A Review on the Dietary Flavonoid Kaempferol

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Abstract: Epidemiological studies have revealed that a diet rich in plant-derived foods has a protective effect on human health. Identifying bioactive dietary constituents is an active area of scientific investigation that may lead to new drug discovery. Kaempferol (3,5,7-trihydroxy-2-(4-hydroxyphenyl)-4H-1-benzopyran-4-one) is a flavonoid found in many edible plants (e.g. tea, broccoli, cabbage, kale, beans, endive, leek, tomato, strawberries and grapes) and in plants or botanical products commonly used in traditional medicine (e.g. *Ginkgo biloba, Tilia spp, Equisetum spp, Moringa oleifera, Sophora japonica* and propolis). Some epidemiological studies have found a positive association between the consumption of foods containing kaempferol and a reduced risk of developing several disorders such as cancer and cardiovascular diseases. Numerous preclinical studies have shown that kaempferol and some glycosides of kaempferol have a wide range of pharmacological activities, including antioxidant, anti-inflammatory, antimicrobial, anticancer, cardioprotective, neuroprotective, antidiabetic, anti-osteoporotic, estrogenic/antiestrogenic, anxiolytic, analgesic and anti-allergic activities. In this article, the distribution of kaempferol in the plant kingdom and its pharmacological properties are reviewed. The pharmacokinetics (e.g. oral bioavailability, metabolism, plasma levels) and safety of kaempferol are also analyzed. This information may help understand the health benefits of kaempferol-containing plants and may contribute to develop this flavonoid as a possible agent for the prevention and treatment of some diseases.

Keywords: Flavonoids, antioxidant, anti-inflammatory, cancer, kaempherol, astragalin, tiliroside, kaempferitrin, robinin.

1. INTRODUCTION

Flavonoids are a group of plant secondary metabolites characterized by a diphenylpropane structure. They are widely distributed in the plant kingdom and are common constituents of fruits, vegetables and some beverages. Flavonoids may play a role in the decreased risk of chronic diseases associated with a diet rich in plant-derived foods. A positive relationship between the ingestion of foods containing flavonoids and a reduced risk of developing cancer and cardiovascular diseases has indeed been observed in some epidemiological studies [1-5]. *In vitro* and *in vivo* investigations have shown plausible mechanisms by which flavonoids may confer cancer and cardiovascular protection [6]. Evidence also suggests that certain flavonoids may be useful in the treatment of several diseases [7-12]. Some of this evidence comes from the study of plants used in traditional medicine to treat a wide range of pathologies, which has revealed that flavonoids are common bioactive constituents of these plants [10].

The flavonoid kaempferol (3,5,7-trihydroxy-2-(4-hydroxyphenyl)-4H-1-benzopyran-4-one) is a yellow compound with a low molecular weight (MW: 286.2 g/mol) that is commonly found in plant-derived foods and in plants used in traditional medicine. Although there are over two thousand articles in PubMed reporting the isolation and/or biological properties of this flavonoid, there is not any report summarizing or analyzing all this information. The purpose of this article is to review the distribution and biological activities of kaempferol. First we show a compilation of plant species and foods where kaempferol and/or glycosides of kaempferol have been identified. Then, after reviewing the epidemiological evidence linking the consumption of kaempferol-containing foods to the incidence of several diseases, we provide an overview of the pharmacological and toxicological properties of this polyphenol. Finally, we analyze the bioavailability and metabolism of kaempferol, which may help identify which of the many biological activities of this flavonoid may be relevant in an *in vivo* situation. This information may help understand the preventive and therapeutic properties of kaempferol-containing plants and may help develop this flavonoid as a possible agent for the prevention and treatment of some diseases.

2. DISTRIBUTION IN THE PLANT KINGDOM AND DIETARY SOURCES

Like other flavonoids, kaempferol has a diphenylpropane structure (C6-C3-C6) and is synthesized by condensation of 4-coumaroyl-CoA (C6-C3) with three molecules of malonyl-CoA (C6) [13, 14]. This reaction, catalyzed by the enzyme chalcone synthase (EC 2.3.1.74), results in the formation of the flavonoid naringenin chalcone (C6-C3-C6). This chalcone is transformed into the flavanone naringenin by the enzyme chalcone isomerase (EC 5.5.1.6), which catalyzes the closure of the C3 ring. The enzyme flavanone 3-dioxygenase (EC 1.14.11.9) introduces a hydroxyl group in naringenin at C3 to form dihydrokaempferol. Finally, the enzyme flavonol synthase (EC 1.14.11.23) introduces a double bond in dihydrokaempferol at C2-C3 to produce kaempferol (Fig. **1**). Because the enzymes involved in the

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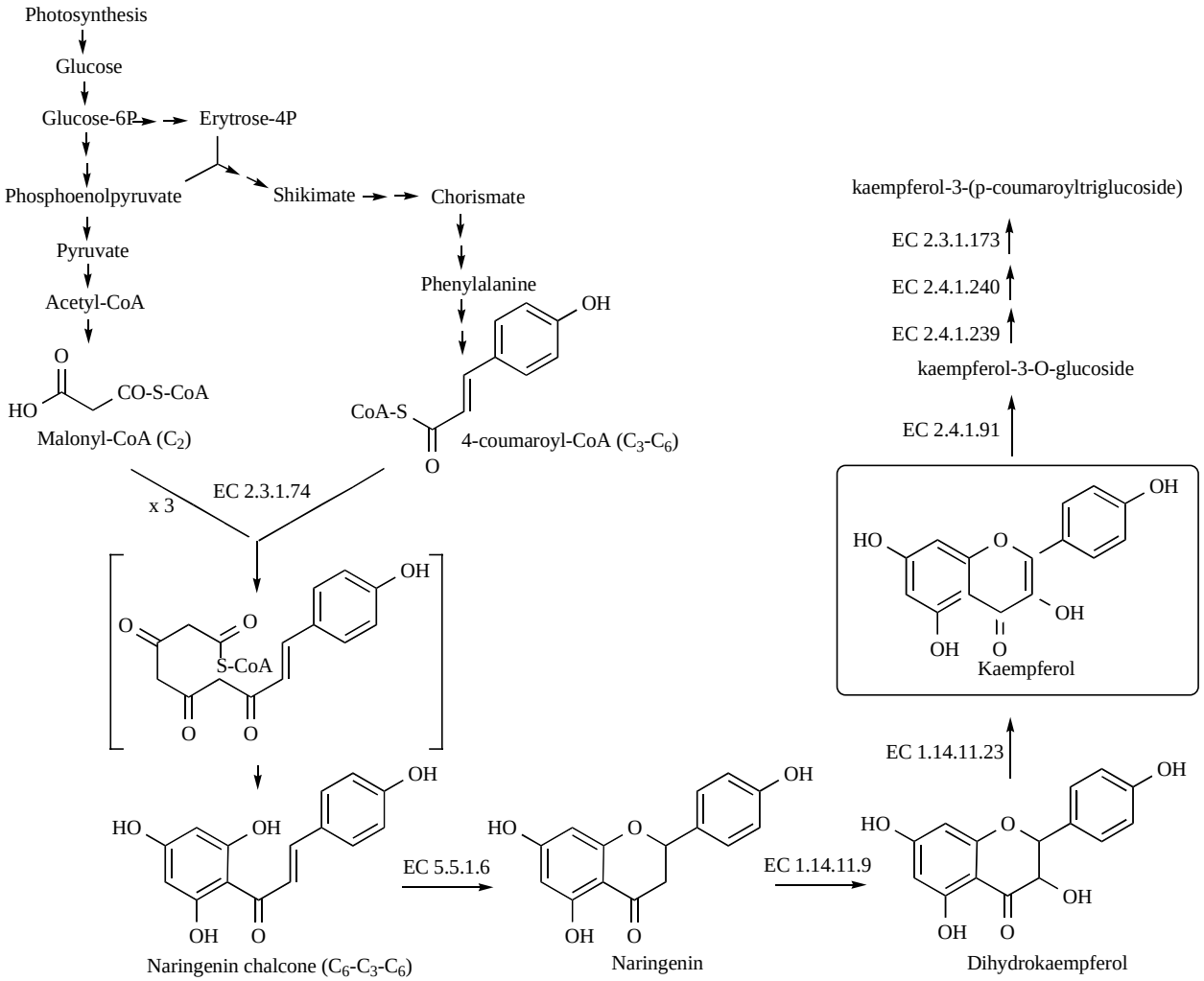

