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

(Table 1. Contd….)

Species	Family	Aglycone/Glycoside	Reference
Balbisia calycina	Ledocarpaceae	luteolin	[276]
Ballota nigra	Lamiaceae	luteolin-7-lactate, luteolin-7-glucosyl-lactate	[277]
Bauhinia tarapotensis	Caesalpiniaceae	luteolin 4'-O-beta-D-glucopyranoside	[33]
Begonia malabarica	Begoniaceae	luteolin	[278]
Bidens tripartita	Asteraceae	cynaroside, luteolin	[279]
Biebersteinia orphanidis	Geraniaceae	luteolin	[280]
Brandisia hancei	Scrophulariaceae	luteolin	[58]
Brassica napus	Brassicaceae	luteolin	[173]
Broussonetia papyrifera	Moraceae	luteolin	[281]
Buddleja globosa	Buddlejaceae	luteolin-7-O-glucoside	[282]
Buddleja officinalis	Buddlejaceae	luteolin, luteolin, luteolin-7-O-beta-D-glucopyranoside	[283, 284]
Bupleurum flavum	Apiaceae	luteolin	[285]
Cajanus cajan	Fabaceae	luteolin	[286]
Cannabis sativa	Cannabaceae	orientin, luteolin-7-O-beta-D-glucuronide	[287]
Capparis himalayensis	Capparaceae	luteolin	[288]
Capparis spinosa	Capparaceae	luteolin 7-O-glucoside, luteolin.	[105]
Capsicum annuum	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]
Caralluma attenuata	Asclepiadaceae	luteolin-4'-O-neohesperidoside = (luteolin-4'-O-[alpha-(L-rhamnopyranosyl-(1-->2)-beta-D-glucopyranoside)])	[74]
Caralluma negevensis	Asclepiadaceae	luteolin 3'-O-beta-D-glucopyranoside-4'-O-alpha-L-rhamnopyranosyl-(1-->2)-beta-D-glucopyra noside, luteolin 3',4'-di-O-beta-D-glucopyranoside	[293]
Caralluma russeliana	Asclepiadaceae	luteolin 4'-O-beta-D-neohesperidoside.	[294]
Caralluma tuberculata	Asclepiadaceae	luteolin.4'-beta-D-glucopyranosyl-(2-->1)-alpha-L-rhamnopyranoside	[295]
Carduus crispus	Asteraceae	luteolin-7-glucoside	[296]
Carduus micropterus	Asteraceae	luteolin	[297]
Carthamus lanatus	Asteraceae	luteolin 7-O-glucoside	[298]
Carthamus tinctorius	Asteraceae	luteolin, luteolin 7-O-beta-D-glucopyranoside, luteolin-7-O-(6"-O-acetyl)-beta-D-glucopyranoside	[43]
Cassia nigricans	Caesalpiniaceae	luteolin	[299]
Cayratia japonica	Vitaceae	luteolin, luteolin-7-O-beta-D-glucopyranoside	[300]
Cecropia lyratiloba	Cecropiaceae	isoorientin	[301]
Cecropia obtusifolia	Cecropiaceae	isoorientin	[226]
Centaurea scoparia	Asteraceae	luteolin	[302]
Ceratonia siliqua	Caesalpiniaceae	luteolin	[303]
Chaenomeles sinensis	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
Chaerophyllum hirsutum	Apiaceae	6-methylluteolin, luteolin-7-O-beta-D-glucopyranoside	[305]
Chamomilla recutita	Asteraceae	luteolin, luteolin-7-O-glucoside	[306]
Chromolaena odorata	Asteraceae	luteolin	[307]
Chrozophora brocchiana	Euphorbiaceae	luteolin 7-O-glucoside	[37]
Chrysanthemum morifolium	Asteraceae	luteolin-7-O-beta-D-glucoside, luteolin	[133, 308]
Chrysanthemum segetum	Asteraceae	luteolin-7-glucoside	[263]
Chrysanthemum sinense	Asteraceae	luteolin	[309]
Cirsium japonicum	Asteraceae	luteolin	[310]
Cirsium rivulare	Asteraceae	luteolin	[311]
Citrus bergamia	Rutaceae	orientin 4'-methyl ether	[312]
Colchicum cilicicum	Colchicaceae	luteolin	[313]
Coleus parvifolius	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]
Commelina communis	Commelinaceae	orientin, isoorientin	[315]
Conyza bonariensis	Asteraceae	luteolin	[316]
Cornulaca monacantha	Chenopodiaceae	luteolin-7-O-rhamnoside, luteolin-7-O-glucoside	[317]
Crataegus oxyacantha	Rosaceae	luteolin, luteolin-3', 7-diglucoside	[318]
Crataegus pentagyna	Rosaceae	isoorientin, orientin, isoorientin-2''-O-rhamnoside, orientin-2''-O-rhamnoside	[319, 320]
