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Flavonoids: isolation, characterization, and health benefits

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Abstract

Background: The unique and vast pharmacological activities of flavonoids have made them of research interest. This led to the use of various techniques to isolate and characterize them, intending to determine their potential health benefits.

Main text: The medicinal values of plant-based flavonoids that this literature review tends to summarize the pharmacological activities of these secondary metabolites from 22 selected plant families. The pharmacological shreds of evidence reported in the literature have proven that flavonoids have shown anti-cancer, anti-microbial, anti-oxidant, anti-inflammatory, anti-fungal, anti-ulcer, and anti-edematogenic activities. Out of these, 30% showed to have anti-oxidant activity, key in protecting the body against free radicals. Besides, 18% of the references showed anti-microbial and anti-cancer activities. Further literature reports indicated that flavonoids from these families exhibited anti-inflammatory and anti-edematogenic (9%), anti-viral and anti-ulcer (5%), anti-fungal, anti-nociceptive, and anti-histamine (2%).

Conclusion: The pharmacological activities of flavonoids from the various sources reviewed in this study show that the secondary metabolites could provide a scaffold for the development of potent anti-cancer drugs in the future.

Keywords: Flavonoids, Isolation, Characterization, Health benefits

1 Background

Flavonoids are phytochemicals responsible for the various colors in the seeds, flowers, fruits, leaves, and bark [1]. Flavonoids are a large class of natural aromatic compounds as there are reported to be the most common plants' phenolics [2, 3]. Over the years, flavonoids have represented a vast percentage of phytochemicals from natural sources. It has been reported that more than 10, 000 different classes of flavonoids have been found in kingdom Plantae [4–6]. Flavonoids are secondary metabolites found in organs of these plants with different functions [7, 8]. Also, they have been reported from sources such as vegetables, wine, fruits, and beverages (tea) [9].

The chemical structures of flavonoids consist of C6-C3-C6 [10] rings which correspond to two aromatic rings A and B linked by three carbon atoms, which may lead to the formation of a third ring (C). Variations in this basic structure give the various subclasses of flavonoidal compounds. These are flavanones, isoflavones, flavones, flavanols (catechins), chalcones, flavonols, and anthocyanins [11–14]. The flavonoids present in the diet help in the prevention of cardiovascular disease [15]. The biological and oxidative properties of flavonoids are responsible for their anti-allergic, cardioprotective, anti-diabetic, anti-inflammatory, anti-oxidative activity, and free radical scavenging capacity [15, 16]. Also, flavonoids have been reported to exhibit anti-cancer activity [5]. Studies of flavonoids revealed that they are free radical scavengers and reducing agents [17]. Recent researches have focused on the health benefits of these secondary metabolites because of their preventive activity against diseases and anti-oxidative activity, anti-cancer activities, anti-viral activities, and anti-inflammatory [18, 19]. Aside from the anti-oxidant activity of flavonoids, chelating properties [20],

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their usage as anti-aging substances [21], capillary permeability, and inflammatory response [22], anti-bacterial and therapeutic [23], gastro-protective, and anti-diabetic activity [3] of these phenolics have been reported.

The protective effects such as the anti-inflammatory, anti-oxidant, anti-viral, and anti-tumor activity of flavonoids from natural sources are well documented [24]. The anti-carcinogenic activity of flavonoids has been linked to their anti-oxidant properties [25] which is due to the hydroxyl groups on the structure of the flavonoids [26]. Because of the importance of these phytochemicals, this review summarizes the isolation, characterization, and health benefits of these flavonoids taking into consideration those phytochemicals responsible for these activities. The health benefits reviewed were anti-cancer, anti-microbial, anti-oxidant, anti-inflammatory, anti-fungal, anti-ulcer, and anti-edematogenic activities.

2 Main text

2.1 Methods

The search was done by using keywords such as flavonoids on "science direct," "google scholar," "Scopus" database, and many journal sites. Journals employed in the search are Elsevier and Springer. Other search engines used as well as papers published between 2006 and 2019.

3 Results

3.1 Flavonoids biosynthetic pathway

Flavonoids or stilbenes biosynthetic pathway (Fig. 1) follow the extension of 4-hydroxycinnamoyl-CoA with three malonyl-CoA units, in which the poly-β-keto chain folded in different ways, via Aldo or Claisen reactions. Stilbene synthase and chalcone synthase (enzymes) couple the three malonyl-CoA with cinnamoyl-CoA unit to give chalcones or stilbene. Chalcones are precursors for the vast range of flavonoids and their derivatives found in plants. The nucleophilic attack (Michael type) of a phenolic group on α, β-unsaturated ketone forms a six-membered heterocyclic ring such as naringenin. This isomerization reaction in an acid condition favors the flavanone while in basic condition, the chalcone [27]. Flavanones then give rise to variants of flavonoids such as flavonols, flavones, anthocyanidins, and catechins as shown in Fig. 1

3.2 Sources and classification of flavonoids

The various sources of flavonoids have been reported [28] and are given in Table 1 while their classification [29] is shown in Table 2 showing the subclasses. Similarly, Fig. 2 showed the basic skeleton of flavonoids and their various classes.

3.3 Isolation of flavonoids

The isolation of flavonoids involves various techniques available to natural products researchers that have simplified their isolation from crude extracts. These techniques are column chromatography (CC), high-performance liquid chromatography (HPLC), high-speed counter-current chromatography (HSCCC), counter-current chromatography (CCC), open centrifugal preparative thin layer chromatography (CPTLC), preparative thin-layer chromatography (PTLC), medium pressure liquid chromatography (MPLC), and high-pressure preparative liquid chromatography (HPLC) [29, 30]. The details of the extraction, steps, and the solvents used for the structural elucidation and characterization of the flavonoids summarized in this review are shown in Table 5.

3.4 Techniques used to elucidate the structure of flavonoids

Natural products researchers use the following spectroscopic techniques to elucidate the structure of flavonoids. These are infrared spectroscopy (IR), nuclear magnetic resonance (NMR), ultra-violet spectrophotometry (UV), mass spectrometry (MS), and physical properties as electronic circular dichroism (ECD), melting point (m.pt), and specific rotation power ($[\alpha]_D^T$) for flavonoids with a stereocenter for ECD and [α]D. Flavonoids have unique chemical shifts. These characteristic chemical shifts make it easier to characterize them. The characteristic chemical shift values reported [29] for some flavonoid classes are given (Table 3) and the UV absorption ranges for these flavonoids are shown (Table 4).