Fig. (1). Biosinthesis of kaempferol and some glycosides of kaempferol (see text for further details). EC 2.3.1.74: chalcone synthase; EC 5.5.1.6: chalcone isomerase; EC 1.14.11.9: flavanone 3-dioxygenase; EC 1.14.11.23: flavonol synthase; EC 2.4.1.91: flavonol 3-*O*-glucosyltransferase; EC 2.4.1.239: flavonol-3-O-glucoside glucosyltransferase; EC 2.4.1.240: flavonol-3-O-diglycoside glucosyltransferase; EC 2.3.1.173: flavonol-3-O-triglucoside *p*-coumaroyltransferase.

biosynthesis of kaempferol are relatively common in the plant kingdom, it is not surprising that this flavonoid is widely distributed in plants. Sugars such as glucose, rhamnose, galactose and rutinose are usually bound to kaempferol to form glycosides. Some glycosides of kaempferol are very common in nature (e.g. kaempferol-3-O-glucoside, also called astragalin), because their biosynthesis only requires additional enzymes that are widespread in the plant kingdom (e.g. flavonol 3-O-glucosyltransferase, EC 2.4.1.91). The enzymes involved in the biosynthesis of some other kaempferol glycosides are more restricted in nature and, therefore, these glycosides will only be synthesized by plant species with the genetic information required to code for such enzymes. For instance, kaempferol-3-(*p*-coumaroyltriglucoside) is not widely distributed in plants, as its biosynthesis requires the presence of three additional enzymes that are not widespread: flavonol-3-O-glucoside glucosyltransferase (EC 2.4.1.239), flavonol-3-O-diglycoside glucosyltransferase (EC 2.4.1.240) and flavonol-3-O-triglucoside *p*-coumaroyltransferase (EC 2.3.1.173). Table **1** compiles plant species in which kaempferol and/or kaempferol glycosides have been identified. This table contains over 400 plant species and shows the botanical family, the type of glycoside and the bibliographical reference. Fig. (**2**) shows the structure of kaempferol and selected glycosides of kaempferol.

Kaempferol has been identified in many botanical families and has been found in Pteridophyta, Pinophyta and Magnoliophyta. In Pteridophyta, kaempferol and/or some of its glycosides have been identified in Aspidiaceae, Aspleniaceae, Blechnaceae, Cyatheaceae, Dennstaedtiaceae, Equisetaceae, Ophioglossaceae, Polypodiaceae and Schizaeaceae (see Table **1** for references). In Pinophyta (Gymnosperms) kaempferol and its glycosides have been identified in Cephalotaxaceae [15], Ginkgoaceae [16-21] and Taxaceae [22]. In the division Magnoliophyta (Angiosperms), kaempferol has been found both in Magnoliopsida (Dicotyledons) and Liliopsida (Monocotyledons). In Monocotyledons, kaempferol has been identified in Alliaceae, Araceae, Asphodelaceae, Dioscoreaceae, Hemerocallidaceae, Hostaceae, Iridaceae,

Table 1. Plant Species that Contain Kaempferol and/or Glycosides of Kaempferol

Species	Family	Compounds	Reference
Abutilon grandiflorum	Malvaceae	Kaempferol 3-O-β-(6"-p-coumaroyl)-glucopyranoside, kaempferol 3-O-β-glucopyranoside and kaempferol 3-O-β-rutinoside	[353]
Abutilon theophrasti	Malvaceae	Kaempferol 3-O-β-(6"-p-coumaroyl)-glucopyranoside, kaempferol 3-O-β-glucopyranoside, kaempferol 3-O-α-rhamnopyranosyl-(1→6)-β-glucopyranoside and kaempferol 7-O-β-diglucoside	[354]
Acacia nilotica	Leguminosae	Kaempferol	[355]
Acaena splendens	Rosaceae	7-O-acetyl-3-O-β-D-glucosyl-kaempferol	[356]
Acalypha hispida	Euphorbiaceae	Kaempferol 3-O-rutinoside	[357]
Acanthopanax sieboldianus	Araliaceae	Kaempferol 3-O-rutinoside	[358]
Aceriphyllum rossii	Saxifragaceae	Kaempferol 3-O-β-D-glucopyranoside (astragalin) and kaempferol 3-O-α-L-rhamnopyranosyl-(1→6)-β-D-glucopyranoside	[359]
Aconitum spp	Ranunculaceae	Kaempferol 3-O-(6-trans-caffeoyl)-β-glucopyranosyl-(1→2)-β-glucopyranoside-7-O-α –rhamnopyranoside, kaempferol 3-O-(6-trans-p-coumaroyl)-β-glucopyranosyl-(1→2)-β-glucopyranoside-7-O-α-rhamnopyranoside, kaempferol 7-O-(6-trans-caffeoyl)-β-glucopyranosyl-(1→3)-α-rhamnopyranoside-3-O-β-glucopyranoside, kaempferol 7-O-(6-trans-p-coumaroyl)-β-glucopyranosyl-(1→3)-α-rhamnopyranoside-3-O- β-glucopyranoside, kaempferol 3-O-β-(2"-acetyl)galactopyranoside, kaempferol 3-O-β-(2"-acetyl)galactopyranoside-7-O-α-arabinopyranoside and kaempferol 3,7-di-O-α-rhamnopyranoside	[360]
Aconitum napellus	Ranunculaceae	Kaempferol 7-O-(6-trans-caffeoyl)-β-glucopyranosyl-(1→3)-α-rhamnopyranoside-3-O-β-glucopyranoside and kaempferol 7-O-(6-trans-p-coumaroyl)-β-glucopyranosyl-(1→3)-α-rhamnopyranoside-3-O-β-glucopyranoside	[361]
Aconitum naviculare	Ranunculaceae	3-O-[β-D-glucopyranosyl-(1→3)-(4-O-trans-p-coumaroyl)-α-L-rhamnopyranosyl-(1→6)-β-D-glucopyranosyl]-7-O-[β-D-glucopyranosyl-(1→3)-α-L-rhamnopyranosyl]kaempferol	[362]
Aconitum paniculatum	Ranunculaceae	Kaempferol 3-O-β-(2' '-acetyl)galactopyranoside and kaempferol 3-O-β-(2' '-acetyl)galactopyranoside-7-O-α-arabinopyranoside	[363]
Aconitum variegatum	Ranunculaceae	Kaempferol 3-O-β-D-galactopyranoside-7-O-α-L-arabinopyranoside and kaempferol 3-O-β-D-glucopyranoside	[364]
Actinidia valvata	Actinidiaceae	Kaempferol, kaempferol 3-O-α-L-rhamnopyranosyl-(1→3)-(2,4-di-O-acetyl-α-L-rhamnopyranosyl) (1→6) β-D-galactopyranoside, kaempferol 3-O-α-L-rhamnopyranosyl-(1→3)-(4-O-acetyl- α-L-rhamnopyranosyl)-(1→6)-β-D-galactopyranoside and kaempferol 3-O-β-D-galactopyranoside	[365]
Adina racemosa	Rubiaceae	Kaempferol 3-O-α-L –rhamnopyranosyl-(1→6)-[(4-O-trans-p-coumaroyl)-α-L -rhamnopyranosyl (1→ 2)]-(4-O-trans-p-coumaroyl)-β-D-galactopyranoside	[366]
Ailanthus excelsa	Simaroubaceae	Kaempferol 3-O-α-arabinopyranoside and kaempferol 3-O-β-galactopyranoside	[234]
Alangium salviifolium	Alangiaceae	Kaempferol and kaempferol 3-O-β-D -glucopyranoside	[367]
Albizia lebbeck	Leguminosae	Tri-O-glycoside kaempferol	[368]
Allium cepa	Alliaceae	Kaempferol	[369]

(Table 1). Contd…..

