

Distribution and Biological Activities of the Flavonoid Luteolin

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Abstract. Epidemiological evidence suggests that flavonoids may play an important role in the decreased risk of chronic diseases associated with a diet rich in plant-derived foods. Flavonoids are also common constituents of plants used in traditional medicine to treat a wide range of diseases. The purpose of this article is to summarize the distribution and biological activities of one of the most common flavonoids: luteolin. This flavonoid and its glycosides are widely distributed in the plant kingdom; they are present in many plant families and have been identified in Bryophyta, Pteridophyta, Pinophyta and Magnoliophyta. Dietary sources of luteolin include, for instance, carrots, peppers, celery, olive oil, peppermint, thyme, rosemary and oregano. Preclinical studies have shown that this flavone possesses a variety of pharmacological activities, including antioxidant, anti-inflammatory, antimicrobial and anticancer activities. The ability of luteolin to inhibit angiogenesis, to induce apoptosis, to prevent carcinogenesis in animal models, to reduce tumor growth *in vivo* and to sensitize tumor cells to the cytotoxic effects of some anticancer drugs suggests that this flavonoid has cancer chemopreventive and chemotherapeutic potential. Modulation of ROS levels, inhibition of topoisomerases I and II, reduction of NF- κ B and AP-1 activity, stabilization of p53, and inhibition of PI3K, STAT3, IGF1R and HER2 are possible mechanisms involved in the biological activities of luteolin.

Key Words: Orientin, chemoprevention, cancer, anticancer, antioxidant, anti-inflammatory.

1. INTRODUCTION

Epidemiological studies have shown that a diet rich in plant-derived foods is consistently associated with a reduced risk of developing chronic diseases. A common and important guideline from the American Cancer Society, the American Heart Association and the American Diabetes Association to prevent these diseases is to increase the consumption of plant-derived foods and to eat at least five servings of a variety of vegetables and fruits daily [1]. Although it is not clear which compounds in plant foods are responsible for this preventive effect, evidence suggests that flavonoids may participate in this activity.

Flavonoids comprise a large group of plant secondary metabolites characterized by a diphenylpropane structure (C6-C3-C6). They are widely distributed throughout the plant kingdom and are commonly found in fruits, vegetables and certain beverages. Numerous preclinical and some clinical studies suggest that flavonoids have potential for the prevention and treatment of several diseases. Some epidemiological studies support a protective role of diets rich in foods with flavonoids and a reduced risk of developing cancer and cardiovascular diseases [2-7]. Preclinical *in vitro* and *in vivo* investigations have shown plausible mechanisms by which flavonoids may confer cancer and cardiovascular protection [8]. In addition to their preventive potential, certain flavonoids may be useful in the treatment of several diseases. Some evidence supporting the therapeutic potential of flavonoids comes from the study of plants used in traditional medicine

to treat a wide range of diseases, which has shown that flavonoids are common bioactive constituents of these plants [8-11].

Luteolin is one of the most common flavonoids present in edible plants and in plants used in traditional medicine to treat a wide variety of pathologies. Although there are more than one thousand articles in PubMed reporting the isolation or pharmacological properties of luteolin, there is not any article summarizing or analyzing all this information. The purpose of this article is to provide an overview of the distribution and biological properties of luteolin; this knowledge may help understand the preventive and therapeutic properties of luteolin-containing plants and may help develop this flavonoid as a possible agent for the prevention and treatment of some diseases. Because recent research suggests that luteolin has cancer preventive and therapeutic potential, special focus is placed on the anticancer properties of this flavonoid.

2. DISTRIBUTION

Table 1 compiles plant species that contain luteolin and/or luteolin glycosides. Articles written in English and published in PubMed that contain the words luteolin or the trivial name of some common glycosides of luteolin (i.e., orientin, isoorientin, scolymoside or cynaroside) have been used for this review. Around 300 plant species have been found and are compiled in alphabetical order. The botanical family, the type of glycoside and the bibliographical reference is provided.

Luteolin is widely distributed in the plant kingdom. Glycosides of this flavonoid have been identified in fossil *Celtis* and *Ulmus* species (Ulmaceae) 36 to 25 million years old [12]. Luteolin is present in many botanical families and has

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Table 1. Distribution of Luteolin in the Plant Kingdom

Species	Family	Aglycone/Glycoside	Reference
<i>Abutilon indicum</i>	Malvaceae	luteolin, luteolin 7-O-beta-glucopyranoside	[247]
<i>Achillea millefolium</i>	Asteraceae	luteolin	[248]
<i>Achillea nobilis</i>	Asteraceae	luteolin-6-C-apiofuranosyl-(1 ^{'''} ->2 ^{''})-glucoside, orientin, isoorientin, luteolin-7-O-beta-glucuronide, luteolin-4'-O-beta-glucoside	[249]
<i>Achillea pannonica</i>	Asteraceae	luteolin-7-O-glucopyranoside, luteolin-7,4'-O-beta-diglucoside	[250]
<i>Achyrocline satureioides</i>	Asteraceae	luteolin	[251]
<i>Achyrocline satureioides</i>	Asteraceae	luteolin	[252]
<i>Achyrocline satureioides</i>	Asteraceae	luteolin	[253]
<i>Ailanthus excelsa</i>	Simaroubaceae	luteolin	[254]
<i>Aiphanes aculeata</i>	Arecaceae	luteolin	[255]
<i>Ajuga genevensis</i>	Lamiaceae	luteolin	[256]
<i>Ajuga reptans</i>	Lamiaceae	luteolin	[256]
<i>Albizia julibrissin</i>	Mimosaceae	luteolin	[257]
<i>Allophylus edulis</i>		isoorientin 2''-O-rhamnoside, orientin 2''-O-rhamnoside	[258]
<i>Aloe vera</i>	Asphodelaceae	luteolin	[259]
<i>Aloysia triphylla</i>	Verbenaceae	luteolin 7-diglucuronide	[260]
<i>Angelica keiskei</i>	Apiaceae	cynaroside (luteolin 7-O-D-glucoside)	[261]
<i>Annona tomentosa</i>	Annonaceae	luteolin-7-O-glucoside	[262]
<i>Anthemis chia</i>	Asteraceae	luteolin-7-glucoside	[263]
<i>Anthemis cretica</i>	Asteraceae	6- hydroxyluteolin 6- methyl ether, 6- hydroxyluteolin 6,3' - dimethyl ether, 6- hydroxyluteolin 6,7,4' - trimethyl ether, luteolin-7-glucoside	[263]
<i>Anthemis monantha</i>	Asteraceae	6- hydroxyluteolin 6,7,4' - trimethyl ether, luteolin-7-glucuronide, luteolin-7-glucoside	[263]
<i>Anthriscus sylvestris</i>	Apiaceae	luteolin-7-O-glucoside	[264]
<i>Apium graveolens</i>	Apiaceae	luteolin 7-O-apiosylglucoside, luteolin 7-O-glucoside, malonyl derivatives of these glycosides.	[265]
<i>Aquilegia ecalcarata</i>	Ranunculaceae	luteolin	[266]
<i>Aquilegia vulgaris</i>	Ranunculaceae	luteolin derivatives	[267]
<i>Arnica montana</i>	Asteraceae	luteolin 3'- O-beta-glucoside;	[268]
<i>Artemisia giraldii</i>	Asteraceae	luteolin	[269]
<i>Artemisia montana</i>	Asteraceae	luteolin 7-O-rutinoside (scolymoside)	[42]
<i>Arum palaestinum</i>	Araceae	isoorientin, luteolin	[270, 271]
<i>Aspalathus linearis</i>	Leguminosae	luteolin, orientin	[135, 272]
<i>Asplenium normale</i>	Aspleniaceae	luteolin 7-O-dirhamnoside, luteolin 7-O-glucosylrhamnoside	[16]
<i>Avicennia marina</i>	Avicenniaceae	luteolin 7-O-methylether, luteolin 7-O-methylether 3'-O-beta-D-glucoside, luteolin 7-O-methylether 3'-O-beta-D-galactoside	[273]
<i>Bacopa monnieri</i>	Scrophulariaceae	luteolin, luteolin-7-O-beta-glucopyranoside	[274, 275]

(Table 1. Contd....)

Species	Family	Aglycone/Glycoside	Reference
<i>Balbisia calycina</i>	Ledocarpaceae	luteolin	[276]
<i>Ballota nigra</i>	Lamiaceae	luteolin-7-lactate, luteolin-7-glucosyl-lactate	[277]
<i>Bauhinia tarapotensis</i>	Caesalpiniaceae	luteolin 4'-O-beta-D-glucopyranoside	[33]
<i>Begonia malabarica</i>	Begoniaceae	luteolin	[278]
<i>Bidens tripartita</i>	Asteraceae	cynaroside, luteolin	[279]
<i>Biebersteinia orphanidis</i>	Geraniaceae	luteolin	[280]
<i>Brandisia hancei</i>	Scrophulariaceae	luteolin	[58]
<i>Brassica napus</i>	Brassicaceae	luteolin	[173]
<i>Broussonetia papyrifera</i>	Moraceae	luteolin	[281]
<i>Buddleja globosa</i>	Buddlejaceae	luteolin-7-O-glucoside	[282]
<i>Buddleja officinalis</i>	Buddlejaceae	luteolin, luteolin, luteolin-7-O-beta-D-glucopyranoside	[283, 284]
<i>Bupleurum flavum</i>	Apiaceae	luteolin	[285]
<i>Cajanus cajan</i>	Fabaceae	luteolin	[286]
<i>Cannabis sativa</i>	Cannabaceae	orientin, luteolin-7-O-beta-D-glucuronide	[287]
<i>Capparis himalayensis</i>	Capparaceae	luteolin	[288]
<i>Capparis spinosa</i>	Capparaceae	luteolin 7-O-glucoside, luteolin.	[105]
<i>Capsicum annuum</i>	Solanaceae	luteolin 7-O-beta-D-apiofuranosyl-(1-->2)-beta-D-glucopyranoside, luteolin 7-O-[2-(beta-d-apiofuranosyl)-4-(beta-d-glucopyranosyl)-6-malonyl]-beta-d-glucopyranoside, luteolin-7-O-(2-apiofuranosyl-4-glucopyranosyl-6-malonyl)-glucopyranoside, luteolin 6-C-beta-D-glucopyranoside-8-C-alpha-L-arabinopyranoside	[289-292]
<i>Caralluma attenuata</i>	Asclepiadaceae	luteolin-4'-O-neohesperidoside = (luteolin-4'-O-[alpha-(L-rhamnopyranosyl-(1-->2)-beta-D-glucopyranoside)])	[74]
<i>Caralluma negevensis</i>	Asclepiadaceae	luteolin 3'-O-beta-D-glucopyranoside-4'-O-alpha-L-rhamnopyranosyl-(1-->2)-beta-D-glucopyranoside, luteolin 3',4'-di-O-beta-D-glucopyranoside	[293]
<i>Caralluma russeliana</i>	Asclepiadaceae	luteolin 4'-O-beta-D-neohesperidoside.	[294]
<i>Caralluma tuberculata</i>	Asclepiadaceae	luteolin.4'-beta-D-glucopyranosyl-(2-->1)-alpha-L-rhamnopyranoside	[295]
<i>Carduus crispus</i>	Asteraceae	luteolin-7-glucoside	[296]
<i>Carduus micropterus</i>	Asteraceae	luteolin	[297]
<i>Carthamus lanatus</i>	Asteraceae	luteolin 7-O-glucoside	[298]
<i>Carthamus tinctorius</i>	Asteraceae	luteolin, luteolin 7-O-beta-D-glucopyranoside, luteolin-7-O-(6"-O-acetyl)-beta-D-glucopyranoside	[43]
<i>Cassia nigricans</i>	Caesalpiniaceae	luteolin	[299]
<i>Cayratia japonica</i>	Vitaceae	luteolin, luteolin-7-O-beta-D-glucopyranoside	[300]
<i>Cecropia lyratiloba</i>	Cecropiaceae	isoorientin	[301]
<i>Cecropia obtusifolia</i>	Cecropiaceae	isoorientin	[226]
<i>Centaurea scoparia</i>	Asteraceae	luteolin	[302]
<i>Ceratonia siliqua</i>	Caesalpiniaceae	luteolin	[303]
<i>Chaenomeles sinensis</i>	Rosaceae	luteolin-7-O-beta-D-glucuronide, luteolin-3'-methoxy-4'-O-beta-D-glucopyranoside, luteolin-7-O-beta-D-glucuronide methyl ester	[304]