The isolation, characterization, and health benefits of these flavonoids are represented (Scheme 1).

4 Discussion

4.1 Health benefits of flavonoids

Extensive biological studies of flavonoids have revealed their health benefits including disease prevention [5, 72]. They have exhibited anti-oxidant, anti-inflammatory, anti-bacterial, and anti-viral activities [73], anti-oxidant [74], anti-allergic anti-carcinogenic properties [75]. The protective effects of flavonoids have been reported as they help to reduce oxidative stress in the body. The cholesterol-lowering activity, anti-cancer, anti-oxidant of myricetin, tricin, apigenin, luteolin, quercetin, and isorhamnetin has been reported [24]. The anti-viral, anti-bacterial, anti-cancer, cardioprotective, and anti-inflammatory activity [76], as chelating agents and, are strong topoisomerase inhibitors [24] anti-aggregational, anti-atherosclerotic, and detoxification activities [77] of various flavonoids have been reported. These biological activities depend to a larger extent on the hydroxyl group in the flavonoids [78]. Quercetin has reduced the risk of cancer, eye diseases, arthritis, and allergic disorders [9]. The decreased risk of cardiovascular disease by proanthocyanins and flavone-3-ols has been reported [23]. The techniques used for the isolation,

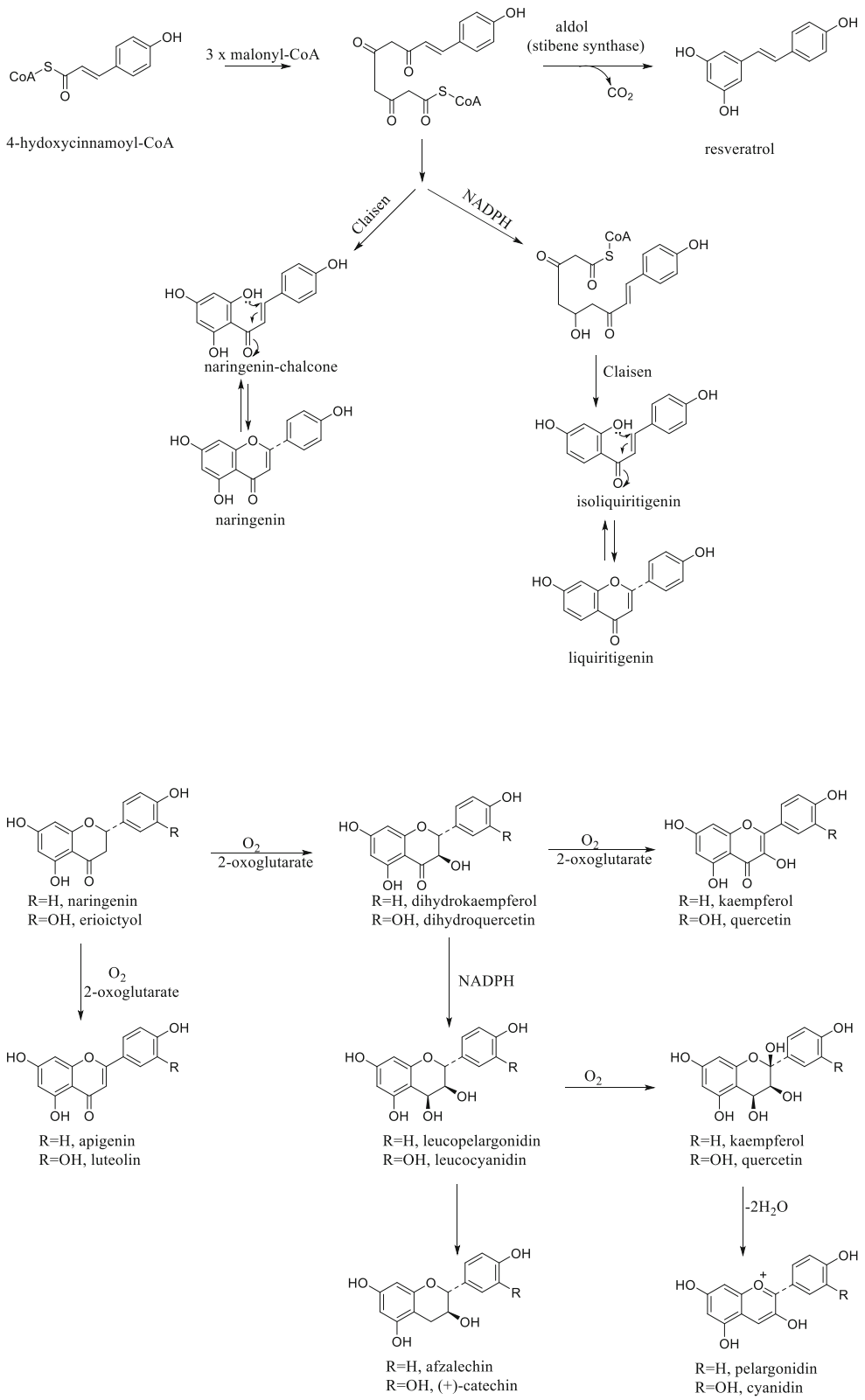


Fig. 1 Biosynthetic pathway of flavonoid

Table 1 Sources of flavonoids [28]

Flavonoids	Sources
Flavonols	Ginger, broccoli, onions, leafy greens
Flavanols	Chocolate, red wine, black, and green tea
Flavonones	Oregano, celery, parsley
Flavanones	Citrus fruits, juices
Anthocyanidins	Red cabbage, grapes, berries, cherries
Isoflavonones	Milk, tofu, soy, tempeh

characterization, and the health benefits of these flavonoids are as shown in Table 5.

The pharmacological activities of the phytochemical constituents from 22 plant families reported in the literature as reviewed in Fig. 3 showed the percentages of these activities. Out of the references cited, 30% of the flavonoids showed anti-oxidant activity. Because of this vast anti-oxidant activity, flavonoids reduce aging by protecting the body against free radicals oxidation [26, 79].