Species	Family	Compounds	Reference
Allium hirtifolium	Alliaceae	Kaempferol 3-O-β-D-rhamnopyranosyl-(1→2)-glucopyranoside, kaempferol 3-O-β-D-glucopyranosyl-(1→4)-glucopyranoside, kaempferol 3-O-glucopyranoside and kaempferol 7-O-glucopyranoside	[370]
Allium neapolitanum	Alliaceae	Kaempferol 3-O-[(2-O-α-L-rhamnopyranosyl-4-O-β-D-glucopyranosyl)-β-D-glucopyranoside]	[371]
Allium porrum	Alliaceae	Kaempferol 3-O-[2-O-(trans-3-methoxy-4-hydroxycinnamoyl)-β-D-galactopyranosyl]-(1→4)-O-β-D-glucopyranoside, kaempferol 3-O-[2-O-(trans-3-methoxy-4-hydroxycinnamoyl)-β-D-glucopyranosyl]-(1→6)-O-β-D-glucopyranoside and other kaempferol glycosides	[372]
Allium triquetrum	Alliaceae	Kaempferol glycosides	[373]
Allium ursinum	Alliaceae	Kaempferol 3-O-β-neohesperidoside-7-O-[2-O-(trans-p-coumaroyl)]-β-D- glucopyranoside, kaempferol 3-O-β-neohesperidoside-7-O-[2-O-(trans-feruloyl)]-β-D-glucopyranoside, kaempferol 3-O-β-neohesperidoside-7-O-[2-O-(trans-p-coumaroyl)-3-O-β-D-glucopyranosyl]-β-D-glucopyranoside, kaempferol 3-O-β-glucopyranoside and kaempferol 3-O-β-neohesperidoside	[374]
Allium victorialis	Alliaceae	Kaempferol 3, 4'-di-O-β-D-glucoside	[375]
Aloe vera	Asphodelaceae	Kaempferol	[376]
Alomia myriadenia	Asteraceae	Kaempferol 7-methylether (rhamnocitrin)	[377]
Alternanthera tenella	Amaranthaceae	Kaempferol	[378]
Althaea rosea	Malvaceae	Kaempferol	[379]
Amaranthus spinosus	Amaranthaceae	Kaempferol glycosides	[380]
Amburana cearensis	Leguminosae	Kaempferol	[381]
Ammi majus	Apiaceae	Kaempferol 3-O-glucoside and kaempferol 3-O-[2"-(4"-acetylrhamnosyl)-(1→2)-6"-glucosyl] glucoside	[382]
Amoora cucullata	Meliaceae	Kaempferol 3-O-β-D-glucopyranoside	[383]
Anaphalis aureopunctata	Asteraceae	Kaempferol 3-O-acetyl-6-O-(p-coumaroyl)-β-D-glucopyranoside	[384]
Annona purpurea	Annonaceae	Kaempferol 3-O-rhamnoside	[385]
Apocynum venetum	Apocynaceae	Kaempferol and kaempferol 6'-O-acetate	[290, 386]
Arabidopsis mutants	Brassicaceae	Kaempferol glycosides	[387]
Arabidopsis thaliana	Brassicaceae	Kaempferol 3-O-β-[β-D-glucopyranosyl(1→6)D-glucopyranoside]-7-O-α-L- rhamnopyranoside, kaempferol 3-O-β-D-glucopyranoside-7-O-α-L-rhamnopyranoside and kaempferol 3-O-α-L-rhamnopyranoside-7-O-α-L-rhamnopyranoside	[388]
Ardisia colorata	Myrsinaceae	Kaempferol	[389]
Ardisia japonica	Epacridaceae	Kaempferol 3-O-α-L-rhamnopyranoside and kaempferol 3,7-O-α-L-di-rhamnopyranoside	[390]
Argyreia speciosa	Convolvulaceae	Kaempferol 7-O methyl 3-sulphate	[209]
Asclepias incarnata	Asclepiadaceae	Kaempferol 3-β-glucopyranoside	[391]
Asclepias syriaca	Asclepiadaceae	Kaempferol, kaempferol 3-O-β-galactopyranoside, kaempferol 3-O-β-xylopyranosyl-(1→2)-β-galactopyranoside, kaempferol 3-O-β-glucopyranosyl-(1→2)-β-galactopyranoside and kaempferol 3-O-α-rhamnopyranosyl-(1→2)-β-galactopyranoside	[392]

(Table 1). Contd…..

Species	Family	Compounds	Reference
Asplenium prolongatum	Aspleniaceae	Kaempferol 3-O-α-L-rhamnopyranoside-7-O-[6-feruloyl- β-D-glucopyranosyl-(1→3)-α-L-rhamnopyranoside]	[393]
Asplenium trichomanes	Aspleniaceae	Kaempferol 3-O-α-[2'acetyl]-arabinofuranosyl-7-O-α-L-rhamnopyranoside	[394]
Astragalus caprinus	Leguminosae	Kaempferol 3-O-[[β-D-xylopyranosyl(1→3)-α-L-rhamnopyranosyl(1→6)][β-D-apiofuranosyl(1→2)]]-β-D-galactopyranosyl	[395, 396]
Astragalus shikokianus	Leguminosae	Kaempferol 3-O-α-L-rhamnopyranosyl -(1→6)-[α-L-rhamnopyranosyl-(1→2)]-β-D-galactopyranosyl-7-O-α L-rhamnopyranoside (astrasikokioside I) and kaempferol 3-O-α-L-rhamnopyranosyl-(1→2)-β-D-galactopyranosyl-7-O-α-L-rhamnopyranoside	[397]
Baseonema acuminatum	Asclepiadaceae	Kaempferol 3-O-(6''-galloyl)-β-D-glucopyranoside	[398]
Bauhinia forficata	Leguminosae	Kaempferol 3,7-O-α-di-rhamnoside (kaempferitrin)	[246]
Bauhinia malabarica	Leguminosae	Kaempferol and 6,8-di-C-methylkaempferol 3-methylether	[399]
Bauhinia megalandra	Leguminosae	Kaempferol 3-O-α-rhamnoside	[400]
Bauhinia microstachya	Leguminosae	Kaempferol 3-O-rhamnosyl	[401]
Bauhinia variegata	Leguminosae	Kaempferol, kaempferol 7,4'-dimethyl ether 3-O-β-D-glucopyranoside and kaempferol 3-O-β-D-glucopyranoside	[99]
Berchemia floribunda	Rhamnaceae	Kaempferol and kaempferol 3-O-α-L-arabinofuranoside	[175]
Blackstonia perfoliata	Gentianaceae	Kaempferol 3-O-α-L-rhamnopyronasyl-(1→2)-β-D-galactopyranoside and kaempferol 3-O-α-L-rhamnopyronasyl-(1→2)-β-D-galactopyranoside-7-O-β-D-glucopyranoside	[402, 403]
Blechnum novae-zelandiae	Blechnaceae	Kaempferol 3-O-β-D-glucuronopyranoside	[404]
Brassica spp	Brassicaceae	Kaempferol 3-O-β-D- sophoroside-7-O-β-D-glucoside and kaempferol 3-O-β-D-(2-sinapoylsophoroside)-7-O-β-D-glucoside	[405]
Brassica campestris	Brassicaceae	Kaempferol and kaempferol 3-O-hydroxyferuloylsophoroside-7-O-glucoside	[406]
Brassica juncea	Brassicaceae	Kaempferol 7-O-β-D-glucopyranosyl-(1→3)-[β-D-glucopyranosyl-(1→6)]-glucopyranoside	[407]
Brassica oleracea	Brassicaceae	Kaempferol and kaempferol 3-sinapoyl-di-glucoside-7-di-glucoside	[408]
Brassica rapa	Brassicaceae	Kaempferol	[409]
Bunias orientalis	Brassicaceae	Kaempferol and kaempferol glycosides	[410]
Bunium persicum	Apiaceae	Kaempferol	[411]
Bupleurum flavum	Apiaceae	Kaempferol	[412]
Calligonum comosum	Polygonaceae	Kaempferol 3-O-rhamnopyranoside and kaempferol 3-O-glucuronide	[413]
Callistemon lanceolatus	Myrtaceae	Kaempferol 3-O-β-D-galacturonopyranoside	[414]
Calluna vulgaris	Ericaceae	Kaempferol 3-O-β-D-galactoside	[85]
Camellia sinensis	Theaceae	Kaempferol 3-O-(2-O-β-D- galactopyranosyl-6-O-α-L-rhamnopyranosyl)-β-D-glucopyranoside, kaempferol 3-O-(2-O-β-D-xylopyranosyl-6-O-α-L-rhamnopyranosyl)-β-D-glucopyranoside, kaempferol 3-glucosyl-(1→3)-rhamnosyl(1→6)galactosides, kaempferol 3-O-β-D-galactopyranosyl-(1→2)-β-D-glucopyranoside and kaempferol 3-O-[2-coumaroyl-3-O-β-D-glucosyl-3-O-β-D-glucosylrutinoside]	[415-420]