(Table 1. Contd....)

Species	Family	Aglycone/Glycoside	Reference
<i>Chaerophyllum hirsutum</i>	Apiaceae	6-methyluteolin, luteolin-7-O-beta-D-glucopyranoside	[305]
<i>Chamomilla recutita</i>	Asteraceae	luteolin, luteolin-7-O-glucoside	[306]
<i>Chromolaena odorata</i>	Asteraceae	luteolin	[307]
<i>Chrozophora brocchiana</i>	Euphorbiaceae	luteolin 7-O-glucoside	[37]
<i>Chrysanthemum morifolium</i>	Asteraceae	luteolin-7-O-beta-D-glucoside, luteolin	[133, 308]
<i>Chrysanthemum segetum</i>	Asteraceae	luteolin-7-glucoside	[263]
<i>Chrysanthemum sinense</i>	Asteraceae	luteolin	[309]
<i>Cirsium japonicum</i>	Asteraceae	luteolin	[310]
<i>Cirsium rivulare</i>	Asteraceae	luteolin	[311]
<i>Citrus bergamia</i>	Rutaceae	orientin 4'-methyl ether	[312]
<i>Colchicum cilicicum</i>	Colchicaceae	luteolin	[313]
<i>Coleus parvifolius</i>	Lamiaceae	luteolin, luteolin 5-O-beta-d-glucopyranoside, luteolin 7-methyl ether , luteolin 5-O-beta-d-glucuronide, 5-O-beta-d-glucopyranosyl-luteolin 7- methyl ether	[314]
<i>Commelina communis</i>	Commelinaceae	orientin, isoorientin	[315]
<i>Conyza bonariensis</i>	Asteraceae	luteolin	[316]
<i>Cornulaca monacantha</i>	Chenopodiaceae	luteolin-7-O-rhamnoside, luteolin-7-O-glucoside	[317]
<i>Crataegus oxyacantha</i>	Rosaceae	luteolin, luteolin-3', 7-diglucoside	[318]
<i>Crataegus pentagyna</i>	Rosaceae	isoorientin, orientin, isoorientin-2"-O-rhamnoside, orientin-2"-O-rhamnoside	[319, 320]
<i>Crataegus x macrocarpa</i>	Rosaceae	luteolin-7-O-beta-D-glucuronide	[321]
<i>Crotalaria sessiliflora</i>	Fabaceae	isoorientin, orientin	[322]
<i>Cucumis sativus</i>	Cucurbitaceae	luteolin-8-C-beta-D-glucopyranoside (orientin), luteolin-6-C-beta-D- glucopyranoside (isoorientin)	[98, 323]
<i>Cuphea pinetorum</i>	Lythraceae	luteolin-7-O-beta-D-glucopyranoside	[324]
<i>Cyclopia subternata</i>	Leguminosae	luteolin	[325]
<i>Cymbopetalum brasiliense</i>	Annonaceae	luteolin-6-hydroxy-7-O-rhamnosylglucoside	[262]
<i>Cymbopogon citratus</i>	Poaceae	isoorientin, isoorientin 2' '-O-rhamnoside, orientin,	[326]
<i>Cynara scolymus</i>	Asteraceae	luteolin, luteolin-7-O-glucoside, luteolin-7-rutinoside, cynaroside	[47, 109, 327]
<i>Cynomorium songaricum</i>	Cynomoriaceae	luteolin	[328]
<i>Cyperus alopecuroides</i>	Cyperaceae	luteolin 5,3'-dimethylether	[329]
<i>Cyperus alopecuroides</i>	Cyperaceae	orientin	[330]
<i>Cyperus conglomeratus</i>	Cyperaceae	luteolin, luteolin 7-methyl ether	[331]
<i>Daphne genkwa</i>	Thymelaeaceae	luteolin, luteolin 7-methyl ether	[332]
<i>Daphne gnidium</i>	Thymelaeaceae	luteolin-3',7-di-O-glucoside	[333]
<i>Daucus carota</i>	Apiaceae	luteolin, luteolin 3'-O-beta-D-glucopyranoside and luteolin 4'-O-beta-D- glucopyranoside	[334, 335]
<i>Deschampsia antarctica</i>	Poaceae	luteolin, orientin, orientin 2"-O-arabinopyranoside, isoswertiajaponin (7-O- methylorientin), isoswertiajaponin 2"-O-beta-arabinopyranoside	[336, 337]

(Table 1. Contd....)

Species	Family	Aglycone/Glycoside	Reference
<i>Deschampsia borealis</i>	Poaceae	orientin	[336]
<i>Dianthus chinensis</i>	Caryophyllaceae	isoorientin-2"-O-glucoside	[338]
<i>Dicranum scoparium</i>	Dicranaceae	luteolin-7-O-neohesperidoside	[14]
<i>Digitaria exilis</i>	Poaceae	luteolin	[339]
<i>Dioclea lasiophylla</i>	Fabaceae	luteolin 3'beta-D-glucopyranoside	[340]
<i>Dracocephalum subcapitatum</i>	Lamiaceae	luteolin	[341]
<i>Dystaenia takeshimana</i>	Umbelliferae	luteolin	[80]
<i>Echinochloa utilis</i>	Poaceae	luteolin	[50]
<i>Eclipta alba</i>	Asteraceae	luteolin	[342]
<i>Ehretia ovalifolia</i>	Boraginaceae	luteolin	[343]
<i>Elodea nuttallii</i>	Hydrocharitaceae	luteolin-7-O-diglucuronide	[344]
<i>Elsholtzia blanda</i>	Lamiaceae	luteolin	[345]
<i>Elsholtzia bodinieri</i>	Lamiaceae	luteolin 7-O-[6"-(3"-hydroxy-4"-methoxy cinnamoyl)]-beta-D-glucopyranoside	[346]
<i>Elsholtzia rugulosa</i>	Lamiaceae	luteolin, luteolin 3'-glucuronyl acid methyl ester	[111]
<i>Epimedium hunanense</i>	Berberidaceae	luteolin	[347]
<i>Epimedium sagittatum</i>	Berberidaceae	luteolin	[348]
<i>Equisetum arvense</i>	Equisetaceae	luteolin	[21]
<i>Erigeron acris</i>	Asteraceae	luteolin	[349]
<i>Euterpe oleracea</i>	Arecaceae	orientin	[350]
<i>Fagopyrum esculentum</i>	Polygonaceae	isoorientin, orientin	[351]
<i>Fallopia species</i>	Polygonaceae	luteolin glycosides	[352]
<i>Ficaria verna</i>	Ranunculaceae	luteolin 8-C-beta-D-glucopyranoside	[353]
<i>Ficus carica</i>	Moraceae	luteolin	[303]
<i>Genista corsica</i>	Leguminosae	luteolin, luteolin 4'-O-beta-glucoside, luteolin 7-O-beta-glucoside	[354]
<i>Genista morisii</i>	Leguminosae	luteolin, luteolin 7-O-beta-D-glucopyranoside, luteolin 4'-O-beta-D-glucopyranoside	[355]
<i>Genista tenera</i>	Leguminosae	luteolin-7-O-glucoside, luteolin-7,3'-di-O-glucoside	[356]
<i>Gentiana algida</i>	Gentianaceae	orientin	[357]
<i>Gentiana arisanensis</i>	Gentianaceae	luteolin-7-O-beta-D-glucoside, isoorientin-6"-O-glucoside	[41, 358]
<i>Gentiana olivieri</i>	Gentianaceae	isoorientin	[359]
<i>Gentiana piasezkii</i>	Gentianaceae	isoorientin, luteolin	[360]
<i>Gentianella nitida</i>	Gentianaceae	isoorientin	[361]
<i>Ginkgo biloba</i>	Ginkgoaceae	luteolin	[22, 362]
<i>Glechoma hederacea</i>	Labiatae	luteolin 7-O-beta-D-glucopyranoside	[363]
<i>Globularia alypum</i>	Globulariaceae	6-hydroxyluteolin 7-O-laminaribioside, 6-hydroxyluteolin 7-O-beta-D-glucopyranoside, luteolin 7-O-sophoroside	[36]
<i>Glochidion zeylanicum</i>	Euphorbiaceae	isoorientin	[364]

(Table 1. Contd....)

