when cellular changes cause the uncontrolled growth and division of cells. Some types of cancer cause rapid cell growth, while others cause cells to grow and divide at a slower rate. The global menace of cancer is on the steady increase. Reports have shown that a large number of people are being affected and this estimate shows and increase in 70 % of the cases that would be reported in the next decades (Cherukupalli *et al.*, 2017). The stages of cancer growth are the cell with genetic mutation, hyperplasia, dysplasia, in situ cancer and the invasive cancer stage.

Flavonoids are regarded as versatile sources of anticancer drugs (Sharma *et al.*, 2011). Naturally occurring flavonoids have being known to be good candidates for the treatment and prevention of cancer diseases.Previous epidemiological studies have shown the anticancer properties of flavonoids against lung, pancreas, colon, prostate, liver and breast cancer cells (Maheswari *et al.*, 2016; Rawson *et al.*, 2019). Flavonoids induced apoptosis and thuscontrol the cell cycle thereby regulating other signaling pathways that lead to cancer development and progression (Martinez-Perez *et al.*, 2014). The complex manner of activity of these flavonoids confers on them these anticancer effects. Because flavonoids have shown varieties of biological activities and as anticancer therapeutics are good for the design of DNA-binding agents (Ragazzon *et al.*, 2009). Both *in vitro* and *in vivo* studies have revealed that flavonoids isolated from plants have notable anticancer activity (Saul Ruiz- Cruz *et al.*, 2018). The investigation of the inhibition of flavonoids on mammalian TrxR led to the conclusion that flavonoids are cancer chemoprevention agents that showed tremendous antioxidant activities. This was further demonstrated by the fact that quercetin and myricetin showed strong inhibitory effects on mammalian TrxRs with IC_{50}values of 0.97 and 0.62 Mmol/L respectively (Zhivotovsky *et al.*, 2006). Also, quercetin (10 µM) display *in vivo* antitumor activity as it inhibitedbromodeoxyuridine in transitional cell carcinoma cells (Kandaswami *et al.*, 2007). Nobiletin (20 µM) caused 41 % decrease in tumor size. This was possible because it decreased the concentration of the vascular endothelial growth factor (VEGF) and prevented angiogenesis in human ovarian cancer (Sandu *et al.*, 2017). Many *in vitro* studies have shown strong anticancer activities of flavonoids (Rawson *et al.*, 2019). For instance, hesperetin and hesperidin have shown promising activities against hepatic, colon, lung, prostate and bladder cancer (Stanisic *et al.*, 2018). Furthermore, a natural flavonoid, quercetin caused tumor regression when it activates the mitochondrial pathway of apoptosis in interacting with DNA as it controls the cell cycle (Srivastava *et al.*, 2016). This was possible because quercetin interacts with DNA directly. By using MTT assay in leukemic cell lines and the human breast cancer cell line, T47D, quercetin exhibited high toxicity (Srivastava *et al.*, 2016). Apoptasis removes damaged or unwanted cells in living organisms. Therefore,the anticancer properties of theses flavonoids are due to apoptosis (Sharma *et al.*, 2011). The antitumor and immunomodulatory activities of total flavonoids on H22 liver tumor-bearing mice at various stages have been well documented. The total flavonoids effectively suppressed the tumor growth (***p< 0.001)(Chen *et al.*, 2018)(Figure 2). The results of the anticancer studies of two flavonoids on HeLa cells showed that flavanone (117 µM) resulted in a loss of MMP (~55 % of cells) inducing apoptosis (~51 % of cells). While the treatment of the cells with flavone (80 µM) showed a loss of MMP (~88 % of cells) that induced apoptosis in (~70 %) of the cells (Cherukupalli *et al.*, 2017). These results clearly showed the apoptosis is a consequence of concentration of the flavonoid used.

Three flavonoids, quercimeritrin, scutellarein and rutin have been reported for their anticancer activity against MCF-7 (IC50, 4.0 µg/µL), HeLa (IC50, 5.45 µg/µL), Hep2 (IC50, 7.28 µg/µL) and lowcytotoxicity against HCEC (IC50, 21.09 µg/µL) (Ahmed *et al.*, 2016). Flavonoids decreased the amount of uptake of [3H] thymidine by cancer cells. By so doing, they have inhibited the growth of cancer cells.This mechanism of action of flavonoids has being of interest to researchers over the years. Many reported anticancer activity of flavonoids focused on their ability to inhibit they normal growth. Also, flavonoids have been reported to inhibit the normal growth of prostate cancer (DU-145), breast cancer (ER- MDA-MB-435) and melanoma

(SK-MEL5) cancer cell lines (Manthey and Guthrie, 2002).