4.2 Anti-oxidant activity

Anti-oxidants are compounds that slow or prevent oxidation in living cells. They act against the effects of free radicals. Flavonoids protect the body against reactive oxygen species. Chemically, flavonoids have hydroxyl groups and a highly conjugated π-electron system, which allows them to act as free radical scavengers [80]. Anti-oxidant activity of flavonoids [16, 20, 33, 76, 81], chelating properties [20], makes them acts as protective agents against free radicals [26, 79]. In the body, anti-oxidants protect the human body from free radicals oxidation [17] thereby retarding the progress of many chronic diseases. Epicatechin, epigallocatechin, and gallocatechin have exhibited anti-oxidant activity [31].

Naringenin has shown anti-oxidant, anti-diabetic, anti-atherogenic, anti-depressant, immunomodulatory, antitumor, antiinflammatory, and hypolipidaemic, activity [12]. Catechin, epicatechin, rutin, quercetin, and naringin have been reported for anti-oxidant activity against free radicals [32]. The anti-oxidant activity of spectaflovoside A, kaempferol-3-O-(2′′,3′′-di-O-acetyl)-α-L-rhamnopyranoside, kaempferol-3-O(3′′,4′′-di-O-acetyl)-α-L-rhamnopyranoside, kaempferol-3-O- (2′′,4′′-di-O-acetyl)-α-L-rhamnopyranoside, kaempferol, and kaempferol-3-O-(4′′-Oacetyl)-α-L-rhamnopyranoside were documented [36]. The anti-oxidant activity of flavonoids extracted from *Phlomis bovei* De Noé [82], quercetin, taxifolin, catechin, and galangin, anthocyanidin, kaempferol, catechins, and catechin gallate esters have been reported [83]. Quercetin, anthocyanidin and kaempferol, catechins, and catechin gallate esters are effective anti-oxidants against free radicals. Quercetin had showed excellent in vitro anti-oxidant capacity [59]. Quercimeritrin, scutellarein, and rutin isolated from *C. angustifolia* showed strong anti-oxidant activity against oxidative stress [54]. The phytochemical investigation of the ethanol extract of *Ximenia parviflora* Benth. Var led to the isolation of quercetin, kaempferol, and apigenin with anti-oxidant activity. Similarly, the naringenin, quercetin, and kaempferol isolated from the ethanolic extract of *Viscum album* L showed anti-oxidant activity [62]. Catechins have been reported for its protection against oxidative stress, cancer, and cardiovascular disorder [84]. In Fig. 4, the chemical structures of flavonoids reported for their benefits are as shown.

4.3 Anti-microbial activity

The broth microdilution assay of spectaflovoside A, kaempferol-3-O-(2′′,3′′-di-O-acetyl)-α-L-rhamnopyranoside, kaempferol-3-O-(3′′,4′′-di-O-acetyl)-α-L-rhamnopyranoside, kaempferol-3-O-(4′′-Oacetyl)-α-L-rhamnopyranoside, kaempferol, and kaempferol-3-O-(2′′,4′′-di-O-acetyl)-α-L-rhamnopyranoside showed that these flavonoids exhibited remarkable anti-bacterial activities with a MIC values between 62.50 μg/mL and 500 μg/mL against *E. coli*, *K. pneumoniae*, *S. aureus*, and *B. cereus* [36]. In another study, luteolin, 3,5-dihydroxy-6,7,8,4′tetramethoxyflavone, apigenin, 3,5-dihydroxy-6,7,8-trimethoxyflavone, apigenin 7-O-glucoside, apigenin 4′-O-glucoside, kaempferol 3-O-glucoside, luteolin 4′-O-glucoside, luteolin 4′,7-O-diglucoside, kaempferol, kaempferol 7-O-glucoside, and quercetin 3-O-glucoside

Table 2 Classification of flavonoids [29]

Flavonoids	Subclasses
Flavanones	Hesperidin, naringenin, naringin, erioditol, hesperidin
Flavones	Galangin, apigenin, chrysin, rpoifolin, baicalein, nobiletin, tangeretin, luteolin,
Anthocyanins	Catechin, cyanidin, epicatechin, pelargonidin, epicatechin gallate (ECG), malvidin, delphinidin, epigallocatechin (EGC),
Flavanols	Gallocatechin, epigallocatechin gallate (EGCG)
Chalcones	Arbutin, phloretin, chalconaringenin
Flavonols	Quercetin, rutin, myricetin, kaempferol, morin, fisetin, isorhamnetin
Isoflavonoids	Genistin, glycitein, daidzin, genistein

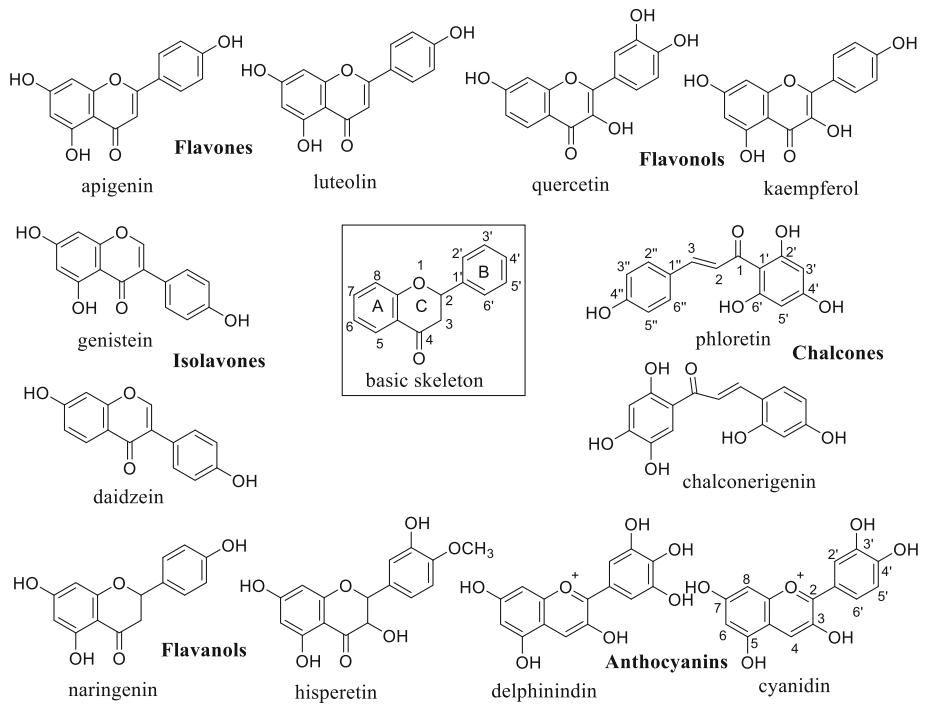


Fig. 2 The basic skeleton of flavonoids and their various classes

were reported for their vast anti-microbial activities against *P. aeruginosa* [38]. Apigenin and isoflavones exhibited anti-bacterial activity [16]. Genistein, kaempferol, naringenin, and catechin isolated from Brassica *oleracea* var. Capitata L. possessed anti-bacterial activity against *E. coli* and *S. aureus* [52].