Species	Family	Aglycone/Glycoside	Reference
<i>Glossogyne tenuifolia</i>	Asteraceae	luteolin, luteolin-7-glucoside	[38]
<i>Glycine soja</i>	Leguminosae	luteolin, luteolin-7-O-beta-D-glucoside	[365]
<i>Gnidia involucreta</i>	Thymelaeaceae	isoorientin	[366]
<i>Gypsophila repens</i>	Caryophyllaceae	luteolin-7-O-alpha-L-arabinopyranosyl-6-C-beta-glucopyranoside	[367]
<i>Hebe parviflora</i>	Scrophulariaceae	luteolin-7-O-beta-glucoside, luteolin-3'-O-beta-glucoside, luteolin-7, 3'-di-O-beta-glucoside, luteolin-4'-O-beta-glucoside, luteolin-7-O-beta-glucuronide, 8-hydroxyluteolin-8-beta-glucoside, 8-hydroxyluteolin-7-beta-glucoside, 6-hydroxyluteolin-7-O-beta-[2-O-beta-xyloglucoside], 6-hydroxyluteolin-7-O-beta-[6-O-beta-xyloglucoside], luteolin-7-O-beta-[6-O-alpha-rhamnosylglucoside], luteolin-7-O-beta-[6-O-beta-xyloglucoside], 4'-O-methyluteolin-7-O-beta-[6-O-beta-xyloglucoside]	[368]
<i>Hebe stenophylla</i>	Scrophulariaceae	luteolin-7-O-beta-glucoside, luteolin-4'-O-beta-glucoside, 8-hydroxyluteolin-8-beta-glucoside, 8-hydroxyluteolin-7-beta-glucoside, 6-hydroxyluteolin-7-beta-glucoside, 6-hydroxyluteolin-7-O-beta-[2-O-beta-xyloxyloside], 6-hydroxyluteolin-7-O-beta-[2-O-beta-xyloglucoside], 6-hydroxyluteolin-7-O-beta-[2-O-beta-glucoglucoside], 6-hydroxyluteolin-7-O-beta-[6-O-beta-xyloglucoside]	[368]
<i>Hebe strictissima</i>	Scrophulariaceae	luteolin-7-O-beta-glucoside, luteolin-4'-O-beta-glucoside, luteolin-7-O-beta-glucuronide, 8-hydroxyluteolin-7-beta-glucoside, 6-hydroxyluteolin-7-O-beta-[2-O-beta-xyloglucoside], 6-hydroxyluteolin-7-O-beta-[6-O-beta-xyloglucoside], luteolin-7-O-beta-[6-O-alpha-rhamnosylglucoside], luteolin-7-O-beta-[6-O-beta-xyloglucoside]	[368]
<i>Hebe traversi</i>	Scrophulariaceae	luteolin-7-O-beta-glucoside, luteolin-7, 3'-di-O-beta-glucoside, luteolin-4'-O-beta-glucoside, 8-hydroxyluteolin-8-beta-glucoside, 8-hydroxyluteolin-7-beta-glucoside, 6-hydroxyluteolin-7-O-beta-[2-O-beta-xyloxyloside], 6-hydroxyluteolin-7-O-beta-[2-O-beta-xyloglucoside], 6-hydroxyluteolin-7-O-beta-[2-O-beta-glucoglucoside], 4'-O-methyluteolin-7-O-beta-[6-O-beta-xyloglucoside]	[368]
<i>Hedwigia ciliata</i>	Hedwigiaceae	luteolin 7-O-Neohesperidoside-4'-O-sophoroside	[13]
<i>Helichrysum compactum</i>	Asteraceae	luteolin, luteolin-7-O-glucoside, luteolin-4',7-di-O-glucoside	[369]
<i>Helichrysum pamphylicum</i>	Asteraceae	luteolin, luteolin-4' glucoside	[370]
<i>Homalium brachybotrys</i>	Flacourtiaceae	luteolin-7-O-beta-glucopyranoside	[371]
<i>Hordeum vulgare</i>	Poaceae	isoorientin, isoorientin-7-O-glucoside	[372, 373]
<i>Hydnocarpus wightiana</i>	Flacourtiaceae	luteolin	[374]
<i>Hypericum brasiliense</i>	Clusiaceae	luteolin	[375]
<i>Hypericum perforatum</i>	Clusiaceae	isoorientin	[376]
<i>Impatiens textori</i>	Balsaminaceae	luteolin	[377]
<i>Inula britannica</i>	Asteraceae	luteolin	[378]
<i>Ismelia versicolor</i>	Asteraceae	luteolin-7-glucoside, luteolin-7-glucuronide	[263]
<i>Isoplexis chalcantha</i>	Scrophulariaceae	luteolin, luteolin 7- O-beta- D-glycoside	[379]
<i>Ixeridium gracile</i>	Asteraceae	luteolin 7-O-glucoside	[380]
<i>Ixeris denticulata</i>	Asteraceae	luteolin-7-O-glucoside, luteolin-7-O-glucuronide-6'-methyl ester	[381]
<i>Ixeris sonchifolia</i>	Asteraceae	luteolin, luteolin 7-glucuronide methylester, luteolin 7-glucuronide ethylester, luteolin 7-glucoside, luteolin 7-glucopyranosyl-(1-->6)-glucoside, luteolin 7-glucopyranosyl-(1-->2)-glucoside	[382, 383]

(Table 1. Contd....)

Species	Family	Aglycone/Glycoside	Reference
<i>Japonolirion osense</i>	Melanthiaceae	isoorientin, orientin	[384]
<i>Jatropha ciliata</i>	Euphorbiaceae	isoorientin and orientin	[385]
<i>Kitaibelia vitifolia</i>	Malvaceae	luteolin	[386]
<i>Kummerowia striata</i>	Leguminosae	luteolin 4'-O-glucopyranoside	[82]
<i>Lactuca indica</i>	Asteraceae	luteolin, luteolin 7-O-glucuronide	[387]
<i>Lactuca sativa</i>	Asteraceae	luteolin 7-O-glucuronide	[388]
<i>Lactuca scariola</i>	Asteraceae	luteolin-7-O-beta-D-glucopyranoside, luteolin	[389]
<i>Lamiophlomis rotata</i>	Lamiaceae	luteolin-7-O-glucoside, luteolin	[390]
<i>Lavandula stoechas</i>	Lamiaceae	luteolin 7-O-glucoside	[391]
<i>Lawsonia inermis</i>	Lythraceae	luteolin	[44]
<i>Leandra lacunosa</i>	Melastomataceae	luteolin	[227]
<i>Leontodon croceus</i>	Asteraceae	luteolin, luteolin 7-O-beta-D-gentiobioside, luteolin 7-O-beta-D-glucoside, luteolin 7-O-beta-D-glucuronide, luteolin 4'-O-beta-D-glucoside	[392]
<i>Leontodon duboisii</i>	Asteraceae	luteolin, luteolin 7-O-beta-D-gentiobioside, luteolin 7-O-beta-D-glucoside, luteolin 7-O-beta-D-glucuronide, luteolin 4'-O-beta-D-glucoside	[392]
<i>Leontodon helveticus</i>	Asteraceae	luteolin, luteolin 7-O-beta-D-gentiobioside, luteolin 7-O-beta-D-glucoside, luteolin 7-O-beta-D-glucuronide, luteolin 4'-O-beta-D-glucoside	[392]
<i>Leontodon montaniformis</i>	Asteraceae	luteolin, luteolin 7-O-beta-D-gentiobioside, luteolin 7-O-beta-D-glucoside, luteolin 7-O-beta-D-glucuronide	[392]
<i>Leontodon autumnalis</i>	Asteraceae	luteolin, luteolin 7-O-beta-D-gentiobioside, luteolin 7-O-beta-D-glucoside, luteolin 7-O-beta-D-glucuronide, luteolin 4'-O-beta-D-glucoside	[392]
<i>Leontodon pyrenaicus</i>	Asteraceae	luteolin, luteolin 7-O-beta-D-gentiobioside, luteolin 7-O-beta-D-glucoside, luteolin 7-O-beta-D-glucuronide, luteolin 4'-O-beta-D-glucoside	[392]
<i>Leontodon rilaensis</i>	Asteraceae	luteolin, luteolin 7-O-beta-D-gentiobioside, luteolin 7-O-beta-D-glucoside, luteolin 7-O-beta-D-glucuronide, luteolin 4'-O-beta-D-glucoside	[392]
<i>Leontopodium alpium</i>	Asteraceae	luteolin-7-O-beta-D-glucoside, luteolin-3'-O-beta-D-glucoside, luteolin-4'-O-beta-D-glucoside, 6-hydroxy-luteolin-7-O-beta-D-glucoside, luteolin-7,4'-di-O-beta-D-glucoside,	[393]
<i>Lepechinia graveolens</i>	Lamiaceae	luteolin-7-O-glucuronide	[394]
<i>Leucanthemum adjutum</i>	Asteraceae	luteolin-7-glucoside, luteolin-7-glucuronide	[263]
<i>Leucanthemum vulgare</i>	Asteraceae	luteolin-7-glucuronide	[263]
<i>Leucas cephalotes</i>	Lamiaceae	luteolin 4'-O-beta-D-glucuronopyranoside	[395]
<i>Ligustrum vulgare</i>	Oleaceae	luteolin, luteolin 7-O-glucoside	[396]
<i>Lippia alba</i>	Verbenaceae	luteolin-7-diglucuronide	[397]
<i>Lisianthus nigrescens</i>	Gentianaceae	luteolin 8-C-glucoside	[398]
<i>Lobelia chinensis</i>	Campanulaceae	luteolin	[399]
<i>Lonicera confusa</i>	Caprifoliaceae	luteolin	[400]
<i>Lonicera japonica</i>	Caprifoliaceae	luteolin, luteolin 7-O-beta-D-glucopyranoside	[35, 401]
<i>Lophira alata</i>	Ochnaceae	luteolin	[402]
<i>Luffa cylindrica</i>	Cucurbitaceae	luteolin-7-O-beta-D-glucuronide methyl ester	[403]

(Table 1. Contd....)