(Table 1). Contd…..

Species	Family	Compounds	Reference
Campanula alliariifolia	Campanulaceae	Kaempferol 3-O-glucoside	[421]
Campanula barbata	Campanulaceae	Kaempferol 3-O-glucoside and kaempferol 3-O-rutinoside	[422]
Camptosorus sibiricus	Aspleniaceae	Kaempferol 3-O-(6-trans-caffeoyl)-β-D-glucopyranosyl-(1→2)-β-D-glucopyranoside, kaempferol 3-O-(6-trans-caffeoyl)-β-D-glucopyranosyl-(1→2)-β-D-glucopyranoside-7-O-β-D-glucopyranoside and kaempferol 3-O-(6-trans-p-coumaroyl)-β-D-glucopyranosyl-(1→2)-β-D-glucopyranoside-7-O-β-D-glucopyranoside	[423]
Canavalia gladiata	Leguminosae	Kaempferol 3-O-β-D-galactopyranosyl-7-O-α-L-rhamnopyranoside	[424]
Cannabis sativa	Cannabaceae	Kaempferol 3-O-sophoroside	[425]
Capparis spinosa	Capparaceae	Kaempferol derivatives	[46]
Carthamus lanatus	Asteraceae	Kaempferol 3-O-β-D-sophoroside	[426]
Carthamus tinctorius	Asteraceae	Kaempferol 7-O-β-D-glucopyranoside	[427]
Cassia alata	Leguminosae	Kaempferol 3-O-gentiobioside	[428, 429]
Cassia angustifolia	Leguminosae	Kaempferol	[430]
Cassia nodosa	Leguminosae	Kaempferol 3-O-rhamnoside	[431]
Cassia siamea	Leguminosae	Kaempferol	[432]
Cassipourea gummiflua	Rhizophoraceae	Kaempferol 3-O-α-L-rhamnopyranoside	[433]
Celastrus hindsii	Celastraceae	Kaempferol 3-rutinoside	[434]
Celastrus tatarinovii	Celastraceae	Heterosides derivatives of kaempferol	[435]
Centaurea hierapolitana	Asteraceae	Kaempferol 3-O-rutinoside	[436]
Centella asiatica	Apiaceae	Kaempferol and kaempferol 3-O-β-D-glucoside	[437, 438]
Cephalocereus senilis	Cactaceae	Kaempferol 7-rhamnoside, kaempferol 3-rhamnosyl-(1→6)-galactoside-7-rhamnoside and kaempferol 3-O-β-D-glucopyranosyl-(1→2)-O-[α-L-rhamnopyranosyl-(1→6)]-β-D-galactopyranoside-7-O-α-L-rhamnopyranoside	[439]
Cephalotaxus koreana	Cephalotaxaceae	Kaempferol 3-O-α-L-rhamnopyranosyl-(1'''→6")-β-D-glucopyranoside	[15]
Chenopodium murale	Chenopodiaceae	Kaempferol 3-O-[(4-β-D-apiofuranosyl)-α-L- rhamnopyranoside]-7-O-α-L-rhamnopyranoside, kaempferol 3-O-[(4-β-D-xylopyranosyl)-α-L-rhamnopyranoside]-7-O- α-L-rhamnopyranoside and kaempferol 3-O-β-D-glucopyranoside-7-O-α-L-rhamnopyranoside.	[440]
Chenopodium quinoa	Chenopodiaceae	Kaempferol 3-apiofuranosyl-(1'''→2")-rhamnopyranosyl-(1→6")-galactoside and kaempferol 3-apiofuranosyl-(1'''→2")-rhamnopyranosyl-(1''''→6")-galactoside	[441]
Chionanthus retusus	Oleaceae	Kaempferol	[442]
Chromolaena odorata	Asteraceae	Kaempferol 4'-methyl ether and kaempferol 3-O-rutinoside	[443]
Chuquiraga spinosa	Asteraceae	Kaemperol 3-O-glucuronide, kaemperol 3-O-rutinoside and kaempherol 3-O-glucoside	[444]
Cichorium endivia	Asteraceae	Kaempferol 3-O-glucoside, kaempferol 3-O-glucuronide and kaempferol 3-O-(6-O-malonyl)glucoside	[445]

(Table 1). Contd…..