The flavonoids, 3-hydroxy flavone derivatives, and 3-methyl flavanone showed activity against Gram +ve bacteria [75]. Scandenone, kaempferol-3,7-O-α-L-dirhamnoside tiliroside, quercetin-3,7-O-α-L-dirhamnoside showed anti-microbial activity [43]. 7-Methoxy-3, 3′,4′,6-tetrahydroxyflavone, 3,3′,4′, 7-tetrahydroxyflavone (fisetin), naringenin, 2′,7-dihydroxy-4′, 5′-dimethoxyisoflavon, 3′-hydroxydaidzein and xenognosin B exhibited the anti-bacterial activities against *B. subtili* ATCC 6633, *S. aureus* ATCC25932, and *B. cereus* ATCC7064 [48]. The 2′,4′-dihydroxy-4methoxy-3′-prenyldihydrochalcone, 4-hydroxyonchocarpin, isobavachalcone, 2′,4′-dihydroxy-3,4-(2′′,2′′dimethylchromeno)-3′-prenyldihydrochalcone, 5,7-dihydroxy4′-methoxy-6-prenylflavanone, 5-hydroxy-6,7-(2, 2dimethylchromano)-4′-methoxyflavanone, 4′,5-dihydroxy-6,

Table 3 Characteristic chemical shifts for flavonoids [29]

Chemical shifts (ppm)	^{1}H
2–3	H-3 (flavanone, CH_3 aromatic)
4–6	H-2 (dihydroflavonol, flavanone)
6–8	A and B ring protons
8–8.5	H-2 (isoflavone)
12–14	5-OH when C═O at C4 (DMSO d6)
Chemical shifts (ppm)	^{13}C
28–35	C-4 (flavanol)
40–80	Non-oxygenated (C-2,-C-3-flavanone/flavanol)
90–125 (with ortho/para oxygenation)	Non-oxygenated aromatic carbons
125–135 (para substitution)	Non-oxygenated aromatic carbons
130–150 (with ortho/para oxygenation)	Oxygenated aromatic carbons
155–165 (no ortho/para oxygenation)	Oxygenated aromatic carbons
170–210	C═O

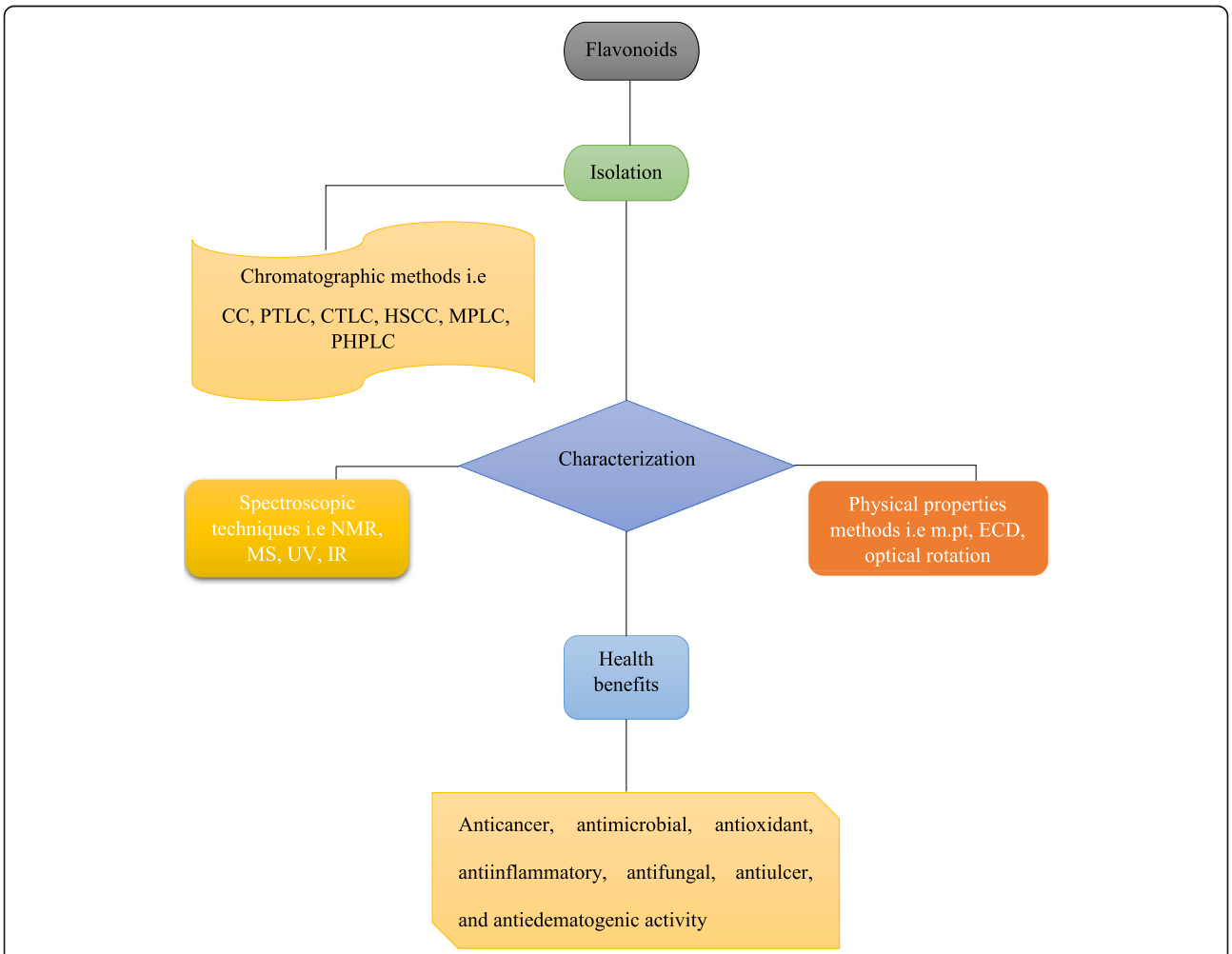
Table 4 UV absorption ranges for flavonoids [29]