Species	Family	Aglycone/Glycoside	Reference
<i>Lychnis flos-cuculi</i>	Caryophyllaceae	luteolin, luteolin 8-C-beta-D: -glucopyranoside	[404]
<i>Lychnophora pohlii</i>	Asteraceae	luteolin	[405]
<i>Lycopus europaeus</i>	Lamiaceae	luteolin-7-glucoside, luteolin-7-glucuronide	[406]
<i>Lycopus lucidus</i>	Labiatae	luteolin, luteolin-7-O-beta-D-glucuronide methyl ester	[51]
<i>Lycopus virginicus</i>	Lamiaceae	luteolin	[407]
<i>Lythrum salicaria</i>	Lythraceae	isoorientin, orientin	[408]
<i>Medicago sativa</i>	Leguminosae	luteolin, luteolin 7-O-[2-O-feruloyl-beta-D-glucuronopyranosyl(1-->2)-O-beta-D-glucuronopyranosyl]-4'-O-beta-D-glucuronopyranoside, luteolin 7-O-beta-D-glucuronopyranoside	[409, 410]
<i>Medicago truncatula</i>	Leguminosae	luteolin 7-O-[beta-D-glucuronopyranosyl-(1-->2)]-O-beta-D-glucuronopyranoside, luteolin 7-O-beta-D-glucuronopyranoside	[411]
<i>Melissa officinalis</i>	Lamiaceae	luteolin, luteolin 7-O-beta-D-glucopyranoside, luteolin 7-O-beta-D-glucuronopyranoside, luteolin 3'-O-beta-D-glucuronopyranoside, luteolin 7-O-beta-D-glucopyranoside-3'-Obeta-D-glucuronopyranoside	[412-414]
<i>Mentha x piperita</i>	Lamiaceae	luteolin-7-O-rutinoside	[234]
<i>Monoclea forsteri</i>	Monocleaceae	6-methoxyluteolin 7-O-[2-O-alpha-rhamnosyl-3-O-alpha-arabinosyl-beta-glucuronide]-4'-O-[2-O-alpha-rhamnosyl-3-O-beta-xylosyl-beta-glucuronide], 6-methoxyluteolin 7-O-[2-O-alpha-rhamnosyl-beta-glucuronide]-4'-O-[2-O-alpha-rhamnosyl-3-O-beta-xylosyl-beta-glucuronide].	[15]
<i>Morinda citrifolia</i>	Rubiaceae	luteolin	[415]
<i>Morinda morindoides</i>	Rubiaceae	luteolin, luteolin-7-O-glucoside	[416]
<i>Nepeta cataria</i>	Lamiaceae	luteolin 7-O-glucuronide, luteolin 7-O-glucurono-(1-->6)-glucoside, luteolin	[417]
<i>Nepeta sibthorpii</i>	Lamiaceae	luteolin-7-O-glucoside	[73]
<i>Newbouldia laevis</i>	Bignoniaceae	luteolin	[418]
<i>Ocimum gratissimum</i>	Lamiaceae	luteolin	[419]
<i>Ocimum sanctum</i>	Lamiaceae	luteolin-7-O-beta-D-glucuronic acid 6"-methyl ester, luteolin-7-O-beta-D-glucopyranoside, luteolin-5-O-beta-D-glucopyranoside,	[420]
<i>Olea europaea</i>	Oleaceae	luteolin, luteolin-4'-O-glucoside, luteolin-7-O-glucoside	[421-423]
<i>Ophioglossum petiolatum</i>	Ophioglossaceae	luteolin	[17]
<i>Origanum vulgare</i>	Lamiaceae	luteolin	[424]
<i>Oxalis corniculata</i>	Oxalidaceae	isoorientin	[425]
<i>Oxalis triangularis</i>	Oxalidaceae	luteolin 6-C-(2"-O-beta-xylopyranosyl-beta-glucopyranoside)	[426]
<i>Paeonia suffruticosa</i>	Paeoniaceae	luteolin-7-O-glucoside	[427]
<i>Papaver rhoeas</i>	Papaveraceae	luteolin	[428]
<i>Passiflora alata</i>	Passifloraceae	2"-rhamnosyl-orientin, isoorientin, orientin	[429, 430]
<i>Passiflora caerulea</i>	Passifloraceae	isoorientin, orientin	[430]
<i>Passiflora edulis</i>	Passifloraceae	luteolin -7-O-[2-rhamnosyl]glucoside], isoorientin, orientin, luteolin glycosides	[430] [431, 432]
<i>Passiflora incarnata</i>	Passifloraceae	isoorientin-2"-O-glucopyranoside, isoorientin, orientin	[430, 433]
<i>Patrinia villosa</i>	Valerianaceae	isoorientin	[434]

(Table 1. Contd....)

Species	Family	Aglycone/Glycoside	Reference
<i>Pelargonium reniforme</i>	Geraniaceae	2"-O-galloylisorientin	[435]
<i>Penstemon gentianoides</i>	Plantaginaceae	luteolin	[436]
<i>Perilla frutescens</i>	Lamiaceae	luteolin, luteolin 7-O-glucuronide-6"-methyl ester	[437, 438]
<i>Perilla ocimoides</i>	Lamiaceae	luteolin 7-0-(glucuronosyl(beta-1-->2-glucuronide)	[439]
<i>Phagnalon rupestre</i>	Asteraceae	luteolin-7-O-beta-glucoside, luteolin-7-O-beta-glucuronide	[440]
<i>Phillyrea latifolia</i>	Oleaceae	luteolin, luteolin 7-O-glucoside, luteolin 4'-O-glucoside	[396]
<i>Phlomis aurea</i>	Lamiaceae	luteolin-7-O-beta-glucopyranoside	[441]
<i>Phlomis brunneogaleata</i>	Lamiaceae	luteolin 7- O-beta- D-glucopyranoside	[118]
<i>Phlomis lunariifolia</i>	Lamiaceae	luteolin 7-O-[4-O-acetyl-alpha-rhamnopyranosyl-(1-->2)]-beta-glucuronopyranoside,	[442]
<i>Phoenix dactylifera</i>	Arecaceae	rhamnosyl diglucosyl luteolin, diglucosyl luteolin sulphate, rhamnosyl diglucosyl methyl luteolin, , rhamnosyl glucosyl methyl luteolin, glucosyl luteolin sulphate, glucosyl methyl luteolin sulphate	[443]
<i>Phyllanthus emblica</i>	Euphorbiaceae	luteolin-4'-O-neohesperidoside	[444]
<i>Phyllostachys nigra</i>	Poaceae	luteolin-7-O-glucoside, luteolin 6-C-(6"-O-trans-caffeoylglucoside)	[445, 446]
<i>Picnomon acarna</i>	Asteraceae	luteolin-7, 3'-dimethyl ether and luteolin-3'-methyl ether	[447]
<i>Piper solmsianum</i>	Piperaceae	orientin	[115]
<i>Pistacia lentiscus</i>	Anacardiaceae	luteolin	[303, 448]
<i>Plantago lagopus</i>	Plantaginaceae	luteolin-7-O-beta-glucoside	[209, 449]
<i>Plantago lanceolata</i>	Plantaginaceae	luteolin	[450]
<i>Plantago maritima</i>	Plantaginaceae	luteolin	[451]
<i>Platycodon grandiflorum</i>	Campanulaceae	luteolin, luteolin 7-O-glucoside	[452]
<i>Pogonatherum crinitum</i>	Poaceae	luteolin 6-C-beta-boivinopyranoside, luteolin, luteolin 6-C-beta-fucopyranoside, luteolin 6-C-beta-glucopyranoside	[453]
<i>Potamogeton ssp</i>	Potamogetonaceae	isoorientin, luteolin 7- O-glucoside, luteolin 7-O-glucuronide, luteolin 3'-O-glucoside, luteolin	[454]
<i>Potentilla multifida</i>	Rosaceae	luteolin-7-O-beta-D-glucuronide	[455]
<i>Pteris cretica</i>	Pteridaceae	luteolin 8-C-rhamnoside-7-O-rhamnoside, luteolin 7-O-robinobioside, luteolin 7-O-rutinoside, luteolin 7-O-glucoside	[19, 456]
<i>Pteris multifida</i>	Pteridaceae	luteolin 7-Omicron-beta-D: -glucopyranoside, luteolin	[18, 20]
<i>Punica granatum</i>	Lythraceae	luteolin	[457]
<i>Retama raetam</i>	Leguminosae	luteolin 4'-O-neohesperidoside	[458]
<i>Retama sphaerocarpa</i>	Leguminosae	orientin	[459]
<i>Rosmarinus officinalis</i>	Lamiaceae	luteolin 3'-O-beta-D-glucuronide, luteolin 3'-O-(4"-O-acetyl)-beta-D-glucuronide, luteolin 3'-O-(3"-O-acetyl)-beta-D-glucuronide	[460]
<i>Rumex induratus</i>	Polygonaceae	6-C-hexosyl-luteolin	[461]
<i>Rumex luminiastrum</i>	Polygonaceae	orientin	[462]

(Table 1. Contd....)

Species	Family	Aglycone/Glycoside	Reference
<i>Saccharum officinarum</i>	Poaceae	orientin, luteolin-8-C-(rhamnosylglucoside), 4',5'-dimethyl-luteolin-8-C-glycoside	[463]
<i>Salix gilgiana</i>	Salicaceae	luteolin-7-O-beta-D-glucuronopyranoside, luteolin	[464]
<i>Salix matsudana</i>	Salicaceae	luteolin-7-O-d-glucoside	[465]
<i>Salix matsudana</i>		luteolin 7-O-beta-D-glucopyranuronide	[466]
<i>Salvia officinalis</i>	Lamiaceae	luteolin 7-O-beta-D-glucoside, luteolin 7--O-beta-D-glucuronide, luteolin 3'-O-beta-D-glucuronide, 6-hydroxyluteolin 7-O-beta-D-glucoside, 6-hydroxyluteolin 7-O-glucuronide,	[467]
<i>Salvia palaestina</i>	Labiatae	luteolin, luteolin glycosides	[468]
<i>Salvia sclarea</i>	Labiatae	luteolin	[469]
<i>Santolina insularis</i>	Asteraceae	luteolin and luteolin 7-O-beta-D-glucopyranoside	[78]
<i>Sasa borealis</i>	Poaceae	isoorientin, isoorientin 2"-O-alpha-L-rhamnoside	[470]
<i>Satureja obovata</i>	Lamiaceae	luteolin	[471]
<i>Satureja parvifolia</i>	Lamiaceae	luteolin	[125]
<i>Saussurea tridactyla</i>	Asteraceae	luteolin, luteolin-7-O-beta-D-glucoside	[472]
<i>Schizonepeta tenuifolia</i>	Lamiaceae	luteolin	[473]
<i>Scorzonera austriaca</i>	Asteraceae	luteolin 3'-(6-E-p-coumaroyl-beta-d-glucopyranoside)	[474]
<i>Scutellaria barbata</i>	Lamiaceae	luteolin	[104]
<i>Scutellaria species</i>	Lamiaceae	luteolin	[475, 476]
<i>Secale cereale</i>	Poaceae	luteolin 7-O-diglucuronyl-4'-O-glucuronide, luteolin 7-O-diglucuronide	[477]
<i>Sechium edule</i>	Cucurbitaceae	luteolin glycosides	[478]
<i>Senna petersiana</i>	Caesalpiniaceae	luteolin	[106]
<i>Senna siamea</i>	Caesalpiniaceae	luteolin	[479]
<i>Serratula coronata</i>	Asteraceae	luteolin, luteolin 4'beta-D-glucoside	[480]
<i>Setaria viridis</i>	Poaceae	orientin 2"-O-xyloside	[481]
<i>Spartium junceum L.</i>	Fabaceae	luteolin 4'-beta-glucoside	[482]
<i>Stapelia hirsuta L.</i>	Asclepiadaceae	luteolin-7-O-beta-D-glucopyranoside	[483]
<i>Stevia rebaudiana</i>	Asteraceae	luteolin	[484]
<i>Striga lutea</i>	Scrophulariaceae	luteolin	[485]
<i>Striga orobanchioides</i>	Scrophulariaceae	luteolin	[486]
<i>Swertia punctata</i>	Gentianaceae	isoorientin	[487]
<i>Tamarindus indica L.</i>	Caesalpiniaceae	luteolin	[488]
<i>Tanacetum vulgare</i>	Asteraceae	luteolin, 6-hydroxyluteolin 6-methyl ether, 6-hydroxyluteolin 6,3'-dimethyl ether, 6-hydroxyluteolin 6-hydroxyluteolin	[489]
<i>Tanacetum parthenium</i>	Asteraceae	luteolin 7-glucuronide, luteolin 7-glucoside, luteolin	[489, 490]
<i>Taraxacum officinale</i>	Asteraceae	luteolin 7-glucoside, luteolin 7-diglucosides, luteolin,	[491]
<i>Tecoma stans Juss.</i>	Bignoniaceae	luteolin 7-O-beta-D-neohesperidoside, luteolin 7-O-beta-D-glucopyranoside	[492]
<i>Terminalia arjuna</i>	Combretaceae	luteolin	[103]