Quercetin has shown antibreast tumour activity, inhibited the proteasomal chymotrypsin-like activity and induces apoptosis in MCF-7 cell lines and MCF-7 tissue graft without toxicity (Pradhan *et al*., 2015). This makes quercetin, a good anticancer agent as this antitumor activity suggests breast cancer treatment and prevention using the flavonoids. Futhermore, quercetin and luteolin have shown potential anticancer property against breast cancer cells (MCF7) with IC_{50} (19 and 14 µg/mL), respectively (Vijayalakshmi *et al*., 2015).

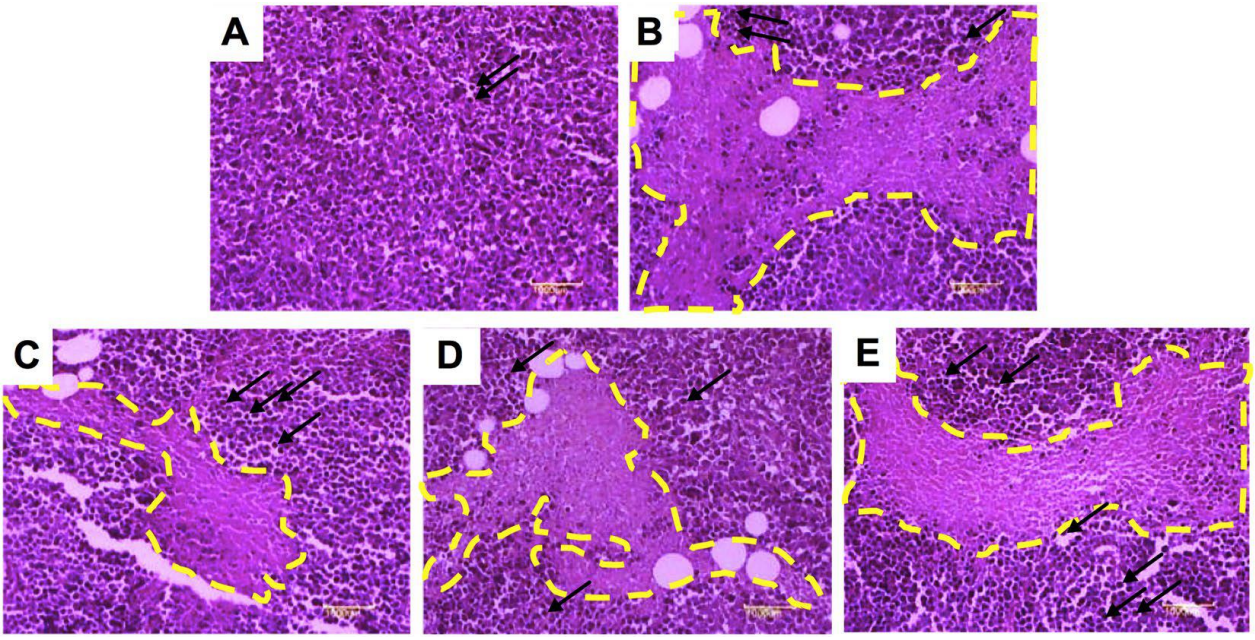

Figure 2. Representation of H22 tumor-bearing mice tissues. Hematoxylineosin was used to stain the tissues. The dark purple color represents the nuclei, the yellow dotted linesrepresents the necrotic tumor foci while the black arrows represent the lymphocyte infiltrations. (**A**) Indicated the vehicle group, (**B**) the CTX group, (**C**) the PLF-L group, (**D**) the PLF-M group and (**E**) the PLF-H group (Chen et al., 2018).