Species	Family	Compounds	Reference
Cinnamomum osmophloeum	Lauraceae	Kaempferol 3-O-β-D-glucopyranosyl-(1→4)-α-L-rhamnopyranosyl-7-O-α-L-rhamnopyranoside, kaempferol 3-O-β-D-apiofuranosyl-(1→2)-α-L-arabinofuranosyl-7-O-α-L-rhamnopyranoside and kaempferol 3-O-β-D-apiofuranosy-(1→4)-α-L-rhamnopyranosyl-7-O-α-L-rhamnopyranoside	[446]
Cirsium rivulare	Asteraceae	Kaempferol 3-galactoside	[447]
Cissus sicyoides	Vitaceae	Kaempferol 3-rhamnoside	[448]
Cistus ladanifer	Cistaceae	Kaempferol 3,7-di-O-methyl, kaempferol 3-O-(6"-galloyl)-β-D-glucopyranoside and kaempferol 3-O-methyl	[449, 450]
Cistus laurifolius	Cistaceae	Kaempferol 3,7-O-dimethyl and kaempferol 3,4'-O-dimethyl	[451, 452]
Citrus aurantifolia	Rutaceae	Kaempferol 3-O-β-rutinoside, kaempferol 3-O-β-D-glucopyranoside-6"-(3-hydroxy-3-methyl glutarate) and kaempferol 3-O-β-D-glucopyranoside-6"-(3-hydroxy-3-methyl glutarate)-7-O-β-D-glucopyranoside	[453]
Clitoria ternatea	Leguminosae	Kaempferol, kaempferol 3-(2- rhamnosylrutinoside) and kaempferol 3-O-(2"-O-α-rhamnosyl-6"-O-malonyl)-β-glucoside	[454]
Cnidoscolus aconitifolius	Euphorbiaceae	Kaempferol 3-O-glycosides	[455]
Cnidoscolus chayamansa	Euphorbiaceae	Kaempferol 3-O-glycosides	[455]
Colubrina asiatica	Rhamnaceae	Kaempferol 3-O-rutinoside	[456]
Consolida oliveriana	Ranunculaceae	Kaempferol	[229]
Conyza aegyptiaca	Asteraceae	Kaempferol 3-O-β-D-glucopyranoside	[457]
Conyza filaginoides	Asteraceae	Kaempferol 3-O-(6"-O-caffeoyl)-β-D-galactopyranoside	[458]
Cornus kousa	Cornaceae	Kaempferol 3-O-rhamnoside and kaempferol 3-O-glucoside	[68]
Corylus avellana	Corylaceae	Kaempferol 3-rhamnoside	[459]
Crassocephalum crepidioides	Asteraceae	Kaempferol glycosides	[50]
Crescentia alata	Bignoniaceae	Kaempferol and kaempferol 3-O-rutinoside	[460]
Crocus antalyensis	Iridaceae	Kaempferol 3-O-β-D-(2-O-α-rhamnopyranosyl)glucopyranoside, kaempferol 3-O-β-D-(2-O-β-D-glucopyranosyl)glucopyranoside and kaempferol 3,4'-di-O-β-D-glucopyranoside	[461]
Crocus sativus	Iridaceae	Kaempferol and kaempferol 7-O-β-d-glucopyranoside	[462, 463]
Crocus speciosus	Iridaceae	Kaempferol 3-O-α-(2,3-di-O-β-D-glucopyranosyl)rhamnopyranoside and kaempferol 3-O-α-(2-O-β-D-glucopyranosyl)rhamnopyranoside	[461]
Croton cajucara	Euphorbiaceae	Kaempferol 3,4',7-trimethylether and kaempferol 3,7-dimethylether	[464]
Croton gossypifolius	Euphorbiaceae	Kaempferol 3-O-rhamnopyranoside	[465]
Crypteronia paniculata	Crypteroniaceae	Kaempferol 3-O-α-L-rhamnoside	[466]
Cudrania tricuspidata	Moraceae	Kaempferol, 6-p-hydroxybenzyl kaempferol 7-O-β-D-glucopyranoside and kaempferol 7-O-β-D-glucopyranoside	[467, 468]
Cuphea pinetorum	Lythraceae	Kaempferol	[226]
Cuscuta australis	Convolvulaceae	Kaempferol	[469]
Cuscuta chinensis	Convolvulaceae	Kaempferol	[470]
Cussonia racemosa	Araliaceae	Kaempferol rutinoside	[471]
Cyathea phalerata	Cyatheaceae	kaempferol 3-neohesperidoside	[257]

(Table 1). Contd…..

Species	Family	Compounds	Reference
Cynanchum acutum	Asclepiadaceae	Kaempferol 3-O-β-galacturonopyranoside	[252]
Cynanchum chinense	Asclepiadaceae	Kaempferol 3-O-β-D-glucopyranoside-7-O-α-L-rhamnopyranosyl and kaempferol 3-O-α-L-rhamnopyranoside-7-O-α-L-rhamnopyranosyl	[472]
Daphniphyllum calycinum	Daphniphyllaceae	Kaempferol 3-O-neohesperidoside	[473]
Datura suaveolens	Solanaceae	Kaempferol 3-O-α-L-arabinopyranosyl-7-O-β-D-glucopyranoside and kaempferol 3-O-α-L-arabinopyranoside	[474]
Delphinium gracile	Ranunculaceae	Kaempferol 3-O-[β-D-glucopyranosyl-(1→3)-4-O-(E-p-coumaroyl)-α-L-rhamnopyranosyl-(1→6)][β-D-glucopyranoside-7-O-(4-O-acetyl)-α-L-rhamnopyranoside and kaempferol 3-O-[β-D-glucopyranosyl-(1→3)-4-O-(E-p-coumaroyl)-α-D-rhamnopyranosyl (1→6)][β-D-glucopyranoside-7-O-(4-O-acetyl)-α-D-rhamnopyranoside	[475]
Dendrophthoe falcata	Loranthaceae	Kaempferol 3-O-α-L-rhamnopyranoside	[476]
Dennstaedtia scabra	Dennstaedtiaceae	Kaempferol	[477]
Derris trifoliata	Leguminosae	Kaempferol 3-O-[(6""-feruloyl)-β-D-glucopyranosyl-(1→3)]-[α-L-rhamnopyranosyl-(1→6)]-β-D-glucopyranoside, kaempferol 3-O-α-L-rhamnopyranosyl-(1→6)-β-D-glucopyranosyl-(1→3)-β-D-glucopyranoside, kaempferol 3-O-α-L-rhamnopyranosyl-(1→6)-β-D-glucopyranoside and kaempferol 3-O-α-L-rhamnopyranosyl-(1→6)-β-D-glucopyranosyl-(1→2)-β-D-glucopyranoside	[478, 479]
Dianthus barbatus	Caryophyllaceae	Kaempferol 3-O-β-D-sophoroside	[480]
Diodia teres	Rubiaceae	Kaempferol 3-O-rutinoside	[481]
Dioscorea bulbifera	Dioscoreaceae	Kaempferol 3,5-dimethyl ether	[482]
Diospyros crassiflora	Ebenaceae	Kaempherol 3-O-α-L-rhamnopyranosyl-(1→2)-β-D-glucopyranoside	[483]
Diospyros kaki	Ebenaceae	Kaempferol 3-O-(2"-O-galloyl)-glucoside, kaempferol 3-O-β-D-galactopyranoside and kaempferol 3-O-β-D-glucopyranoside	[235, 484]
Diospyros lotus	Ebenaceae	Kaempferol	[485]
Dipladenia martiana	Apocynaceae	Kaempferol, kaempferol 3-O-β-D-glucopyranoside (astragalin)	[486]
Diplotaxis erucoides	Brassicaceae	Kaempferol and kaempferol glycosides	[410]
Diplotaxis tenuifolia	Brassicaceae	Kaempferol and kaempferol glycosides	[410]
Dorycnium rectum	Leguminosae	Kaempferol-3,7-O-α-di-rhamnopyranoside, kaempferol-3-O-β-glucopyranoside-7-α-rhamnopyranoside	[487]
Draba nemorosa	Brassicaceae	Kaempferol glycosides	[488]
Dracocephalum peregrinum	Lamiaceae	Kaempferol 3-O-glucopyranoside	[489]
Drynaria fortunei	Polypodiaceae	Kaempferol 3-O-β-D-glucopyranoside-7-O-α-L-arabinofuranoside	[490]
Dryopteris crassirhizoma	Aspidiaceae	Kaempferol glycosides	[218]
Dysosma versipellis	Berberidaceae	Kaempferol	[491]
Echinops echinatus	Asteraceae	Kaempferol, kaempferol 4'-methylether, kaempferol 7-methylether and kaempferol 3-O-α-L-rhamnoside	[492]
Echites hirsuta	Apocynaceae	Kaempferol	[493]
Elateriospermum tapos	Euphorbiaceae	Kaempferol	[494]
Ellipeiopsis cherrevensis	Annonaceae	Kaempferol 3-O-rutinoside	[495]

(Table 1). Contd…..