(Table 1. Contd....)

Species	Family	Aglycone/Glycoside	Reference
<i>Terminalia chebula retz.</i>	Combretaceae	luteolin	[493]
<i>Terminalia myriocarpa</i>	Combretaceae	orientin, isoorientin	[494]
<i>Teucrium species</i>	Lamiaceae	luteolin	[495]
<i>Theobroma cacao</i>	Sterculiaceae	luteolin, luteolin 7-O-glucoside, orientin, isoorientin	[496]
<i>Thymus broussonettii</i>	Lamiaceae	luteolin, luteolin-7-O-glucoside, luteolin-3'-O-glucuronide	[497]
<i>Thymus piperella</i>	Lamiaceae	luteolin-7- O-beta- D-glucoside	[498]
<i>Thymus vulgaris</i>	Lamiaceae	luteolin 7-glucuronide	[499]
<i>Thymus willdenowii</i>	Lamiaceae	luteolin-3'-O-glucuronide	[500]
<i>Torenia fournieri</i>	Scrophulariaceae	luteolin-7-O-beta-glucoside	[501]
<i>Tripleurospermum maritimum</i>	Asteraceae	luteolin, luteolin-7-glucoside, luteolin-7-glucuronide	[263]
<i>Tripleurospermum perforatum</i>	Asteraceae	luteolin, luteolin-7-glucoside	[263]
<i>Triticum durum</i>	Poaceae	luteolin glycosides	[502]
<i>Trollius chinensis</i>	Ranunculaceae	orientin	[114]
<i>Trollius ledibouri</i>	Ranunculaceae	orientin	[503]
<i>Turnera diffusa</i>	Turneraceae	luteolin 8-C-E-propenoic acid (1), luteolin 8-C-beta-[6-deoxy-2-O-(alpha-l-rhamnopyranosyl)-xylo-hexopyranos-3-uloside]	[504]
<i>Urtica laetevirens</i>	Urticaceae	luteolin 7-O-neohesperidoside, luteolin 7-O-beta-D: -glucopyranoside , 5-methoxyluteolin 7-O-beta-D: -glucopyranoside	[505]
<i>Verbascum salviifolium</i>	Scrophulariaceae	luteolin 7-O-glucoside, luteolin 3'-O-glucoside	[506]
<i>Verbena officinalis</i>	Verbenaceae	luteolin 7-diglucuronide	[260]
<i>Vernoniopsis caudatawith</i>	Asteraceae	luteolin 4'-beta-d-O-glucopyranosyl	[507]
<i>Veronica chamaedrys</i>	Scrophulariaceae	luteolin, apigenin, luteolin-3'-methyl ether	[508]
<i>Veronica thymoides</i>	Scrophulariaceae	luteolin 7-O-beta-glucopyranoside	[509]
<i>Viola tricolor</i>	Violaceae	luteolin-6-C-hexoside, luteolin-6-C-deoxyhexoside-8-C-hexoside, luteolin-6-C-hexoside-8-C-deoxyhexoside	[510]
<i>Viola yedoensis</i>	Violaceae	luteolin 6-C-beta-D-glucopyranoside (isoorientin), luteolin 6-C-alpha-L-arabinopyranosyl-8-C-beta-D-glucopyranoside (isocarlinoside)	[511]
<i>Vitex agnus-castus</i>	Lamiaceae	luteolin 6-C-(4"-methyl-6"-O-trans-caffeoylglucoside), luteolin 6-C-(6"-O-trans-caffeoylglucoside), luteolin 6-C-(2"-O-trans-caffeoylglucoside), luteolin 7-O-(6"-p-benzoylglucoside), luteolin, orientin	[512, 513]
<i>Vitex polygama</i>	Lamiaceae	orientin, isoorientin	[514]
<i>Vitex rotundifolia</i>	Lamiaceae	luteolin	[515]
<i>Vriesea sanguinolenta</i>	Bromeliaceae	6-hydroxyluteolin-7-O-(1"-alpha-rhamnoside)	[516]
<i>Washingtonia filifera</i>	Apiaceae	luteolin 7-O-glucoside 4"-sulfate (2), luteolin 7-O-glucoside 2"-sulfate	[517]
<i>Wedelia paludosa</i>	Asteraceae	luteolin	[518]
<i>Youngia japonica</i>	Asteraceae	luteolin-7-O-glucoside	[519]
<i>Zataria multiflora</i>	Lamiaceae	luteolin	[520]
<i>Zostera marina</i>	Zosteraceae	luteolin	[40]

been identified in Bryophyta, Pteridophyta, Pinophyta and Magnoliophyta. In Bryophyta, luteolin glycosides have been found in mosses of the families Hedwigiaceae [13] and Dicranaceae [14], as well as in liverworts of the family Monocleaceae [15]. In Pteridophyta, luteolin and luteolin glycosides have been identified in ferns of the families Asplenaceae [16], Ophioglossaceae [17] and Pteridaceae [18-20], as well as in the family of horsetails Equisetaceae [21]. In the division Pinophyta (Gymnosperms) luteolin has been found in Ginkgoaceae [22]. Most families containing luteolin are included in the division Magnoliophyta (Angiosperms), both in Magnoliopsida (Dicotyledons) and Liliopsida (Monocotyledons). In Dicotyledons, luteolin has been identified in many families, including Anacardiaceae, Annonaceae, Apiaceae (Umbelliferae), Asclepiadaceae, Asteraceae, Avicenniaceae, Balsaminaceae, Begoniaceae, Berberidaceae, Bignoniaceae, Boraginaceae, Brassicaceae, Buddlejaceae, Caesalpiniaceae (Leguminosae), Campanulaceae, Cannabaceae, Capparaceae, Caprifoliaceae, Caryophyllaceae, Cecropiaceae, Chenopodiaceae, Clusiaceae, Combretaceae, Cucurbitaceae, Cynomoriaceae, Euphorbiaceae, Fabaceae (Leguminosae), Flacourtiaceae, Gentianaceae, Geraniaceae, Globulariaceae, Lamiaceae (Labiatae), Ledocarpaceae, Leguminosae, Lythraceae, Malvaceae, Melastomataceae, Mimosaceae (Leguminosae), Moraceae, Ochnaceae, Oleaceae, Oxalidaceae, Paeoniaceae, Papaveraceae, Passifloraceae, Piperaceae, Plantaginaceae, Ranunculaceae, Rosaceae, Rubiaceae, Rutaceae, Salicaceae, Scrophulariaceae, Simaroubaceae, Solanaceae, Sterculiaceae, Thymelaeaceae, Turneraceae, Urticaceae, Valerianaceae, Verbenaceae, Violaceae and Vitaceae. In Monocotyledons, luteolin has been identified in Araceae, Arecaceae, Asphodelaceae, Bromeliaceae, Colchicaceae (Liliaceae), Commelinaceae, Cyperaceae, Hydrocharitaceae, Melanthiaceae, Poaceae (Graminaceae) and Zosteraceae (see Table 1 for references).

Luteolin has been identified in many edible plants. It has been found in carrots (*Daucus carota*), peppers (*Capsicum annuum*), celery (*Apium graveolens*), olive oil (*Olea europaea*), peppermint (*Mentha x piperita*), thyme (*Thymus vulgaris*), rosemary (*Rosmarinus officinalis*), oregano (*Origanum vulgare*), lettuce (*Lactuca sativa*), Perilla leaves (*Perilla frutescens*), pomegranate (*Punica granatum*), artichoke (*Cynara scolymus*), chocolate (*Theobroma cacao*), rooibos tea (*Aspalathus linearis*), buckwheat sprouts (*Fagopyrum esculentum*), turnip (*Brassica napus*), capers (*Capparis spinosa*) and cucumber (*Cucumis sativus*) (see Table 1 for references). It has also been identified in lemon, beets, Brussels sprouts, cabbage, cauliflower, chives, fennel, harwort, horseradish, kohlarabi, parsley, spinach and green tea (see "USDA database for the flavonoid content of selected foods").