Crataegus x macrocarpa	Rosaceae	luteolin-7-O-beta-D-glucuronide	[321]
Crotalaria sessiliflora	Fabaceae	isoorientin, orientin	[322]
Cucumis sativus	Cucurbitaceae	luteolin-8-C-beta-D-glucopyranoside (orientin), luteolin-6-C-beta-D-glucopyranoside (isoorientin)	[98, 323]
Cuphea pinetorum	Lythraceae	luteolin-7-O-beta-D-glucopyranoside	[324]
Cyclopia subternata	Leguminosae	luteolin	[325]
Cymbopetalum brasiliense	Annonaceae	luteolin-6-hydroxy-7-O-rhamnosylglucoside	[262]
Cymbopogon citratus	Poaceae	isoorientin, isoorientin 2' '-O-rhamnoside, orientin,	[326]
Cynara scolymus	Asteraceae	luteolin, luteolin-7-O-glucoside, luteolin-7-rutinoside, cynaroside	[47, 109, 327]
Cynomorium songaricum	Cynomoriaceae	luteolin	[328]
Cyperus alopecuroides	Cyperaceae	luteolin 5,3'-dimethylether	[329]
Cyperus alopecuroides	Cyperaceae	orientin	[330]
Cyperus conglomeratus	Cyperaceae	luteolin, luteolin 7-methyl ether	[331]
Daphne genkwa	Thymelaeaceae	luteolin, luteolin 7-methyl ether	[332]
Daphne gnidium	Thymelaeaceae	luteolin-3',7-di-O-glucoside	[333]
Daucus carota	Apiaceae	luteolin, luteolin 3'-O-beta-D-glucopyranoside and luteolin 4'-O-beta-D-glucopyranoside	[334, 335]
Deschampsia antarctica	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
Deschampsia borealis	Poaceae	orientin	[336]
Dianthus chinensis	Caryophyllaceae	isoorientin-2"-O-glucoside	[338]
Dicranum scoparium	Dicranaceae	luteolin-7-O-neohesperidoside	[14]
Digitaria exilis	Poaceae	luteolin	[339]
Dioclea lasiophylla	Fabaceae	luteolin 3'beta-D-glucopyranoside	[340]
Dracocephalum subcapitatum	Lamiaceae	luteolin	[341]
Dystaenia takeshimana	Umbelliferae	luteolin	[80]
Echinochloa utilis	Poaceae	luteolin	[50]
Eclipta alba	Asteraceae	luteolin	[342]
Ehretia ovalifolia	Boraginaceae	luteolin	[343]
Elodea nuttallii	Hydrocharitaceae	luteolin-7-O-diglucuronide	[344]
Elsholtzia blanda	Lamiaceae	luteolin	[345]
Elsholtzia bodinieri	Lamiaceae	luteolin 7-O-[6"-(3'''-hydroxy-4'''-methoxy cinnamoyl)]-beta-D-glucopyranoside	[346]
Elsholtzia rugulosa	Lamiaceae	luteolin, luteolin 3'-glucuronyl acid methyl ester	[111]
Epimedium hunanense	Berberidaceae	luteolin	[347]
Epimedium sagittatum	Berberidaceae	luteolin	[348]
Equisetum arvense	Equisetaceae	luteolin	[21]
Erigemn acris	Asteraceae	luteolin	[349]
Euterpe oleraceae	Arecaceae	orientin	[350]
Fagopyrum esculentum	Polygonaceae	isoorientin, orientin	[351]
Fallopia species	Polygonaceae	luteolin glycosides	[352]
Ficaria verna	Ranunculaceae	luteolin 8-C-beta-D-glucopyranoside	[353]
Ficus carica	Moraceae	luteolin	[303]
Genista corsica	Leguminosae	luteolin, luteolin 4'-O-beta-glucoside, luteolin 7-O-beta-glucoside	[354]
Genista morisii	Leguminosae	luteolin, luteolin 7-O-beta-D-glucopyranoside, luteolin 4'-O-beta-D-glucopyranoside	[355]
Genista tenera	Leguminosae	luteolin-7-O-glucoside, luteolin-7,3'-di-O-glucoside	[356]
Gentiana algida	Gentianaceae	orientin	[357]
Gentiana arisanensis	Gentianaceae	luteolin-7-O-beta-D-glucoside, isoorientin-6"-O-glucoside	[41, 358]
Gentiana olivieri	Gentianaceae	isoorientin	[359]
Gentiana piasezkii	Gentianaceae	isoorientin, luteolin	[360]
Gentianella nitida	Gentianaceae	isoorientin	[361]
Ginkgo biloba	Ginkgoaceae	luteolin	[22, 362]
Glechoma hederacea	Labiatae	luteolin 7-O-beta-D-glucopyranoside	[363]
Globularia alypum	Globulariaceae	6-hydroxyluteolin 7-O-laminaribioside, 6-hydroxyluteolin 7-O-beta-D-glucopyranoside, luteolin 7-O-sophoroside	[36]
Glochidion zeylanicum	Euphorbiaceae	isoorientin	[364]