Species	Family	Compounds	Reference
Epimedium sagittatum	Berberidaceae	Kaempferol, kaempferol 3-O-(2"-E-p-coumaroyl,4"-Z-p-coumaroyl)-α-L-rhamnopyranoside and kaempferol 3-O-(3"-Z-p-coumaroyl,4"-E-p-coumaroyl)-α-L-rhamnopyranoside	[496, 497]
Equisetum arvense	Equisetaceae	Kaempferol 3-O-glucoside	[498]
Equisetum debile	Equisetaceae	Kaempferol 3-O-sophoroside, kaempferol 3,7-O-β-D-di-glucopyranoside and kaempferol 3-O-sophoroside-7-O-β-D-glucopyranoside	[499]
Equisetum myriochaetum	Equisetaceae	Kaempferol glucosides	[248]
Equisetum palustre	Equisetaceae	Kaempferol 3-O-1"-β-D -glucopyranosyl-3-O-1"'-β-D-glucopyranoside	[500]
Eriobotrya japonica	Rosaceae	Kaempferol 3-rhamnosides	[501]
Eruca sativa	Brassicaceae	Kaempferol and kaempferol glycosides	[410]
Eucalyptus spp	Myrtaceae	Kaempferol	[502]
Eucalyptus occidentalis	Myrtaceae	6,8-di-C-methylkaempferol 3-methyl ether	[177]
Euonymus alatus	Celastraceae	Kaempferol	[260]
Euphorbia aleppica	Euphorbiaceae	Kaempferol	[503]
Euphorbia pekinensis	Euphorbiaceae	Kaempferol 3-O-(2"-O-galloyl)-β-D-glucoside	[221]
Euphorbia petiolata	Euphorbiaceae	Kaempferol 3-O-(2-O-galloyl)-glucoside, kaempferol 3-O-glucoside and kaempferol 3-O-rhamnoside	[504]
Euscaphis Japonica	Staphyleaceae	Kaempferol and kaempferol 3-O-β-D-glucopyranoside	[505]
Evolvulus alsinoides	Convolvulaceae	Kaempferol 7-O-β-glucopyranoside, kaempferol 4'-O-β-D-glucopyranosyl-(1→2)-β-D-glucopyranoside, kaempferol 4'-O-α-L-rhamnopyranosyl-(1→6)-β-D-glucopyranoside and kaempferol 3-O-β-glucopyranoside	[506, 507]
Fagonia arabica	Zygophyllaceae	Kaempferol 7-O-rhamnoside	[508]
Fagonia taeckholmiana	Zygophyllaceae	Kaempferol 3-O-glucoside, kaempferol 3,7-di-O-rhamnoside and kaempferol 3-O-β-L-arabinopyranosyl-(1→4)-α-L-rhamnopyranoside-7-O-α-L-rhamnopyranoside	[509]
Ficaria verna	Ranunculaceae	Kaempferol 3-O-β-D-(6"-α-L-rhamnopyranosyl)-glucopyranoside (nicotiflorin)	[510]
Ficus pandurata	Moraceae	Kampferol 3-O-β-neohesperidoside	[511]
Foeniculum vulgare	Apiaceae	Kaempferol 3-O-rutinoside and kaempferol 3-O-glucoside	[512]
Forsteronia refracta	Apocynaceae	Kaempferol 3-O-(2",4"-O-di-acetyl-α-L-rhamnopyranoside), kaempferol 3-O-(3",4"-O-diacetyl-α-L-rhamnopyranoside) and kaempferol 3-O-(4"-O-acetyl-α-L-rhamnopyranoside)	[513]
Fragaria ananassa	Rosaceae	Kaempferol 3-β-D-(6-O-trans-p-coumaroyl)glucopyranoside and kaempferol 3-β-D-(6-O-cis-p-coumaroyl)glucopyranoside	[514, 515]
Frankenia laevis	Frankeniaceae	Kaempferol 3,7-di-sodium sulphate	[516]
Galega officinalis	Leguminosae	Kaempferol 3-[2Gal-(4-acetylrhamnosyl)robinobioside] and kaempferol 3-(2Gal-rhamnosylrobinobioside)	[517]
Geranium bellum	Geraniaceae	Kaempferol and Kaempferol 3-O-β-D-glucopyranoside	[518]
Geranium carolinianum	Geraniaceae	Kaempferol	[519]
Geranium potentillaefolium	Geraniaceae	Kaempferol	[518]

(Table 1). Contd…..

Species	Family	Compounds	Reference
Geranium pratense	Geraniaceae	Kaempferol 3-O-β-galactopyranoside and kaempferol 3-O-β-glucopyranoside	[83]
Ginkgo biloba	Ginkgoaceae	Kaempferol, kaempferol 3-O-α-(6'''-p-coumaroylglucosyl-β-1,4-rhamnoside), kaempferol 3-O-(2''-O-β-D-glucopyranosyl)-α-L-rhamnopyranoside, kaempferol 3-O-glucosyl(1→2)rhamnoside, kaempferol 3-O-rhamnosyl-(1→2)-rhamnosyl-(1→6)-glucoside, kaempferol 3-O-α-L-[6'''-p-coumaroyl-β-D-glucopyranosyl-(1→2)-rhamnopyranoside] and kaempferol 3-O-α-L-[6'''-p-coumaroyl-β-D-glucopyranosyl-(1→2)-rhamnopyranoside]-7-O- β-D-glucopyranoside	[16-21]
Glycine max	Leguminosae	Kaempferol glycosides	[520]
Glycyrrhiza spp	Leguminosae	Kaempferol 3-O-methyl ether	[521]
Gnidia involucrata	Thymelaeaceae	Kaempferol 3-O-glucoside	[522]
Goodyera schlechtendaliana	Orchidaceae	Kaempferol 3-O-rutinoside	[523]
Grindelia robusta	Asteraceae	6-OH-kaempferol-3,6-dimethylether	[524]
Gymnema sylvestre	Asclepiadaceae	Kaempferol 3-O-β-D-glucopyranosyl-(1→4)-α-L-rhamnopyranosyl-(1→6)-β-D-galactopyranoside	[525]
Gynostemma cardiospermum	Cucurbitaceae	Kaempferol	[526]
Hedyosmum bonplandianum	Chloranthaceae	Kaempferol 3-O-[α-L-rhamnopyranosyl (1→6)-β-D-glucopyranoside] and kaempferol 3-O-[β-D-glucopyranoside]	[300]
Hedyotis diffusa	Rubiaceae	Kaempferol 3-O-(2-O-β-D-glucopyranosyl)-β-D-galactopyranoside and kaempferol 3-O-[2-O-(6-O-E-feruloyl)-β-D-glucopyranosyl]-β-D-galactopyranoside	[281]
Helichrysum italicum	Asteraceae	Kaempferol 3-O-β-D-(6''-E-p-coumaroyl)-glucopyranoside (tiliroside)	[527]
Helleborus niger	Ranunculaceae	Kaempferol 3-O-α-L-arabinopyranosyl-(1→2)-β-D-galactopyranoside-7-O-β-D-glucopyranoside	[528]
Hemerocallis spp	Hemerocallidaceae	Kaempferol 3-O-glycoside	[529]
Heterotheca inuloides	Asteraceae	Kaempferol	[530]
Hippophae rhamnoides	Elaeagnaceae	Kaempferol	[531]
Hosta ventricosa	Hostaceae	Kaempferol glycosides	[532]
Hydrangea macrophylla	Hydrangeaceae	Kaempferol oligoglycosides	[533]
Hypericum brasiliense	Clusiaceae	Kaempferol	[534]
Hypericum perforatum	Clusiaceae	Kaempferol	[535]
Ilex pernyi	Aquifoliaceae	Kaempferol 3-O-sambubioside	[536]
Impatiens balsamina	Balsaminaceae	Kaempferol, kaempferol 3-glucoside, kaempferol 3-glucosylrhamnoside, kaempferol 3-rutinoside and kaempferol 3-(p-coumaroyl)glucoside	[210, 537, 538]
Impatiens textori	Balsaminaceae	Kaempferol, kaempferol 3-glucoside and kaempferol 3-rhamnosyldiglucoside	[539]
Indigofera hebepetala	Leguminosae	Kaempferol 3-omicron-α-L-rhamnopyranosyl-(1→2)-β-D-galactopyranoside-7-O-α-L-arabinofuranoside, kaempferol 3-O-α-rhamnopyranosyl-(1→6)-β-D-galactopyranoside-7-O- α-L-arabinofuranoside, kaempferol 3-omicron-α-L-arabinopyranoside-7-O-α-L-rhamnopyranoside, kaempferol 3-O-α-L-rhamnopyranoside-7-O-α-L-arabinopyranoside and kaempferol 7-rhamnoside	[540]

(Table 1). Contd…..