Table 1 shows that luteolin is present in plants as an aglycone (molecule without any sugars bound to it) and as glycosides (aglycone with one or several sugars bound to it). Most glycosides of luteolin are O-glycosides, i.e., the sugar moieties are bound to the aglycone through one or several free hydroxyl (OH) groups. These glycosides usually have sugar moieties at positions 5, 7, 3' and 4', as luteolin is 5,7,3',4'-tetrahydroxyflavone. Cynaroside (luteolin 7-O-glucoside) and scolymoside (luteolin 7-O-rutinoside) are

classical examples of luteolin 7-O-glycosides. Sugars can also be bound to luteolin through a C-C bond, forming C-glycosides. Luteolin-8-C-glucoside (orientin) and luteolin 6-C-glucoside (isoorientin) are the most common C-glycosides of luteolin. Glucose is the most frequent sugar found in luteolin glycosides; apiose, rhamnose, rutinose, galactose, arabinose, glucuronic acid and xylose are other sugars commonly found in luteolin glycosides (see Table 1). The structures of luteolin and three common glycosides of luteolin are shown in Fig. (1).

3. BIOLOGICAL ACTIVITIES OF LUTEOLIN

Several epidemiological studies have evaluated the possible association between a high consumption of foods containing luteolin and the risk of developing some chronic diseases. The association between the intake of several common dietary flavonoids and the incidence of epithelial ovarian cancer among 66,940 women was evaluated in a prospective study (Nurses' Health Study); a significant 34% decrease in incidence for the highest versus lowest quintile of luteolin intake was observed (RR = 0.66, 95% CI = 0.49-0.91; p = 0.01) [23]. A high dietary intake of luteolin was also associated with lowered risk of acute myocardial infarction in a population-based health survey (p = 0.0096); the study population consisted of 361 men and 394 women aged 65-99 years, who were followed up for up to 10 years [24]. Two case-control studies, however, did not find a significant positive correlation between consumption of foods rich in luteolin and a lower incidence of lung cancer (103 cases and 206 controls) [25] or gastric cancer (354 cases of gastric cancer and 354 controls) [7]. Likewise, a prospective study conducted in 38,018 women aged 45 years or more revealed a lack of significant correlation between consumption of foods rich in luteolin and a lower incidence of type 2 diabetes [26]. Although some of these studies suggest that luteolin might protect against some chronic diseases, the low number of studies and the possible presence of other active constituents in luteolin-containing foods (e.g. vitamins, minerals and other phytochemicals) make these data insufficient to draw any conclusion. Numerous experimental data, however, have shown that luteolin possesses a wide range of biological activities involved in the prevention and treatment of these and other diseases. This section of the article summarizes and analyzes such experimental data.

3.1. Antioxidant Activity

Cells primarily use oxygen to generate energy through oxidative phosphorylation. In this process, ATP generation is coupled with a reaction in which four electrons and four protons are added to O₂ to form two molecules of H₂O. But when a molecule of O₂ gains only one electron to form superoxide anion (O₂^{•-}), this highly reactive oxygen species (ROS) tends to gain three more electrons and four protons to form H₂O; this process involves several reactions and results in the production of other ROS such as hydrogen peroxide (H₂O₂), hydroxyl radical (OH[•]) and peroxynitrite (ONOO⁻). Although the controlled production of ROS has an important physiological role, a high production of ROS that is not counterbalanced by the cellular antioxidant defense originates oxidative stress. Oxidative stress has been proposed to play an important role in the pathogenesis of cancer, cardio-

vascular disease, atherosclerosis, hypertension, ischemia/reperfusion injury, diabetes mellitus, neurodegenerative disorders (Alzheimer's disease and Parkinson's disease), rheumatoid arthritis, and ageing [27, 28]. Antioxidant agents may therefore play a protective role in the development of these processes.

The antioxidant properties of flavonoids are widely acknowledged [29-31]. The two classical antioxidant structural features of flavonoids are the presence of a B-ring catechol group and the presence of a C2-C3 double bond in conjugation with an oxo group at C4; the first serves to donate hydrogen/electron to stabilize a radical species and the second serves to bind transition metal ions such as iron and copper [31, 32]. Because luteolin and some of its glycosides fulfill these two structural requirements (see Fig. 1), it is not surprising that many luteolin-containing plants possess antioxidant properties [33-52]. The antioxidant activity of luteolin and its glycosides has been associated with their capacity to scavenge reactive oxygen and nitrogen species [41, 53-56], to chelate transition metals that may induce oxidative damage through the Fenton reaction [32, 57], to inhibit pro-oxidant enzymes [39, 58-60] and to induce antioxidant enzymes [61-63] (Fig. 2). The antioxidant activity of luteolin has not only been observed *in vitro* but also *in vivo* [64-66].

3.2. Anti-inflammatory Activity

Inflammation is a physiological process in response to tissue damage resulting from microbial pathogen infection, chemical irritation, and/or wounding. After tissue injury, a multifactorial network of chemical signals initiates and maintains a host response designed to heal the damaged tissue. The activation and migration of leukocytes (neutrophils, monocytes and eosinophils) from the venous system to the site of damage and the release of growth factors, cytokines and reactive oxygen and nitrogen species are known to play a crucial role in the inflammatory response. Inflamma-

tory processes are required for immune surveillance, optimal repair, and regeneration after injury. When acute inflammation is not resolved, however, chronic inflammation occurs, which has a detrimental effect in several diseases including atherosclerosis, cancer, asthma and some neurological disorders, such as Alzheimer's disease and Parkinson's disease [67].

Flavonoids are known to have anti-inflammatory properties [68]. Luteolin, its glycosides and plants containing luteolin have been reported to exert anti-inflammatory effects *in vitro* and *in vivo* [69-86]. Several mechanisms seem to be involved in the anti-inflammatory activity of this flavonoid. The activation of the nuclear factor-kappa B (NF-kappa B) increases the expression of pro-inflammatory cytokines, chemokines and enzymes (e.g. TNF, IL-1, IL-6, IL8, COX-2, iNOS), and several works have shown that luteolin inhibits NF-kappa B activity at concentrations in the low micromolar range [71, 75, 87-89]. For instance, Xagorari *et al.* identified luteolin as the most potent of the flavonoids tested in inhibiting TNF-alpha release in macrophages, and showed that luteolin blocked lipopolysaccharide (LPS)-induced activation of NF-kappa B, as well as NF-kappa B-driven gene expression [75]. Activator protein 1 (AP-1) is a transcriptional regulator composed of members of the Fos and Jun families that participates in the inflammatory response; expression of the inflammatory cytokine IL-6 is mediated by AP-1 in addition to NF-kappa B. Luteolin has been shown to inhibit the activation of AP-1 [69, 87, 90, 91]. Jang *et al.* have recently observed that luteolin reduced LPS-induced IL-6 production *in vitro* and *in vivo* by inhibiting the JNK and AP-1 signaling pathway. They found that mice supplemented with luteolin in the drinking water had decreased IL-6 levels in plasma and reduced IL-6 production in hippocampus [91]. The enzymes cyclooxygenases (COX), lipoxygenases (LOX) and inducible nitric oxide synthase (iNOS) are known to play important roles in inflammation by participating in the syn-

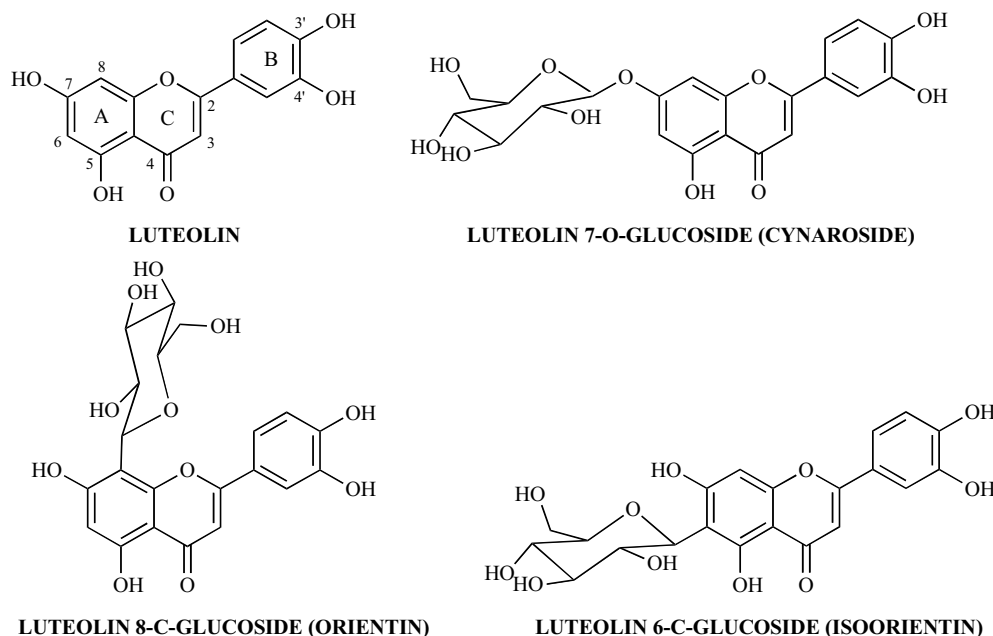


Fig. (1). Structures of luteolin, cynaroside (luteolin 7-O-glucoside), orientin (luteolin 8-C-glucoside) and isoorientin (luteolin 6-C-glucoside).

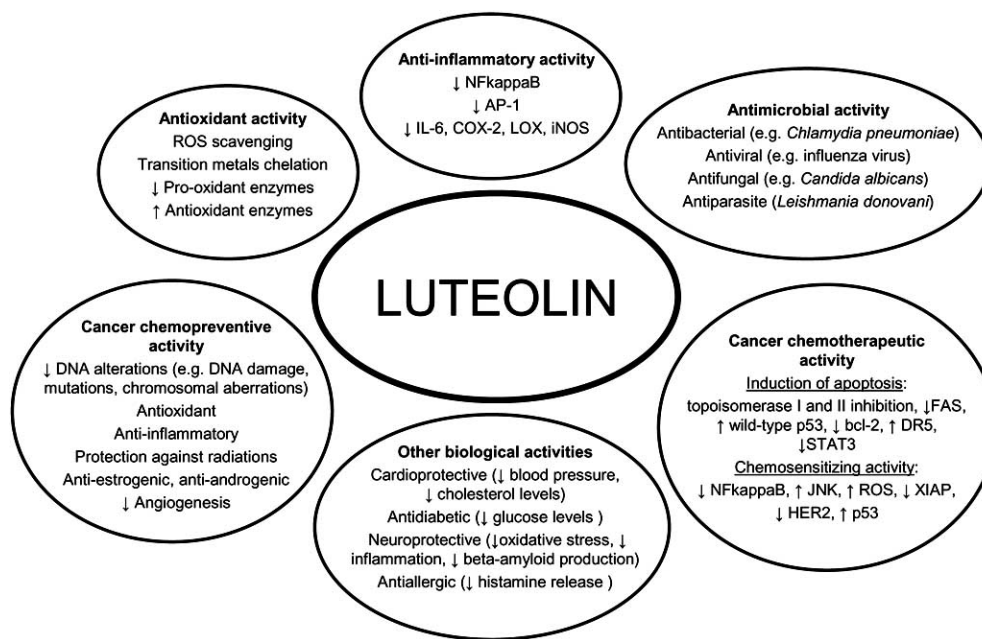


Fig. (2). Biological activities and possible mechanisms of action of luteolin.

thesis of eicosanoids (e.g. prostaglandins, leukotrienes) and in the production of reactive species. Some reports have shown that luteolin can inhibit COX-2 [39, 80, 85, 92], LOX [60, 80] and iNOS [39, 93, 94]. The inhibitory effects of luteolin on these pro-inflammatory enzymes may contribute to its anti-inflammatory activity.