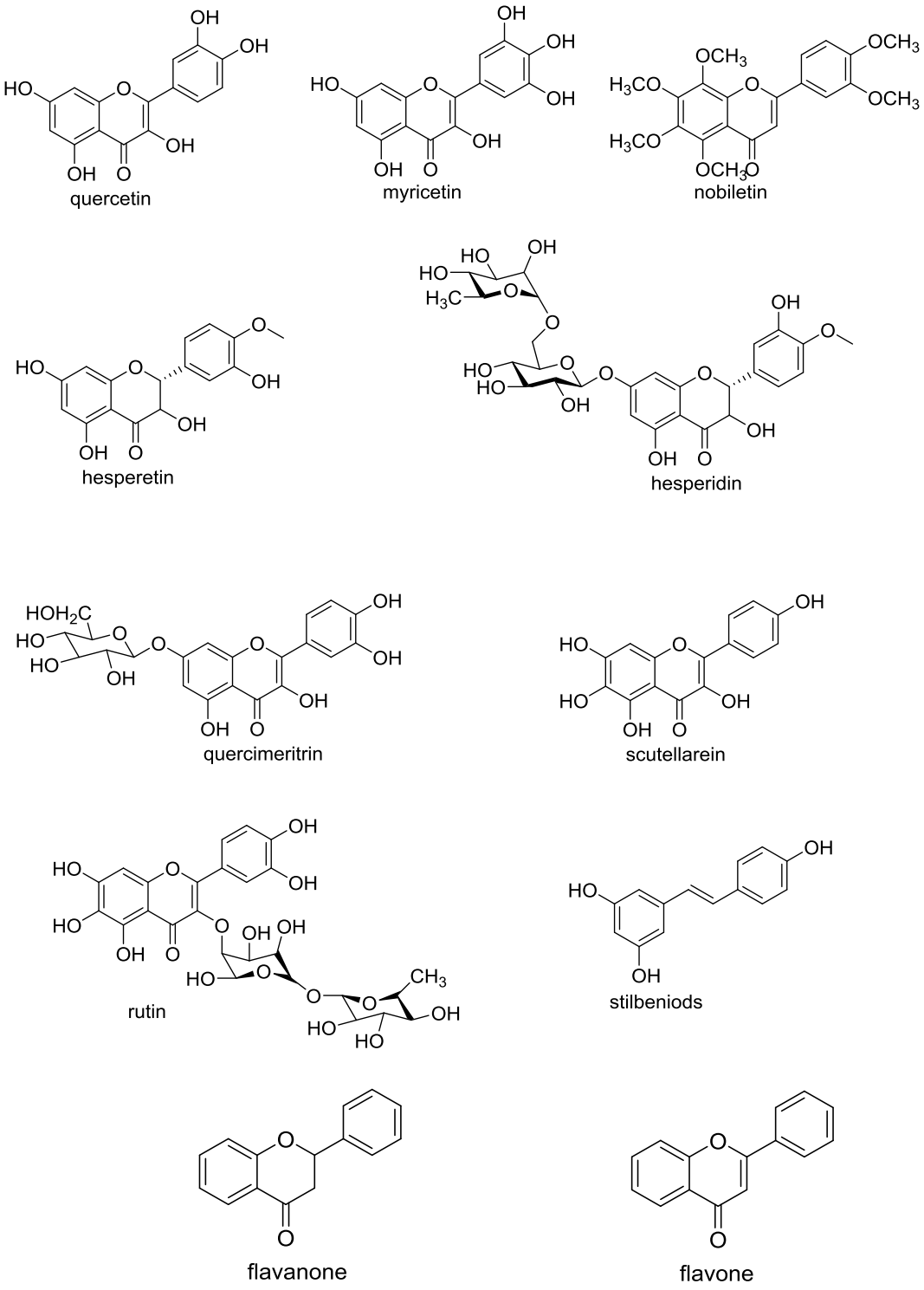

Figure 3. Structure of the flavonoids with anticancer activities.

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3. Antibacterial activity of flavonoids

The activities of drug resistant microorganisms have affected human population graviously. In order to curtail this menace, many researches have focused on plants derived bioactive compounds and their derivatives. Among reported activities of plants derived phytoconstituents, flavonoids have showed diverse pharmacological activities. The antibacterial activities of flavonoids against a wide range of microorganisms are well known and reported. Recently, a dihydroflavonol-3-O-a-L-rhamnoside exhibited significant antibacterial activity against four strains of *S.aureus*, *S.pneumoniae*, *E. coli* and *S.typhi*<3 mg/ml (Ekalu *et al.*, 2019). Six flavonoids have exhibited significant *in vitro* antimicrobial activity against *K. pneumoniae* (32-64 µg ml^{-1}) (Özçelik *et al.*, 2015). Flavonoids have shown the best spectrum of antibactericidal activity (MBC/MIC ≤ 4) (Alghazeer *et al.*, 2017). The flavonoids, isobavachalcone and artocarpin exhibited strong antibacterial activity (Jamil *et al.*, 2014) .