Species	Family	Compounds	Reference
Indigofera suffruticosa	Leguminosae	Kaempferol	[541]
Indigofera truxillensis	Leguminosae	Kaempferol	[541]
Ixeridium gracile	Asteraceae	Kaempferol	[542]
Kalanchoe pinnata	Crassulaceae	Kaempferol 3-O-α-L-arabinopyranosyl-(1→2)-α-L-rhamnopyranoside (kapinnatoside)	[230]
Kanahia laniflora	Asclepiadaceae	Kaempferol 3-O-(6-O-α-L-rhamnopyranosyl)-β-D-glucopyranoside and kaempferol 3-O-(2,6-di-O-α-L-rhamnopyranosyl)-β-D-glucopyranoside	[543]
Kitaibelia vitifolia	Malvaceae	Kaempferol 3-O-(6"-p-coumaroyl)-β-glucoside, kaempferol 3-O-β-xylopyranosyl-(1→2)-β-glucopyranoside and kaempferol 3-O-sambubioside-7-O-glucoside	[544]
Koelreuteria henryi	Sapindaceae	Kaempferol, kaempferol 3-O-α-rhamnopyranoside and kaempferol 3-O-α-arabinopyranoside	[545, 546]
Koelreuteria paniculata	Sapindaceae	Kaempferol 3-O-arabinopyranoside and kaempferol 3-O-α-L-rhamnoside	[547]
Lactuca scariola	Asteraceae	Kaempferol	[548]
Lamium album	Lamiaceae	Kaempferol 3-O-glucoside	[549]
Lamium amplexicaule	Lamiaceae	Kaempferol 3-O-[β- D-glucopyranosyl-(1→4)][α- L-rhamnopyranosyl-(1→6)]-β- D-glucopyranoside	[550]
Laurus nobilis	Lauraceae	Kaempferol 3-O-α-L-(2",4"-di-E-p-coumaroyl)-rhamnoside and kaempferol 3-O-α-L-(2"-Z-p-coumaroyl-4"-E-p-coumaroyl)-rhamnoside	[211]
Lavatera trimestris	Malvaceae	Kaempferol 7-O-β-D-glucoside and kaempferol 3-O-β-D-glucoside	[551]
Leonurus persicus	Lamiaceae	Kaempferol 3-O-glucoside	[552]
Leptothyrsa sprucei	Rutaceae	Kaempferol 3-O-α-L-rhamnopyranoside	[553]
Licania licaniaeflora	Chrysobalanaceae	Kaempferol 3-O-α-rhamnoside	[554]
Ligustrum sinense	Oleaceae	Kaempferol 3-O-α-L-rhamnopyranosyl-7-O-β-D-glucopyranoside	[555]
Lilium candidum	Liliaceae	Kaempferol	[556]
Lilium longiflorum	Liliaceae	Kaempferol and kaempferol glycosides	[557]
Lilium pumilum	Liliaceae	Kaempferol 3-O-rutinoside	[558]
Lonicera japonica	Caprifoliaceae	Kaempferol 3-O-β-D-glucopyranoside	[559]
Loranthus tanakae	Loranthaceae	Kaempferol 3-O-α-L-rhamnoside	[165]
Lotus polyphyllos	Leguminosae	Kaempferol 3,7-di-O-glucosides and kaempferol 3-O-β-(6"-O-E-p-coumaroylglucoside)-7-O-β-glucoside	[560]
Lycium barbarum	Solanaceae	Kaempferol, kaempferol 3-O-rutinoside and kaempferol 3-O-rutinoside-7- O-glucoside	[561, 562]
Lygodium Flexuosum	Schizaeaceae	Kaempferol, kaempferol 3-β-D-glucoside	[563]
Lysimachia vulgaris	Primulaceae	Heterosides derivatives of kaempferol	[564]
Machilus philippinensis	Lauraceae	Kaempferol 3-O-α-L-rhamnopyranoside 3",4"-di-E-P-coumaroic acid ester and kaempferol 3-O-α-L-rhamnopyranoside 3"-E,4"-Z-di-p-coumaroic acid ester	[565]
Magnolia fargesii	Magnoliaceae	Kaempferol 3-O-β-D-(6"-O-coumaroyl)glucopyranoside (tiliroside)	[566]

(Table 1). Contd…..

Species	Family	Compounds	Reference
Malva crispa	Malvaceae	Kaempferol glycosides	[567]
Malus domestica	Rosaceae	Kaempferol 3-O-rhamnoside	[568]
Manihot esculenta	Euphorbiaceae	Kaempferol 3-O-rutinoside	[569]
Maytenus aquifolium	Celastraceae	Kaempferol 3-O-α-L-rhamnopyranosyl-(1→6)-O-[β-D-glucopyranosyl-(1→3)-O-α-L-rhamnopyranosyl-(1→2)-O-β-D-galactopyranoside	[570]
Maytenus ilicifolia	Celastraceae	Kaempferol 3-O-α-L-rhamnopyranosyl-(1→6)-O-[α-L-arabinopyranosyl-(1→3)-O-α-L-rhamnopyranosyl-(1→2)]-O-β-D-galactopyranoside and other kaempferol glycosides	[571]
Meconopsis spp	Papaveraceae	Kaempferol 3-O-(6-O-β-D-glucopyranosyl)-β-D-glucopyranoside and kaempferol 3-O-(6-O-β-D-glucopyranosyl)-β-D-galactopyranoside	[572]
Meconopsis quintuplinervia	Papaveraceae	Kaempferol 3-O-β-D-glucopyranoside and kaempferol 3-O-[β-D-glucopyranosyl-(1→2)-β-D-glucopyranoside]	[573]
Melastoma malabathricum	Melastomataceae	Kaempferol 3-O-(2",6"-di-O-p-trans-coumaroyl)-β-glucoside	[574]
Melilotus neapolitana	Leguminosae	Kaempferol 3-O-rutinoside and kaempferol 3-O-glucoside	[575]
Miconia cabucu	Melastomataceae	Kaempferol 3-O-β-D-(6"-coumaroyl)-glucopyranoside	[576]
Mitracarpus scaber	Rubiaceae	Kaempferol 3-O-rutinoside	[577]
Monnina sylvatica	Polygalaceae	Kaempferol 3-O-β-D-glucosyl-(1→2)-O-[α-L-rhamnosyl-(1→6)]-β-D- galactoside and other kaempferol glycosides	[578]
Morinda citrifolia	Rubiaceae	Kaempferol	[109]
Morinda morindoides	Rubiaceae	Kaempferol and kaempferol 7-O-[α-L-rhamnopyranosyl-(1→6)]-[β-D-glucopyranosyl-(1→2)]-β-D-glucopyranoside	[579-581]
Moringa oleifera	Moringaceae	Kaempferol, kaempferol 3-O-[β-glucosyl-(1→2)]-[α-rhamnosyl-(1→6)]-β-glucoside-7-O-α-rhamnoside, kaempferol 3-O-[α-rhamnosyl-(1→2)]-[α-rhamnosyl-(1→4)]-β-glucoside-7-O-α-rhamnoside and kaempferol 3-O-α-rhamnoside	[582-584]
Morus alba	Moraceae	Kaempferol 3-O-β-D-glucopyranoside (astragalin), kaempferol 3-O-(6"-O-acetyl)-β-D-glucopyranoside and kaempferol 3-O-α-L-rhamnopyranosyl-(1→6)-β-D-glucopyranoside	[585]
Morus insignis	Moraceae	Kaempferol 3-O-β-glucopyranoside	[253]
Musa spp	Musaceae	Kaempferol 3-O-rutinoside	[586]
Nelumbo nucifera	Nelumbonaceae	Kaempferol and kaempferol glycosides	[98, 587]
Neocheiropteris palmatopedata	Polypodiaceae	Kaempferol glycosides	[588]
Nepenthes gracilis	Nepenthaceae	Kaempferol	[589]
Nephelium lappaceum	Sapindaceae	Kaempferol 3-O-β-D-glucopyranoside-7-O-α-L-rhamnopyranoside	[590]
Nicotiana tabacum	Solanaceae	Kaempferol 3-rutinoside	[591]
Nymphaea candida	Nymphaeaceae	Kaempferol, kaempferol 3-O-(2"-O-galloylrutinoside), kaempferol 3-O-β-D-glucopyranoside, kaempferol 3-O-α-L-rhamnopyranoside, kaempferol 3-O-α-L-rhamnopyranosylglucopyranoside and kaempferol 7-O-β-D-glucopyranoside-3-(O-α-L-rhamnopyranosylglucopyranoside)	[282]
Nymphaea odorata	Nymphaeaceae	Kaempferol 3-O-α-l-rhamnopyranoside	[592]
Ochna beddomei	Ochnaceae	Kaempferol, kaempferol 3-O-rhamnoside and kaempferol 3-O-glucoside	[593]