Luteolin and several structurally related flavonoids were examined for their abilities to inhibit enzymes for the synthesis of thromboxane B2 and leukotriene B4 as well as hydrogen peroxide scavenging activity. Luteolin exhibited a high inhibitory activity against both thromboxane and leukotriene synthesis. The glycosides cynaroside (luteolin 7-O- β -D-glucoside) and cesioside (luteolin 7-O- β -D-primeveroside) possessed a moderate inhibition activity against both enzyme synthesis pathways, while isoorientin (luteolin 6-C- β -D-glucoside) and stereolensin (luteolin 6-O- β -D-primeveroside) exhibited high activity against thromboxane synthesis. These results suggest that the activities of luteolin and its related glycosides against arachidonic acid synthesis and hydrogen peroxide scavenging are dependent on their molecular structures. The presence of ortho-dihydroxy groups at the B ring and OH substitution pattern at C-5 position of the A ring could significantly contribute to the antiinflammatory and antioxidant activities of flavonoids [55].

3.3. Antimicrobial Activity

One of the undisputed functions of flavonoids in plants is their protective role against microbial invasion. This involves their presence in plants as constitutive agents as well as their accumulation as phytoalexins in response to microbial attack [95]. Because of this protective role, it is not surprising that plants rich in flavonoids have been used for many years in traditional medicine to treat infectious diseases [96]. Although luteolin is known to facilitate the symbiotic interaction between the bacterium *Rhizobium meliloti* and leguminous plants to form nitrogen-fixing root nodules

[97], this flavonoid and its glycosides are examples of flavonoids that possess antimicrobial activity [98, 99]. Luteolin and its glycosides have been isolated from plants used in popular medicine for their antimicrobial properties. Numerous papers have reported that luteolin, its glycosides, or plants containing luteolin have antibacterial [100-109], antiviral [106, 110-114] and antifungal [109, 115, 116] activity. Tormakangas *et al.* tested the effects of luteolin on the course of acute *Chlamydia pneumoniae* infection *in vivo*. Mice were treated with this flavonoid for 3 days prior to and 10 days after inoculating the bacteria. Analysis of lung tissue revealed that luteolin suppressed the presence of the bacteria in lung tissue, reduced inflammation and inhibited the development of *Chlamydia pneumoniae*-specific antibodies [70]. Liu *et al.* investigated the chemical composition and antiviral activity of *Elsholtzia rugulosa*, a common Chinese herb used in the treatment of cold and fever. They isolated several flavonoids, including luteolin and luteolin 3'-glucuronyl acid methyl ester, and found that luteolin had anti-influenza virus activity at a low concentration ($IC_{50} = 2.06 \mu\text{g/ml}$) [111]. The antifungal activity against 12 pathogenic fungi of a methanol extract and several fractions and compounds from *Piper solmsianum* was evaluated by de Campos *et al.*; some of the compounds, including the luteolin C-glycoside orientin, exhibited pronounced activity with potency similar to that of the standard antifungal drug ketoconazole [115].

Luteolin has also shown activity against several types of parasites, including *Leishmania donovani* [117-123] and *Plasmodium falciparum* [118, 124, 125]. The anti-leishmanial activity of luteolin has been observed at low concentrations ($IC_{50} = 0.8 \mu\text{g/ml}$) and seems to be mediated by topoisomerase II inhibition [117, 123].

3.4. Anticancer Activity

Several *in vivo* studies suggest that luteolin has cancer chemopreventive potential. Elangovan *et al.* observed that

diets containing 1% luteolin reduced the incidence of fibrosarcoma in mice induced by subcutaneous injection of 20-methylcholanthrene. This flavonoid reduced the elevated levels of lipid peroxides and cytochrome P450 as well as the reduced activity of glutathione-S-transferase induced by 20-methylcholanthrene [126]. Three studies by Manju *et al.* showed that luteolin also exerts chemopreventive effects against 1,2-dimethylhydrazine-induced colon carcinogenesis in rats; several mechanisms seem to participate in this anticarcinogenic activity including its antioxidant properties [66, 127, 128]. Ueda *et al.* [129] investigated the chemopreventive activity of an extract from the leaves of *Perilla frutescens* and of one constituent of this extract (luteolin) on 7,12-dimethylbenz[a]anthracene (DMBA)- and 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced skin papillomas in mice. They showed that topical applications of the extract or luteolin prior to TPA treatment in DMBA-initiated mouse skin resulted in a significant reduction in tumor incidence and multiplicity; the chemopreventive effect of luteolin was more potent than that of the extract. The luteolin-containing extract in the drinking water (0.05%) did not change tumor incidence or multiplicity significantly but induced a significant reduction in tumor volume [129].

Several mechanisms may participate in the cancer chemopreventive activity of luteolin. According to the most accepted theory of cancer (the somatic mutation theory of cancer), tumorigenesis is caused by DNA alterations in oncogenes, tumor-suppressor genes and stability genes [130]. Numerous studies have shown that luteolin can prevent the DNA alterations induced by different carcinogenic agents both *in vitro* and *in vivo* [53, 131-140]. Taj *et al.* studied the chemopreventive activity of luteolin against mutagenicity induced by deep-fried fish and mutton extracts in rats; they found that luteolin pre-treatment efficiently protected bone marrow cells against micronuclei and chromosome aberrations induced by these mutagens [138].

A growing body of research suggests that ROS play a crucial role in cancer development [141-143]. Cancer cells produce high levels of the ROS superoxide anion ($O_2^{\cdot-}$) and hydrogen peroxide (H_2O_2) [144, 145], and it has been demonstrated that an increase in the cellular levels of $O_2^{\cdot-}$ and H_2O_2 can induce cell malignant transformation [146-149]. Non-cytotoxic levels of $O_2^{\cdot-}$ and H_2O_2 can induce DNA alterations [150, 151] and play an important role in key aspects of carcinogenesis, including cell proliferation [144, 152], apoptosis resistance [152], angiogenesis [153] and invasion/metastasis [154-160]. Accordingly, the malignant phenotype of cancer cells can be reversed just by increasing the levels of the $O_2^{\cdot-}$ - and H_2O_2 -detoxifying enzymes superoxide dismutases, catalase or glutathione peroxidase [149, 161-164]. Because luteolin has known antioxidant properties, it makes sense to think that the antioxidant activity of this flavonoid is a key mechanism involved in its cancer preventive activity.

Accumulating evidence links inflammation and cancer [165]. It is recognized that inflammatory diseases increase the risk of developing many types of cancer, including bladder, cervical, gastric, intestinal, oesophageal, ovarian, prostate and thyroid cancer. Inflammatory cells, chemokines and cytokines are also present in the microenvironment of all

tumours in experimental animal models and humans from the earliest stages of development. Transfer of inflammatory cells or overexpression of inflammatory cytokines promotes the development of tumours. The targeting of inflammatory mediators (chemokines and cytokines, such as TNF- α and IL-1 β), transcription factors involved in inflammation (such as NF-kappaB and STAT3) or inflammatory cells decreases the incidence and spread of cancer. In addition, non-steroidal anti-inflammatory drugs are known to reduce the risk of developing certain cancers (such as colon and breast cancer) and reduce the mortality caused by these cancers [165]. These data suggest that the anti-inflammatory properties of luteolin [71, 75, 87, 88, 90, 91, 166] may play an important role in the cancer preventive activity of this flavonoid.

It is accepted that flavonoids such as luteolin play an important role in protecting plants against ultraviolet radiation [95, 167]. Several works have shown that luteolin, its glycosides or plants containing these flavonoids exert radioprotective effects *in vitro* and in animal models [65, 135, 137, 139, 140, 168-171]. Shimoi *et al.* observed that administration of rooibos tea (*Aspalathus linearis*) infusion to mice prior to gamma-ray irradiation reduced the frequency of micronucleated reticulocytes. After the fractionation of rooibos tea infusion, luteolin was found to be the most anti-clastogenic and antioxidant compound. The administration of luteolin prior to irradiation suppressed lipid peroxidation in mouse bone marrow and spleen [135]. This and other reports suggest that luteolin exerts radioprotective effects by reducing radiation-induced ROS.

Several works have reported that luteolin possesses anti-estrogenic [172-175] and anti-androgenic activity [176, 177]; these activities may prevent the development of hormone-dependent cancers such as breast and prostate cancers. It has been observed that the constituents of the plant *Wedelia chinensis* indole-3-carboxylaldehyde, wedelolactone, luteolin and apigenin, alone and in combination, had anti-androgenic properties and inhibited the growth of androgen receptor (AR)-dependent prostate cancer cells [177]. Chiu *et al.* have recently found that luteolin significantly inhibited prostate cancer cell proliferation and induced apoptosis in LNCaP cells. Luteolin suppressed intracellular and secreted PSA levels and repressed AR mRNA and protein expression in a dose- and time-dependent manner. It also suppressed tumor growth in mice. The authors concluded that luteolin-mediated AR downregulation contributes to the inhibition of cell proliferation and the induction of apoptosis in LNCaP human prostate cancer cells, and that this flavonoid may act as a chemopreventive or chemotherapeutic agent for prostate cancer [176]. Knowing that insulin-like growth factor 1 receptor (IGF-1R) activation is required for prostate cell proliferation, Fang *et al.* evaluated the effects of luteolin on IGF-1R signaling in prostate cancer cells. They found that luteolin suppressed proliferation and induced apoptosis of prostate cancer cells *in vitro* and *in vivo* via inhibition of the IGF-1R/AKT signaling pathway [178].