Bioassay studies of xenognosin B,7-methoxy-3, 3',4',6-tetrahydroxyflavone, fisetin and naringenin indicated that these flavonoids showed antibacterial activity (Taechowisan *et al.*, 2014). The antibacterial activity of quercitinat various concentrations was reported (Inala *et al.*, 2015). Additionally, quercetin and naringin have been reported for their significant antibacterial activities (Hayat *et al.*, 2017). A previous report on quercetin showed that the flavonoid inhibited the growth of *Staphylococcus aureus* (Tapas *et al.*, 2008). Antibacterial activity of flavonoid compounds against *B.cereus* and *E.coli* have been reported (Kane *et al.*, 2016).

The antibacterial activity of these flavonoids has been reported in the following order: genistein> kaempherol>naringenin and catechin. They have shown activities against the gram +ve *S. aureus* and the gram -ve*E. coli* (Capitata, 2018). In order to combat resistant pathogens, flavonoid has been reported to exhibited antibacterial activity (Jaiswal and Kumar, 2015). Also, flavonoids have shown antibacterial activity against (subtilis ATCC6633, *S. aureus* CNRZ3, B. *E. coli* ATCC25922, *L. monocytogenes* ATCC19115, *S. Enteritidis* E0220) and *P. aeruginosa* ATCC27853(Bouarab-Chibane *et al.*, 2019).

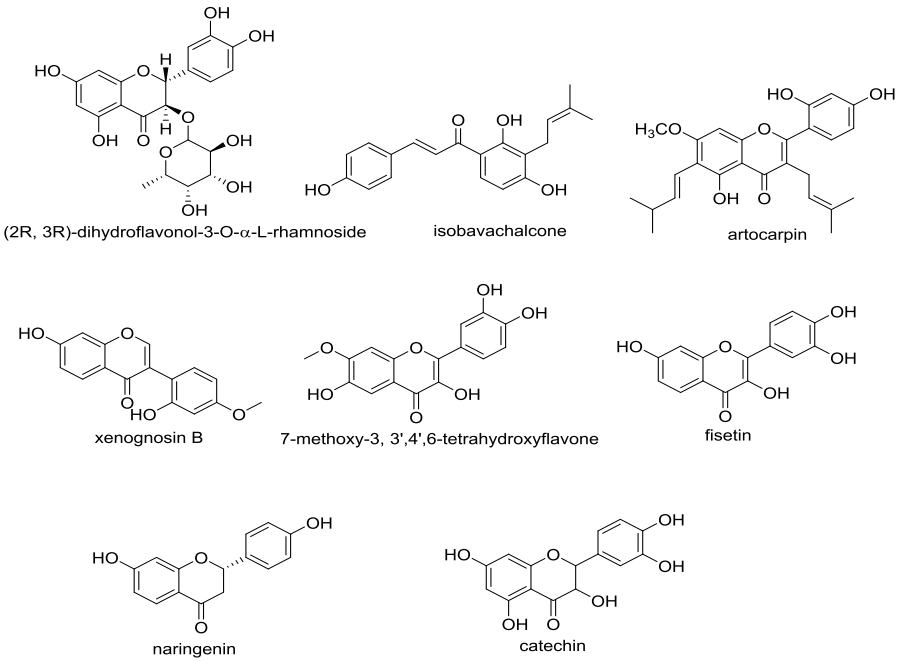

Figure 4. Flavonoids with antibacterial activities.

4. Antifungal activity of flavonoids

A report on the antifungal activity of 5,7,4 -trihydroxy-8- methyl-6-(3-methyl-[2-butenyl])-(2S)-flavanone exhibited the activity of *C.albicans* (Cushnie and Lamb, 2005). A dihydroflavonol-3-O-a-L-rhamnoside has shown significant antifungal activity against *C.albicans*< 3 mg/ml (Ekalu *et al.*, 2019).The flavonoids, nobiletin, hesperidin and langeritin have exhibited fungistatic activity towards *D.tracheiphila* (Tapas *et al.*, 2008).