Absorption 1 (nm)	Absorption 2 (nm)	Types
250–280	310–350	Flavone
250–280	330–360	Flavonols (3-OH-substituted)
250–280	350–385	Flavonols (3-OH-free)
245–275	310–330 shoulder	Isoflavone
	C. 320 peak	Isoflavones (5-deoxy-6,7-deoxygenated)
275–295	300–330 shoulder	Flavonones and dihydroflavonols
230–270	340–390	Chalcones
230–270	380–430	Aurones
270–280	465–560	Anthocyanidins and Anthocyanins

7(2,2-dimethylchromeno)-2′-methoxy-8-γ,γ-dimethylallylflavone, artocarpin, pyranocycloartobiloxanthone A, and cycloheterophyllin isolated from *Artocarpus lowii* King and *Artocarpus anisophyllus* Miq showed activity against *S. aureus*, *P. putida*, *B. cereus*, *E. coli*, *C. albicans*, and *C. glabrata* [49].

4.4 Anti-cancer activity

The term cancer refers to a disease in which cells of a tissue undergo uncontrolled and often rapid proliferation [85]. This is also the loss of control of growth [86]. Alternative medicine has been used to treat cancer [87]



Scheme 1 Flavonoids: isolation, characterization, and health benefits

Table 5 Isolation, characterization, and health benefits of flavonoids

	Isolation/ characterization	Solvents used	Sources	Family	Health benefits	Ref.
Epicatechin, epigallocatechin, and gallocatechin	HPLC	100% H_2O	Kombucha tea		Anti-oxidant activity	[31]
Naringenin	‡	‡	‡	‡	Anti-oxidant activity, hepatoprotective effects, anti-inflammatory effects, anti-carcinogenic effects, cardiovascular effects, obesity, gastrointestinal effect, naringenin enhances immunity	[12]
Catechin, epicatechin, rutin, quercetin, naringin	UV-Vis	80% MeOH and 100% acetone	*Cirsium bulgaricum* DC.	Asteraceae	Anti-bacterial activity, anti-oxidant activity	[32]
Naringin, hesperidin, quercetin	HPLC	0.5 g kg^{-1}	Citrus fruits	Rutaceae	Anti-oxidant activity	[33]
Quercetin. kaempferol, myricetin, luteolin, apigenin	HP20	70% EtOH	*Pluchea indica* (Linn.) Less	Asteraceae	Anti-inflammatory, anti-nociceptive, anti-inflammation activity	[34, 35]
Spectaflovoside A, kaempferol-3-O-(2′′′,3′′-di-O-acetyl)-α-L-rhamnopyranoside, kaempferol-3-O-(3′′,4′′-di-O-acetyl)-α-L-rhamnopyranoside, kaempferol-3-O-(4′′-Oacetyl)-α-L-rhamnopyranoside and kaempferol, kaempferol-3-O-(2′′,4′′-di-O-acetyl)-α-L-rhamnopyranoside	NMR	DCM: EtOAc	*Zingiber spectabile* Griff	Zingiberaceae	Anti-oxidant activity, anti-bacterial activity	[36]
Quercetin glycosides, catechins	HPLC	MeOH	Apple cultivars	Rosaceae	Anti-oxidant activity	[37]
luteolin, apigenin, 3,5-dihydroxy-6,7,8-trimethoxyflavone, kaempferol, 3,5-dihydroxy-6,7,8,4′ tetramethoxyflavone, apigenin 4′-O-glucoside, apigenin 7-O-glucoside, luteolin 4′-O-glucoside, kaempferol 3-O-glucoside, kaempferol 7-O-glucoside, luteolin 4′,7-O-diglucoside and quercetin 3-O-glucoside	PTLC and NMR	95% EtOH	*Helichrysum chasmolycium* P.H Davis	Asteraceae	Anti-oxidant and anti-microbial activity	[38]
Quercetin, morin-3-O-lyxoside, quercetin-3-O-arabinoside, morin-3-O-arabinoside	Column chromatography	MeOH	*Psidium guajava*	Myrtaceae	Anti-bacterial activity	[39]
Rutin, quercetrin, quercetin, naringin, hesperidin, hespertin, kaempferol, apigenin, narengenin, 7-OH flavone	HPLC	62.5% MeOH	*Colvillea racemosa*	Caesalpinioideae	Anti-microbial activity, anti-oxidant activity,	[40]
Quercetin, rutin, and naringenin	LC-ESI/MS	EtOH 70 % (v/v)	*Raphanus sativus* L.	Brassicaceae	Anti-microbial, anti-oxidant, anti-histamine and anti-inflammatory activity	[41]
5,7-dimethoxyflavanone-4′-O-β-D-glucopyranoside, rutin, naringenin-7-O-β-D-glucopyranoside, 5,7,3′-trihydroxy-flavanone-4′-O-β-D-glucopyranoside, 5,7dimethoxyflavanone-4′-O-[2′′-O-(5′′′-O-trans-cinnamoyl)-β-D-apiofuranosyl]-β-D-glucopyranoside, and nicotiflorin	MPLC, NMR and MS	EtOAc: MeOH:n-butanol	*Galium fissurense, Viscum album* ssp. album and *Cirsium hypoleucum*	Rubiaceae, Santalaceae and Asteraceae	Anti-microbial activity	[42]
Tiliroside, scandenone, kaempferol-3, 7-O-α-L-dirhamnoside quercetin-3,7-O-α-L-dirhamnoside	PTLC, TLC, NMR	$CHCl_3$: EtOH	*Maclura pomifera* (Rafin.) Schnider, *T. argentea, Tilia argentea* Desf. ex DC.	Moraceae, Tiliaceae	Anti-cancer, anti-bacterial, anti-fungal activity, and anti-viral activity	[43]
Quercetin	HPLC, FTIR, and NMR.	EtOAc	*Aesculus indica*	Sapindaceae	Anti-oxidant activity	[44]