(Table 1. Contd….)

Species	Family	Aglycone/Glycoside	Reference
Glossogyne tenuifolia	Asteraceae	luteolin,luteolin-7-glucoside	[38]
Glycine soja	Leguminosae	luteolin, luteolin-7-O-beta-D-glucoside	[365]
Gnidia involucrata	Thymelaeaceae	isoorientin	[366]
Gypsophila repens	Caryophyllaceae	luteolin-7-O-alpha-L-arabinopyranosyl-6-C-beta-glucopyranoside	[367]
Hebe parviflora	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-methylluteolin-7-O-beta-[6-O-beta-xyloglucoside]	[368]
Hebe stenophylla	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]
Hebe strictissima	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]
Hebe traversti	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-methylluteolin-7-O-beta-[6-O-beta-xyloglucoside]	[368]
Hedwigia ciliata	Hedwigiaceae	luteolin 7-O-Neohesperidoside-4'-O-sophoroside	[13]
Helichrysum compactum	Asteraceae	luteolin, luteolin-7-O-glucoside, luteolin-4',7-di-O-glucoside	[369]
Helichrysum pamphylicum	Asteraceae	luteolin, luteolin-4'glucoside	[370]
Homalium brachybotrys	Flacourtiaceae	luteolin-7-O-beta-glucopyranoside	[371]
Hordeum vulgare	Poaceae	isoorientin, , isoorientin-7-O-glucoside	[372, 373]
Hydnocarpus wightiana	Flacourtiaceae	luteolin	[374]
Hypericum brasiliense	Clusiaceae	luteolin	[375]
Hypericum perforatum	Clusiaceae	isoorientin	[376]
Impatiens textori	Balsaminaceae	luteolin	[377]
Inula britannica	Asteraceae	luteolin	[378]
Ismelia versicolor	Asteraceae	luteolin-7-glucoside, luteolin-7-glucuronide	[263]
Isoplexis chalcantha	Scrophulariaceae	luteolin, luteolin 7- O-beta- D-glycoside	[379]
Ixeridium gracile	Asteraceae	luteolin 7-O-glucoside	[380]
Ixeris denticulata	Asteraceae	luteolin-7-O-glucoside, luteolin-7-O-glucuronide-6'-methyl ester	[381]
Ixeris sonchifolia	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
Japonolirion osense	Melanthiaceae	isoorientin, orientin	[384]
Jatropha cilliata	Euphorbiaceae	isoorientin and orientin	[385]
Kitaibelia vitifolia	Malvaceae	luteolin	[386]
Kummerowia striata	Leguminosae	luteolin 4'-O-glucopyranoside	[82]
Lactuca indica	Asteraceae	luteolin, luteolin 7-O-glucuronide	[387]
Lactuca sativa	Asteraceae	luteolin 7-O-glucuronide	[388]
Lactuca scariola	Asteraceae	luteolin-7-O-beta-D-glucopyranoside, luteolin	[389]
Lamiophlomis rotata	Lamiaceae	luteolin-7-O-glucoside, luteolin	[390]
Lavandula stoechas	Lamiaceae	luteolin 7-O-glucoside	[391]
Lawsonia inermis	Lythraceae	luteolin	[44]
Leandra lacunosa	Melastomataceae	luteolin	[227]
Leontodon croceus	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]
Leontodon duboisii	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]
Leontodon helveticus	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]
Leontodon montaniformis	Asteraceae	luteolin, luteolin 7-O-beta-D-gentiobioside, luteolin 7-O-beta-D-glucoside, luteolin 7-O-beta-D-glucuronide	[392]
Leontodon autumnalis	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]
Leontodon pyrenaicus	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]
Leontodon rilaensis	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]
Leontopodium alpium	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]
Lepechinia graveolens	Lamiaceae	luteolin-7-O-glucuronide	[394]
Leucanthemum adjustum	Asteraceae	luteolin-7-glucoside, luteolin-7-glucuronide	[263]
Leucanthemum vulgare	Asteraceae	luteolin-7-glucuronide	[263]
Leucas cephalotes	Lamiaceae	luteolin 4'-O-beta-D-glucuronopyranoside	[395]
Ligustrum vulgare	Oleaceae	luteolin, luteolin 7-O-glucoside	[396]
Lippia alba	Verbenaceae	luteolin-7-diglucuronide	[397]
Lisianthius nigrescens	Gentianaceae	luteolin 8-C-glucoside	[398]
Lobelia chinensis	Campanulaceae	luteolin	[399]
Lonicera confusa	Caprifoliaceae	luteolin	[400]
Lonicera japonica	Caprifoliaceae	luteolin, luteolin 7-O-beta-D-glucopyranoside	[35, 401]
Lophira alata	Ochnaceae	luteolin	[402]
Luffa cylindrica	Cucurbitaceae	luteolin-7-O-beta-D-glucuronide methyl ester	[403]