The clinical use of the imaging technique positron-emission tomography using the glucose analogue tracer ^{18}F fluorodeoxyglucose (FDG PET) has shown that most primary and metastatic cancers have increased glucose con-

sumption and up-regulation of glycolysis; this technique has clinical utility for detecting metastatic cancers with high sensitivity and specificity [179, 180]. The increased glycolytic activity found in cancer cells despite the presence of oxygen (the Warburg effect) plays an important role in cancer development. The activation of glycolysis is essential for cancer cells to keep ATP levels and to provide building blocks for biosynthesis during cell proliferation [181, 182]. The inhibition of the high glycolytic activity of cancer cells may therefore reduce their capacity to both generate energy and proliferate, which may prevent tumor development. Evidence suggests that luteolin can inhibit glycolysis and ATP production in cancer cells *in vitro* [183, 184].

The generation of new blood vessels (angiogenesis) is necessary for the formation of solid tumors; without vascular growth, the tumor mass is restricted to a tissue-diffusion distance of approximately 0.2 mm. Malignant tumors are known to activate angiogenesis, and evidence indicates that luteolin can inhibit angiogenesis *in vitro* and *in vivo* at concentrations in the low micromolar range [185, 186]. Bagli *et al.* showed that luteolin inhibited tumor growth and angiogenesis in a murine xenograft model and decreased vascular endothelial growth factor (VEGF)-induced *in vivo* angiogenesis *via* inhibition of the phosphatidylinositol 3'-kinase (PI3K) pathway [186].

From a therapeutic point of view, invasion and metastasis are the most relevant processes of tumorigenesis; it is estimated that approximately 90% of all cancer deaths occur in patients with metastatic disease [187]. Evidence suggests that luteolin may prevent these processes by inhibiting, for instance, matrix metalloproteinases (MMPs) and focal adhesion kinase (FAK) [40, 188-193].

In addition to its cancer preventive effects, recent reports support the idea that luteolin might be developed as a cancer therapeutic agent. Numerous studies have demonstrated that luteolin can induce apoptosis in a variety of cancer cell lines [194-206]; these reports show that this effect usually requires a concentration of luteolin of 10 μ M or higher. DNA topoisomerase (topo) inhibitors are efficient inducers of apoptosis in cancer cells [207] and several works have reported that luteolin inhibits and poisons topo I and topo II [117, 205, 208-213]. Using an *in vivo* technique that employs specific antibodies to detect topoisomerase-interacting drugs in intact cells, it has recently been shown that luteolin poisons topo II and inhibits the catalytic activity of topo I in leukemia cells [213]. The activity of luteolin on topoisomerases I and II may have therapeutic implications, as these enzymes are the target of several drugs commonly used in the treatment of cancer (e.g. etoposide, topotecan, irinotecan).

Luteolin-induced apoptosis in cancer cells has also been associated with its ability to inhibit fatty acid synthase activity [194], to induce activation of wild-type p53 [214], to imbalance the Bcl-2 family of proteins [195, 215], to upregulate death receptor 5 (DR5) [197] and to promote STAT3 degradation [204]. Interestingly, Horinaka *et al.* observed that luteolin induced apoptosis in malignant cells but not in normal human peripheral blood mononuclear cells [197].

Recent data suggests that luteolin may be used to sensitize cancer cells to the cytotoxic effects of some anticancer

agents [184, 196, 216-220]. Shi *et al.* found that luteolin significantly sensitized TNF-induced cell apoptosis *via* inhibition of NF-kappaB and increased activation of JNK [217]. Evidence suggests that luteolin-induced accumulation of ROS may play a key role in suppression of NF-kappaB and potentiation of JNK to sensitize cancer cells to undergo TNF-induced apoptosis [216]. Shi *et al.* also found that luteolin sensitized TNF-related apoptosis-inducing ligand (TRAIL)-induced apoptosis in various human cancer cells; such sensitization was achieved *via* enhanced X-linked inhibitor of apoptosis protein (XIAP) ubiquitination and proteasomal degradation [219]. The sensitization effect of luteolin in cancer cells may also be mediated by its effects on HER2 (Human Epidermal growth factor Receptor-2), as HER2 overexpression confers resistance to various therapeutic regimens and as luteolin is a potent stimulator of HER2 degradation [196]. The authors showed that luteolin significantly inhibited HER2 expression and tumor growth in nude mice in a dose-dependent manner [196]. It has also been observed that luteolin enhances the cancer therapeutic activity of cisplatin *in vitro* and *in vivo* *via* p53 stabilization and accumulation [218]. All these experimental *in vitro* and *in vivo* data suggest that luteolin may have clinical application as a chemosensitizer in cancer therapy.

3.5. Other Biological Activities

Experimental data indicate that luteolin, some of its glycosides or plants with these flavonoids may prevent cardiovascular disease by reducing blood pressure and cholesterol levels [221-224], diabetes by reducing glucose levels [225-228] and neurodegenerative diseases by reducing oxidative stress, inflammation and beta-amyloid production [229-231]. Luteolin has also shown anti-allergic activity *in vitro* and *in vivo* through different mechanisms including inhibition of histamine release [84, 86, 232-237].

Finally, it is important to mention several reports showing that specific concentrations of luteolin may produce toxic effects [205, 210, 238-240]. Some of these reports suggest that luteolin-induced toxic effects may be mediated by its ability to induce topoisomerase II-mediated DNA damage; this activity on topoisomerase II has been observed using *in vitro* and *in vivo* assays [205, 210, 213, 238]. Although luteolin-induced topoisomerase II-DNA damage may lead to cancer cell death and be therapeutically useful, non-cytotoxic levels of DNA damage may accumulate and cause toxicity in the long term [213]. Indeed, the clinical use of topoisomerase II poisons in cancer chemotherapy has been associated with an increased incidence of leukemia [241, 242]. These data suggest that high concentrations of this flavonoid might produce toxic effects in the long term. *In vivo* studies seem necessary to assess the possible long-term toxicity of supplementing luteolin at concentrations higher than those found in a diet rich in plant-derived foods.

4. BIOAVAILABILITY AND METABOLISM OF LUTEOLIN

In vitro studies have revealed that luteolin has a wide range of biological activities. In order for these activities to be relevant in an *in vivo* setting, luteolin has to reach the target tissues at a specific concentration, and such concentra-

tion needs to be maintained for a particular period of time. In other words, the bioavailability of luteolin needs to be sufficiently high and its metabolism sufficiently low; otherwise, many activities of luteolin observed *in vitro* will not be relevant *in vivo*. Since luteolin is a common dietary constituent and since the oral route is the preferred route of administration for most drugs, it is important to know the bioavailability and metabolism of this flavonoid after oral ingestion.

Shimoi *et al.* investigated the intestinal absorption of luteolin and luteolin 7-O-beta-glucoside in rats and humans [243]. They observed that luteolin 7-O-beta-glucoside was absorbed after hydrolysis to luteolin (intestinal microbacteria can hydrolyze glucosides of flavonoids and produce aglycones) and that luteolin was converted to glucuronides during passing through the intestinal mucosa. Luteolin was absorbed more efficiently from the duodeno-jejunum than from the ileum. The plasma of rats administered luteolin orally contained free luteolin, glucuronide and sulfate-conjugates of luteolin and of *o*-methyl luteolin (diosmetin or chrysoeryol). Free luteolin was also observed in human plasma after the oral administration of luteolin. When rats were given luteolin in propyleneglycol (50 $\mu\text{mol/kg}$) orally, the total luteolin concentration in rat plasma 30 min after dosing and after plasma samples were treated with L-glucuronidase/sulfatase was $15.5 \pm 3.8 \mu\text{mol/L}$ [243]. Deglucuronidation of luteolin monoglucuronide has been observed during inflammation, therefore suggesting that the plasma concentrations of free luteolin can increase in some pathological processes such as inflammation [244].

Zhou *et al.* also reported that luteolin was absorbed passively in the intestine of rats and that its absorption was more efficient in the jejunum and duodenum than in the colon and ileum [245]. They observed that the intestinal absorption of luteolin from peanut hull extract (PHE) was more efficient than that from pure luteolin. After oral administration of 14.3 mg/kg luteolin or 92.3 mg/kg PHE (with 14.3 mg/kg luteolin) they observed that the maximum plasma concentration of luteolin (C_{max}) was $1.97 \pm 0.15 \mu\text{g/mL}$ for luteolin and $8.34 \pm 0.98 \mu\text{g/mL}$ for PHE. The time to reach the maximum plasma concentration was $1.02 \pm 0.22 \text{ h}$ for luteolin and $0.520 \pm 0.05 \text{ h}$ for PHE. The half-life of luteolin ($t_{1/2}$) was $4.94 \pm 1.2 \text{ h}$ for luteolin and $2.772 \pm 0.54 \text{ h}$ for PHE [245]. Li *et al.* [246] also determined several pharmacokinetic parameters of luteolin in the plasma of dogs that received orally 102 mg/kg of a *Chrysanthemum morifolium* extract: C_{max} (ng/mL): 463.9 ± 87 ; t_{max} (h): 1.540 ± 0.30 ; $t_{1/2}$ (h): 6.968 ± 3.0 .

Overall, these reports indicate that luteolin can be absorbed after oral administration. Although most luteolin found in plasma is in the form of glucuronide and sulfate-conjugates, low concentrations of free luteolin can be achieved in plasma after oral ingestion of this flavonoid. The plasma concentrations of luteolin depend on the form in which luteolin is ingested. The maximum concentrations of luteolin are achieved after 1-2 h, and luteolin remains in the plasma for several hours. This suggests that the bioavailability of luteolin is sufficiently high and its metabolism sufficiently low to allow this flavonoid to exert some of its biological activities in an *in vivo* setting. Accordingly, several

works discussed throughout this manuscript have revealed that luteolin exerts biological activities *in vivo*.

CONCLUSION

Luteolin and its glycosides are widely distributed in the plant kingdom and have been found in many edible plants. Numerous preclinical studies have shown that luteolin possesses a wide range of biological activities and several possible mechanisms of action have been elucidated. Although the oral bioavailability of luteolin and its glycosides is not too high, animal experiments have shown that luteolin exerts its biological properties *in vivo*. Accumulating evidence suggests that luteolin could be developed as a cancer chemopreventive agent and be useful in cancer therapy to sensitize tumor cells to the cytotoxic effects of some chemotherapeutic drugs. The possible induction of topoisomerase II-mediated DNA alterations in cells by this flavonoid raises some concern about its safety; long-term animal toxicity studies should be conducted before people are able to take high doses of luteolin safely over a long period of time.

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