Table 5 Isolation, characterization, and health benefits of flavonoids *(Continued)*

	Isolation/ characterization	Solvents used	Sources	Family	Health benefits	Ref.
Luteolin-7-O-glucoside	TLC, HPLC-TOF/ MS and FT-IR	MeOH: DCM (1: 22; v/v)	*Tanacetum abrotanifolium* (L.) Druce	Asteraceae	Anti-cancer, anti-microbial, and anti-oxidant activity	[45]
Quercetin	TLC and HPLC	EtOH	*Nicotiana tabacum*	Solanaceae	Anti-oxidant activity	[46]
7-methoxyflavanone, 3-acetoxy-4′,5-dihydroxy-and naringenin	HPLC, NMR and (HR)-EI-MS	n-hex: EtOAc†	*Baccharis dracunculifolia*	Asteraceae	Anti-cancer activity	[47]
2′,7-dihydroxy-4′,5′-dimethoxyisoflavon, 3′-hydroxydaidzein, 7-methoxy-3, 3′, 4′,6-tetrahydroxyflavone 3,3′,4′,7-tetrahydroxyflavone (fisetin), naringenin, and xenognosin B	prep TLC, NMR, MS, IR, m.pt and optical rotation	1/3 EtOAc	*Boesenbergia rotunda* (L.) Mansf.	Streptomyces sp.	Anti-bacterial activity	[48]
2′,4′-dihydroxy-4methoxy-3′-prenyldihydrochalcone, 4-hydroxyonchocarpin, isobavachalcone, 5,7-dihydroxy4′-methoxy-6-prenylflavanone, 2′,4′-dihydroxy-3,4-(2″,2″ dimethylchromeno)-3′-prenyldihydrochalcone, 5-hydroxy-6,7-(2,2dimethylchromano)-4′-methoxyflavanone, 4′,5-dihydroxy-6,7(2,2-dimethylchromeno)-2′-methoxy-8-γ,γ-dimethylallylflavone, artocarpin, pyranocycloartobiloxanthone A, and cycloheterophyllin	TLC and NMR	n-hex: MeOH: DCM	*Artocarpus anisophyllus* Miq. and *Artocarpus lowii* King	Moraceae	Anti-microbial activity	[49]
Apigenin	HPLC	MeOH: H_2O (80: 20)	*Cousinia verbascifolia* Bunge	Asteraceae	Anti-cancer activity	[50]
Luteolin	VLC, PTLC and NMR	$CHCl_3$:n-hex(4:5)	*Struchium sparganophora* (Linn) Ktze	Asteraceae	Anti-cancer activity	[51]
Genistein, kaempherol, naringenin, and catechin	LC-MS	80% MeOH	*Brassica oleracea* var. Capitata L.	Brassicaceae	Anti-bacterial activity	[52]
Quercetin-3-O-β-d-glucuronide, luteolin-7-O-β-glucopyranoside, formononetin-7-O-β-D-glucoside	HPLC	EtOH: H_2O:HCl (50:20:8)	*Cassia Tora* linn.	Fabaceae	Anti-oxidant and anti-cancer activity	[53]
Quercimeritrin, scutellarein, and rutin	HPLC-MS, NMR	MeOH, EtOH, acetone, and EtOAc	*Cassia angustifolia* Vahl.	Caesalpiniaceae	Anti-cancer, anti-oxidants, and anti-microbial activity	[54]
Luteolin	HPLC	$CHCl_3$: MeOH (19:1, v/ v)	*Vitex negundo* Lin	Lamiaceae	Anti-tumor activity	[55]
2′, 5-dihydroxy-7-methoxyflavone, 2′, 5Vdihydroxy-7-methoxyflavanone	LC-MS, NMR	100 % MeOH	*Andrographis glandulosa,*	Acanthaceae,	Anti-cancer activity	[56]
Kaempferol	NMR, MS	$CHCl_3$: MeOH (9: 1, 7:3, 1:1, 3:7 and 1:4)	*Ageratum conyzoides* L.	Asteraceae	Anti-cancer and anti-oxidant activity	[57]
Pinostrobin	VLC, TLC, NMR, EIMS	Hex: EtOAc 80:20 (VLC; 15cm x16 cm)	*Cajanus cojan* Millsp.	Fabaceae	Anti-cancer activity	[58]

Table 5 Isolation, characterization, and health benefits of flavonoids *(Continued)*

	Isolation/ characterization	Solvents used	Sources	Family	Health benefits	Ref.
Cyanarodide	CC, TLC,NMR, GC-MS	EtOH: EtOAc †	*H. chillensis*	Asteraceae	Anti-cancer activity	[59]
Procyanidin A, procyanidin B, and catechin/epicatechin	LC-MS, HPLC DAD-MS/MS	H_2O	*Ximenia americana* L.	Olacaceae	Anti-ulcerogenic activity	[60]
Quercetin, kaempferol, and apigenin	HPLC-DAD	EtOH (50, 80, and 100%, v/v)	*Ximenia parviflora* Benth. var.	Olacaceae	Anti-oxidant activity	[61]
Naringenin, quercetin, and kaempferol	HPLC	EtOH 70% (1:10, w/v)	*Viscum album* L.	Santalaceae	Anti-oxidant activity	[62]
Catechin, rutin, quercitrin, quercetin, and kaempferol	HPLC-DAD	H_2O 100 % EtOH (1:1)	*Ximenia americana* L.	Olacaceae	Anti-edematogenic activity	[63]
Kaempferol 3-Orutinoside, kaempferol 7-O-β-D-glucopyranoside, Spinacetin 3-O-[α-L-rhamnopyranosyl-(1⟶6)-βD-glucopyranoside]-7-O-[α-L-rhamnopyranoside], and quercetin7-O-β-D-glucopyranoside	TLC, NMR and ESI-MS	EtOH	*Anvillea garcinii*	Asteraceae	Anti-ulcer activity	[64]
Hesperidin	TLC, IR and HPLC	MeOH	*Citrus sinensis* (L.) Osbeck	Rutaceae	Anti-ulcer activity	[65].
Apigenin 4′-Oβ-D-glucopyranoside, isoquercetin, nicotiflorin and apigenin 6-Cα-L-arabinopyranoside-8-Cβ-D-glucopyranoside	TLC, NMR	EtOH	*Vicia sativa*	Fabaceae	Anti-edematogenic activity ($P < 0.05$)	[66].
cirsiliol, isorhamnetin 3-O-b-D-glucoside, chrysosplenol D, artemetin	TLC, NMR ,FT-IR	100% MeOH	*Chrysanthemum morifolim* Ramat	Asteraceae	Anti-inflammatory activity	[67]
Artemetin	CC and NMR	Acetone	*Cordia curassavica* DC	Boraginaceae	Anti-edematogenic activity	[68]
3-methoxy quercetin	TLC, NMR	n-butanol	*Garcinia kola* Heckel	Clusiaceae	Anti-inflammatory activity	[69]
Quercetin3-O- -L-arabinopyranosyl (1⟶2) -L-rhamnopyranoside	HPLC, NMR	H_2O: EtOH (1:1).	*Kalanchoe pinnata* (Lamarck) Persoon	Crassulaceae	Anti-inflammatory, anti-nociceptive, and anti-edematogenic activity	[70]
3, 5-dihydro-7-methoxy anthocynidines	PTLC, NMR	$CHCl_3$: EtOAc (9:1)	*Monanthotaxis littoralis*	Annonaceae	Anti-fungal activity	[71]