(Table 1. Contd….)

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

(Table 1. Contd….)

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

(Table 1. Contd….)

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

(Table 1. Contd….)

Species	Family	Aglycone/Glycoside	Reference
Terminalia chebula retz.	Combretaceae	luteolin	[493]
Terminalia myriocarpa	Combretaceae	orientin, isoorientin	[494]
Teucrium species	Lamiaceae	luteolin	[495]
Theobroma cacao	Sterculiaceae	luteolin, luteolin 7-O-glucoside, orientin, isoorientin	[496]
Thymus broussonettii	Lamiaceae	luteolin, luteolin-7-O-glucoside, luteolin-3'-O-glucuronide	[497]
Thymus piperella	Lamiaceae	luteolin-7- O-beta- D-glucoside	[498]
Thymus vulgaris	Lamiaceae	luteolin 7-glucuronide	[499]
Thymus willdenowii	Lamiaceae	luteolin-3'-O-glucuronide	[500]
Torenia fournieri	Scrophulariaceae	luteolin-7-O-beta-glucoside	[501]
Tripleurospermum maritimum	Asteraceae	luteolin, luteolin-7-glucoside, luteolin-7-glucuronide	[263]
Tripleurospermum perforatum	Asteraceae	luteolin, luteolin-7-glucoside	[263]
Triticum durum	Poaceae	luteolin glycosides	[502]
Trollius chinensis	Ranunculaceae	orientin	[114]
Trollius ledibouri	Ranunculaceae	orientin	[503]
Turnera diffusa	Turneraceae	luteolin 8-C-E-propenoic acid (1), luteolin 8-C-beta-[6-deoxy-2-O-(alpha-l-rhamnopyranosyl)-xylo-hexopyranos-3-uloside]	[504]
Urtica laetevirens	Urticaceae	luteolin 7-O-neohesperidoside, luteolin 7-O-beta-D: -glucopyranoside , 5-methoxyluteolin 7-O-beta-D: -glucopyranoside	[505]
Verbascum salviifolium	Scrophulariaceae	luteolin 7-O-glucoside, luteolin 3'-O-glucoside	[506]
Verbena officinalis	Verbenaceae	luteolin 7-diglucuronide	[260]
Vernoniopsis caudatawith	Asteraceae	luteolin 4'-beta-d-O-glucopyranosyl	[507]
Veronica chamaedrys	Scrophulariaceae	luteolin, apigenin, luteolin-3'-methyl ether	[508]
Veronica thymoides	Scrophulariaceae	luteolin 7-O-beta-glucopyranoside	[509]
Viola tricolor	Violaceae	luteolin-6-*C*-hexoside, luteolin-6-*C*-deoxyhexoside-8-*C*-hexoside, luteolin-6-*C*-hexoside-8-*C*-deoxyhexoside	[510]
Viola yedoensis	Violaceae	luteolin 6-C-beta-D-glucopyranoside (isoorientin), luteolin 6-C-alpha-L-arabinopyranosyl-8-C-beta-D-glucopyranoside (isocarlinoside)	[511]
Vitex agnus-castus	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]
Vitex polygama	Lamiaceae	orientin, isoorientin	[514]
Vitex rotundifolia	Lamiaceae	luteolin	[515]
Vriesea sanguinolenta	Bromeliaceae	6-hydroxyluteolin-7-O-(1''-alpha-rhamnoside)	[516]
Washingtonia filifera	Apiaceae	luteolin 7-O-glucoside 4''-sulfate (2), luteolin 7-O-glucoside 2''-sulfate	[517]
Wedelia paludosa	Asteraceae	luteolin	[518]
Youngia japonica	Asteraceae	luteolin-7-O-glucoside	[519]
Zataria multiflora	Lamiaceae	luteolin	[520]
Zostera marina	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 Aspleniaceae [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 O_2 to form two molecules of H_2O. But when a molecule of O_2 gains only one electron to form superoxide anion ($O_2^{\bullet-}$), this highly reactive oxygen species (ROS) tends to gain three more electrons and four protons to form H_2O; this process involves several reactions and results in the production of other ROS such as hydrogen peroxide (H_2O_2), hydroxyl radical ($OH^{\bullet}$) 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, cardiovascular 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, mococytes 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. Inflammatory 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 favonoids 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 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-