5. Antioxidant activity of flavonoids

Antioxidants are those molecules with radical-scavenging ability that canoffer protection against free radicals (Formagio *et al.*, 2014). The method used to measure antioxidant activity determines its definition. Therefore, Halliwell and Gutteridge proposed a definition of an antioxidant as "any substance that delays, prevents or removesoxidative damage to a target molecule (Procházková *et al.*, 2011). Phytochemicals from plants have been reported for antioxidant activities. The presence of polyphenolic flavonoids in plant are responsible for the observable antioxidant activities (Sharma *et al.*, 2017). The major reportedantioxidants property of many flavonoids is in their ability to act as free radical scavengers.As potential reducing agents, flavonoids protect the body from oxidative reactions (Saul Ruiz- Cruz *et al.*, 2018). Though antioxidant activities have being reported for large number of flavonoids, reports have shown the pure flavonoids possess higher antioxidant capacity. Therefore, the antioxidant of these flavonoids follows the following order luteolin> rhamnetin> isorhamnetin> apigenin (Majewska *et al.*, 2011). A study of quercetin, taxifolin, catechin and galangin on mitochondria showed the antioxidant activity of these compounds (Nishigaki *et al.*, 2010).The antioxidative activities of glycosides and quercetin has been attributed to the hydroxyl groups B-ring and C-ring of the flavonoids (Zheng *et al.*, 2017). The antioxidative activities of isoflavonone, genistein and quercetin have been well reported (Hayat *et al.*, 2017).

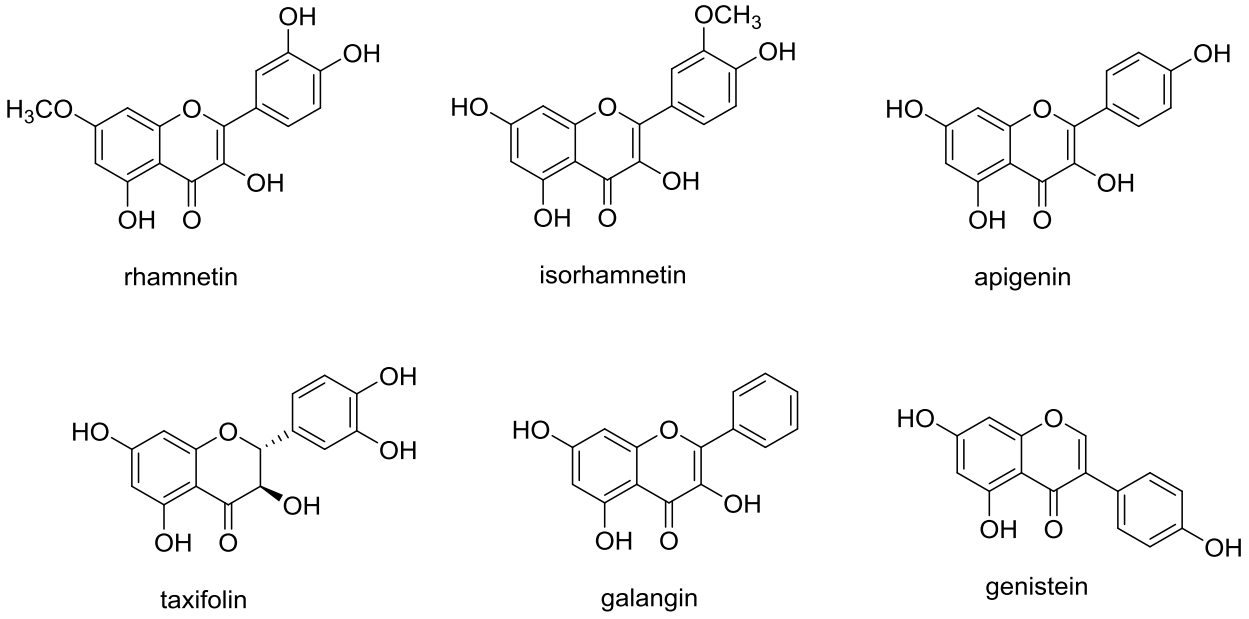

Figure 5. Flavonoids with antioxidant activities

6. Conclusion

In summary, the anticancer, antibacterial, antifungal and antioxidant activities of some flavonoids were reviewed.The huge pharmacological properties of flavonoids have made them of research interest. Among reported activities of plants derived phytoconstituents, flavonoids have shown various pharmacological activities. The antibacterial activities of flavonoids against a wide range of microorganisms

are well known and reported. The radical-scavenging ability of flavonoids has been well reported. Therefore, one can conclude that flavonoids have actually become the emerging therapeutic agents.

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