**MPLC* medium pressure liquid chromatography, *LC-ESI/MS* liquid chromatography electrospray ionization mass spectrometry, *TLC* thin layer chromatography, *VLC* vacuum liquid chromatography, *LC-MS* liquid chromatography-mass spectrometry, *HPLC-MS* high-performance liquid chromatography-mass spectrometry, *EIMS* electrospray ionization mass spectrometry, *HPLC-DAD* high-performance liquid chromatography with diode array detection, *GC-MS* gas chromatography-mass spectrometry, *MIC* minimum inhibitory concentration

† Increasing polarity

‡A review journal

and flavonoids, especially from plant sources, have not been left out. The pharmacological properties of flavonoids have made them useful alternatives to inhibit cell damage [73]. Flavonoids have been reported to be good anti-cancer therapeutics [88]. Quercetin particularly has been reported to be effective in the treatment of stomach, lung, prostate, and breast cancers [29]. Pradhan et al. 2015 reported the anti-tumor activity of quercetin without toxicity on the breast cancer cell, MCF-7 [89]. The anti-cancer activity of quercetin has been linked to the inhibition of the enzyme (DNA gyrase) [90]. Luteolin isolated from the leaves of *Struchium sparganophora* has caused cell death of melanoma and ovarian cancer cell lines [51]. Luteolin-7-O-β-glucopyranoside, formononetin-7-O-β-D-glucoside, and quercetin-3-O-β-d-glucuronide isolated from the leaves of *Cassia tora* linn were active against breast cancer (MCF7) [53]. Luteolin from the *Vitex negundo* Lin was an active anti-tumor agent [55]. In another study, the 2′, 5-dihydroxy-7-methoxyflavanone and 2′, 5-dihydroxy-7-methoxyflavone isolated from *Andrographis glandulosa* were active against HeLa, MIA PaCa, and U-8 [56]. Quercetin has been reported to induce

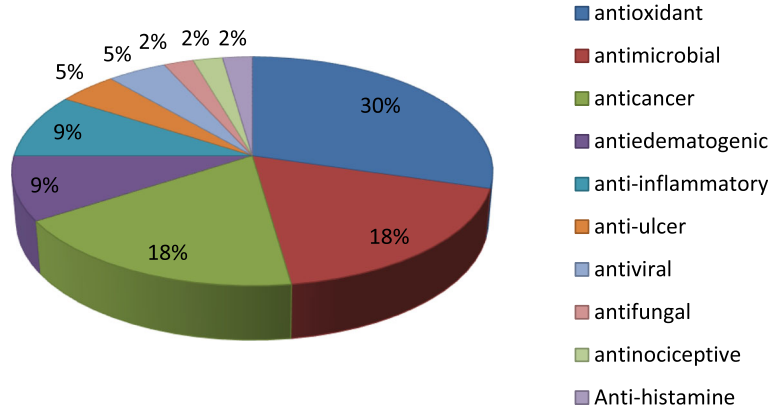


Fig. 3 Representation of the activities of the flavonoids

cytotoxicity in cancer cells [91]. Kaempferol isolated from *Ageratum conyzoides* L. exhibited activity against lung cancer, gastric cancer, colon cancer, and glioma cancer [57]. Pinostrobin isolated from *Cajanus cojan* exhibited anti-leukemia activity [58]. The cynaroside isolated from *H. chillensis* was active against OVACAR-8, HCT-116, and SF-295 [59]. Nobiletin at 20 μM inhibited human ovarian cancer [76].

Quercetin, kaempferol, myricetin, luteolin, and apigenin isolated from the aqueous and/or alcohol extracts of *Khlu* leaves exhibited anti-cancer activities [34]. Quercetin has shown anti-tumor activity [25]. Myricetin and quercetin inhibited mammalian TrxRs with IC_{50} values of 0.62 and 0.97 Mmol/L, respectively [92]. Apigenin has been reported to arrest HT29 colon cancer [50]. Oncamex showed a strong anti-tumor effect against breast cancer while hesperetin was active against lung and carcinoma cancer cells [93]. Hesperidin and naringin isolated from the alcoholic extract of *Colvillea racemosa* were active against colon carcinoma cell lines (HCT-116) [40]. Quercitin, morin, and myricetin have shown protective effects in the prevention of liver, cardiovascular diseases, and cancer [16].