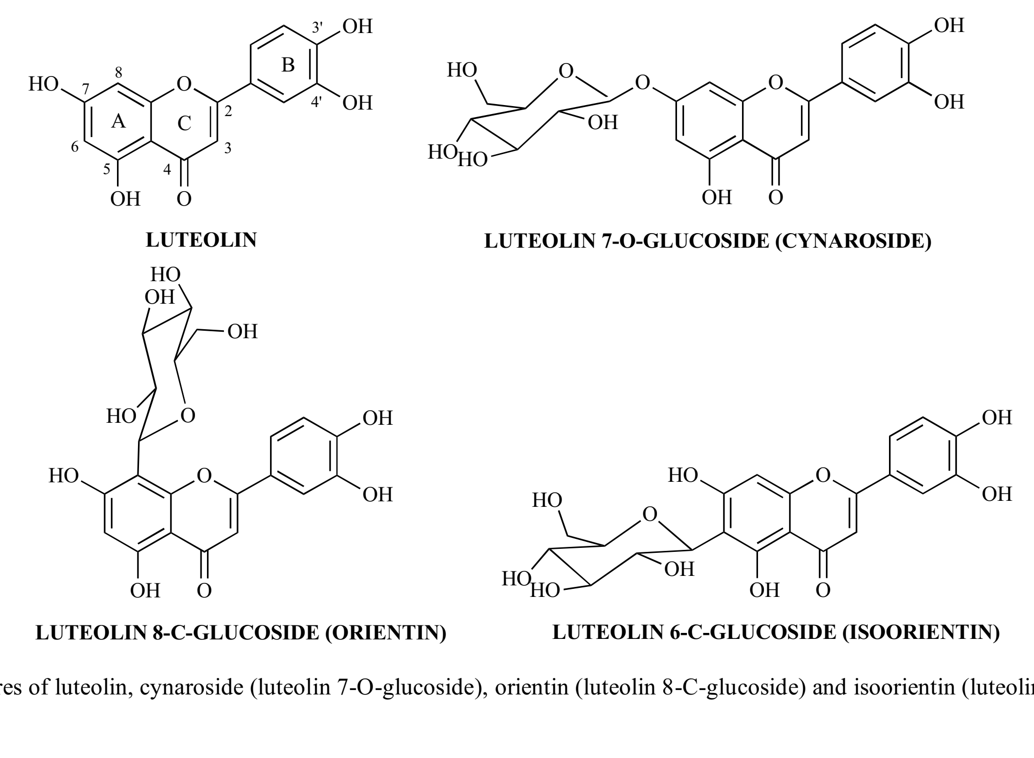

Fig. (1). Structures of luteolin, cynaroside (luteolin 7-O-glucoside), orientin (luteolin 8-C-glucoside) and isoorientin (luteolin 6-C-glucoside).

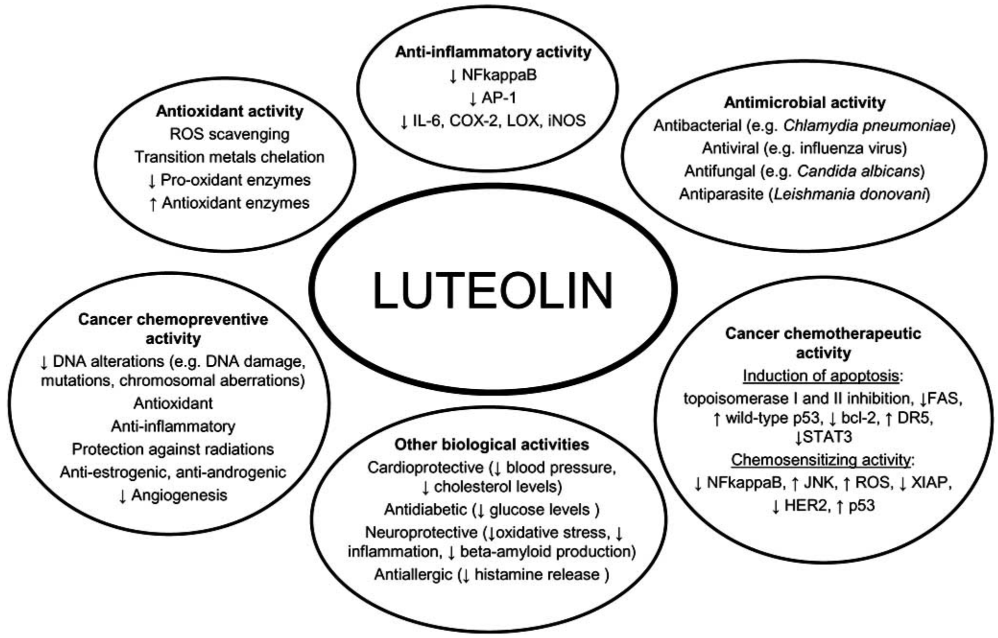

Fig. (2). Biological activities and possible mechanisms of action of luteolin.

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 μg/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 μg/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 gluthathione-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 frutenses* 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 changed 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 oncogen, 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 ($O_2^{\bullet-}$) and hydrogen peroxide (H_2O_2) [144, 145], and it has been demonstrated that an increase in the cellular levels of $O_2^{\bullet-}$ and H_2O_2 can induce cell malignant transformation [146-149]. Non-cytotoxic levels of $O_2^{\bullet-}$ 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 $O_2^{\bullet-}$- 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-1beta), 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 mouse 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 anticlastogenic 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 antiestrogenic [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}fluorodeoxyglucose (FdG PET) has shown that most primary and metastatic cancers have increased glucose consumption 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 μM 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 concentration 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 favonoids 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 μmol/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 ± 3.8 μmol/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 ± 0.15 μg/mL for luteolin and 8.34 ± 0.98 μg/mL for PHE. The time to reach the maximum plasma concentration was 1.02 ± 0.22 h for luteolin and 0.520 ± 0.05 h for PHE. The half-life of luteolin ($t_{1/2}$) was 4.94 ± 1.2 h for luteolin and 2.772 ± 0.54 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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