4.5 Anti-inflammatory

Inflammation is a normal biological process in response to pathogen infection, tissue injury, or chemical irritation [16]. The anti-inflammatory properties of anthocyanins have been reported [81]. Previous in vitro studies of flavonoids showed inhibition against LPS-induced TNF-α production [94]. The report of the phytochemical investigation of *Vicia sativa* led to the isolation of apigenin 4′-Oβ-D-glucopyranoside, isoquercetin, nicotiflorin, and apigenin 6-Cα-L-arabinopyranoside-8-Cβ-D-glucopyranoside that showed significant anti-edematogenic activity ($P < 0.05$) [66]. Isorhamnetin 3-O-b-D-glucoside, cirsiliol, chrysosplenol D, and artemetin isolated from *Chrysanthemum morifolim* Ramat inhibited the NO production in LPS-induced RAW 264.7 cells [67]. Daidzein, quercetin, genistein, and kaempferol have inhibited the production of both STAT-1 and NF-κB [95]. Similarly, the 3-methoxy quercetin isolated from *Garcinia kola* Heckel at concentrations (25 and 125 μM) inhibited the production of TNF-α [69]. The quercetin 3-O- -L-arabinopyranosyl(1→2)- -L-rhamnopyranoside isolated from *Kalanchoe pinnata* (Lamarck) Persoon showed anti-inflammatory activity [70]. At higher doses, flavonoids have shown a decrease in proliferation, CD14 surface marker, and NO production [96]. The flavonoids, artocarpanone A, artocarpanone, and heteroflavanones B and C have shown a remarkable inhibitory effect on iNOS protein expression and NO production in RAW 264.7 cells [97].

4.6 Anti-fungal activity

The flavonoids, diglycosylflavones, flavonol-3-O-glycosides, and proanthocyanidins isolated from *Ephedra alata* showed anti-fungal activity [22], nobiletin and langeritin, and hesperidin exhibited strong and weak anti-fungal activities, respectively [2]. The flavonoid, baicalein, showed anti-candidal activity against *C. tropicalis* 170.06, *C. albicans* ATCC 64550, and *C. parapsilosis* 153.07 with the MIC_{50} of 2.6, 26, and 13 μg ml^{-1}, respectively [98]. The 3, 5-dihydroxy-7-methoxy anthocynidines isolated from *Monanthotaxis littoralis* was active against mycotoxigenic [71]. (-)-epicatechin-3-Ob-glucopyranoside, 6-p-hydroxybenzyltaxifolin-7-O-b-D-glucoside, 5-hydroxy-3-(4-hydroxylphenyl) pyrano[3,2-g]chromene-4(8H)-one (-)-epicatechin(2(3,4-dihydroxyphenyl)-3,4-dihydro-2H-chromene-3,5,7-triol, and quercetin-3-O-a-glucopyranosyl-(1 2)-b-D-glucopyranoside isolated from *Mangifera indica* L exhibited anti-fungal activity [99].

4.7 Anti-ulcer activity

An ulcer is a disease of the alimentary tract caused by an inflamed break in the mucus lining membrane [100]. The anti-ulcer activity of quercetin in animals has been reported [72]. The phytochemical investigation of the

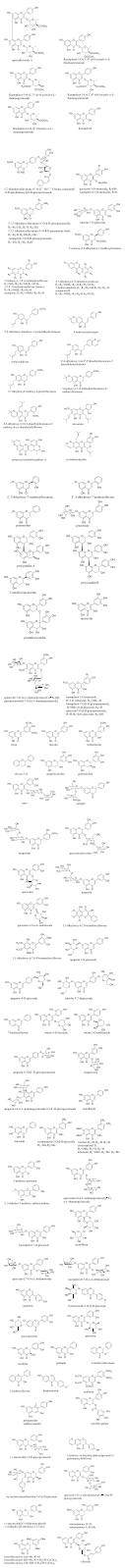


Fig. 4 Chemical structures of flavonoids with health benefits

aqueous extract of *Ximenia americana* led to the isolation of procyanidins B and C as well as catechin/epicatechin which were active against acute gastric ulcer [60]. The spinacetin 3-O-[α-L-rhamnopyranosyl-(1→6)-βD-glucopyranoside]-7-O-[α-L-rhamnopyranoside], kaempferol-3-Orutinoside, kaempferol-7-O-β-D-glucopyranoside, and quercetin-7-O-β-D-glucopyranoside isolated from the ethanol extracts of *Anvillea garcinii* showed a powerful anti-ulcer [64]. The hesperidin isolated from *Citrus sinensis* showed anti-ulcer activity [65].

4.8 Anti-edematogenic activity

Catechin, rutin, quercitrin, quercetin, and kaempferol isolated from the H_2O 100% EtOH (1:1) of *Ximenia americana* L showed anti-edematogenic activity against ear edema in rat [63]. Artemetin isolated from *Cordia curassavica* DC exhibited remarkable anti-edematogenic activity [68].

5 Conclusions

Twenty-two members of the different families containing flavonoids studied for their health benefits confirmed the medicinal importance of these phytochemicals from these sources. The pharmacological pieces of evidence reported in the literature has proven that these flavonoids have shown anti-cancer, anti-microbial, anti-oxidant, anti-inflammatory, anti-fungal, anti-ulcer, and anti-edematogenic activity. Out of the references cited, 30% focused on the anti-oxidant activity of flavonoids, key in protecting the body against free radicals and oxidative stress. Also, 18% of the references showed anti-microbial and anti-cancer activities. Further literature reports indicated that flavonoids from these families exhibited anti-inflammatory and anti-edematogenic (9%), antiviral and anti-ulcer (5%), anti-fungal, anti-nociceptive, and anti-histaminice (2%). The pharmacological activities of flavonoids from the various sources reviewed in this study show that the secondary metabolites could provide a scaffold for the development of potent anti-cancer drugs in the future.

Abbreviations

MPLC: Medium pressure liquid chromatography; LC-ESI/MS: Liquid chromatography electrospray ionization mass spectrometry; TLC: Thin layer chromatography; VLC: Vacuum liquid chromatography; LC-MS: Liquid chromatography-mass spectrometry; HPLC-MS: High-performance liquid chromatography-mass spectrometry; EIMS: Electrospray ionization mass spectrometry; HPLC-DAD: High-performance liquid chromatography with diode array detection; GC-MS: Gas chromatography-mass spectrometry

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Authors' contributions

This research was designed by AE and HDJ. AE wrote the manuscript under the supervision of HDJ. All authors read and approved the final manuscript.

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Availability of data and materials
The search was by using keywords such as flavonoids. Other sources used are "science direct," "google scholar," "Scopus" database and many journal sites. Journals employed in the search are Elsevier and Springer. Other search engines used as well as papers published between 2006 and 2019.

Ethics approval and consent to participate
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Consent for publication
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Competing interests
The authors declare that they have no competing interests.

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