(Table 1). Contd…..

Species	Family	Compounds	Reference
Ochradenus baccatus	Resedaceae	Kaempferol 3-O-β-D-glucopyranoside (astragalin)	[594]
Olea europaea	Oleaceae	Kaempferol	[595]
Ophioglossum petiolatum	Ophioglossaceae	Kaempferol	[596]
Opuntia dillenii	Cactaceae	Kaempferol 7-O-β-D-glucopyranosyl-(1→4)-β-D-glucopyranoside	[597]
Opuntia ficus-indica	Cactaceae	Kaempferol, kaempferol 3-methyl ether	[598]
Origanum dictamnus	Lamiaceae	Kaempferol	[599]
Orostachys japonicus	Crassulaceae	Kaempferol	[600]
Oxytropis falcate	Leguminosae	Kaempferol	[601]
Paeonia suffruticosa	Paeoniaceae	Kaempferol 7-O-glucoside	[602]
Papaver nudicaule	Papaveraceae	Kaempferol 3-O-β-sophoroside, kaempferol 3-O-β-sophoroside-7-O-β-glucoside and other kaempferol derivatives	[603]
Parthenocissus tricuspidata	Vitaceae	Kaempferol and kaempferol 3,5,7,4'-O-tetramethyl	[604]
Pedilanthus tithymaloides	Euphorbiaceae	Kaempferol 3-O-β-D-glucopyranoside-6"-(3-hydroxy-3-methylglutarate)	[605]
Pelargonium quercifolium	Geraniaceae	Kaempferol	[606]
Pemphis acidula	Lythraceae	Kaempferol 6"-O-galloyl-β-D-glycosides	[607]
Pentachondra pumila	Epacridaceae	Kaempferol 3-(2,4-di-E-p-coumaroylrhamnoside)	[608]
Persicaria lapathifolia	Polygonaceae	Kaempferol 3-O-β-D-(6"-p-hydroxybenzoyl)-galactopyranoside	[609]
Peumus boldus	Monimiaceae	Kaempferol glycosides	[610]
Phaleria macrocarpa	Thymelaeaceae	Kaempferol 3-O-β-D-glucoside	[611]
Phaseolus vulgaris	Leguminosae	Kaempferol 3-O-[xylosyl-(1→2)]-rhamnosyl-(1→6)-glucoside, kaempferol 3-O-glucuronide, kaempferol 3-O-β-D-glucopyranoside and kaempferol 3-O-rutinoside	[612, 613]
Phellodendron amurense	Rutaceae	Kaempferol 3-O-β-D-glucoside	[614]
Phlomis aurea	Lamiaceae	Kaempferol 3-O-β-D-glucopyranosyl-(1-6)-β-D-glucopyranoside	[615]
Phlomis caucasica	Lamiaceae	Kaempferol 3-O-glucoside	[616]
Phyllanthus acidus	Euphorbiaceae	Kaempferol	[617]
Phyllanthus emblica	Euphorbiaceae	Kaempferol 3-O-α-L-(6"-methyl)-rhamnopyranoside and kaempferol 3-O-α-L-(6"-ethyl)-rhamnopyranoside	[618]
Phytolacca americana	Phytolaccaceae	Kaempferol 3-O-β-D-glucopyranoside, kaempferol 3-O-β-D-xylopyranosyl-(1→2)-β-D-glucopyranoside, kaempferol 3-O-α-L-rhamnopyranosyl-(1→2)-β-D-glucopyranoside and kaempferol 3-O-di-glucoside	[619]
Pinus densiflora	Pinaceae	Kaempferol 3-O-β-D-glucoside and 6-C-methyl kaempferol 3-O-β-D-glucoside	[620]
Pistacia vera	Anacardiaceae	Kaempferol	[621]
Pisum sativum	Leguminosae	Kaempferol 3-sophorotrioside	[622]
Planchonia grandis	Lecythidaceae	Kaempferol	[623]
Platanus occidentalis	Platanaceae	Kaempferol 3-O-α-L-(2",3"-di-E-p-coumaroyl)rhamnoside, kaempferol 3-O-α-L-(2"-E-p-coumaroyl-3"-Z-p-coumaroyl)rhamnoside, kaempferol 3-O-α-L-(2"-Z-p-coumaroyl-3"-E-p-coumaroyl)rhamnoside and kaempferol 3-O-α-L-(2",3"-di-Z-p-coumaroyl)rhamnoside	[624]

(Table 1). Contd…..

Species	Family	Compounds	Reference
Platanus orientalis	Platanaceae	Kaempferol 3-O-α-L-(2"-E-p-coumaroyl)-rhamnopyranoside, kaempferol 3-O-β-D-(6"-E-p-coumaroyl)-glucopyranoside and kaempferol 3-O-α-L-(2",3"-di-E-p-coumaroyl)-rhamnopyranoside	[625]
Pleurospermum franchetianum	Apiaceae	Kaempferol 3,7-di-O-α-L-rhamnopyranoside and kaempferol 3-O-β-D-glucopyranosyl-7-O-α-L-rhamnopyranoside	[626]
Pogonatherum crinitum	Poaceae	Kaempferol, kaempferol 3-O-α-L-rhamnopyranoside and kaempferol 3-O-rutinoside	[627]
Polygala japonica	Polygalaceae	Kaempferol 3-gentiobioside and kaempferol glycosides	[628]
Polygonum spp	Polygonaceae	Kaempferol 3-O-glucoside-2"-gallate	[629]
Polygonum amphibium	Polygonaceae	Kaempferol 3-O-α-rhamnosyl-(1 → 2)-β-glucuronide	[630]
Polygonum salicifolium	Polygonaceae	Kaempferol 3-O-β-D-glucopyranoside (astragalin) and kaempferol 3-O-β-D-galactopyranoside	[631]
Polygonum tinctorium	Polygonaceae	Kaempferol	[208]
Polypodium decumanum	Polypodiaceae	Kaempferol glycosides	[632]
Polypodium triseriale	Polypodiaceae	Kaempferol glycosides	[632]
Pongamia pinnata	Leguminosae	Kaempferol, kaempferol 3-O-β-D-rutinoside and kaempferol 3-O-β-D-glucopyranoside	[633]
Populus davidiana	Salicaceae	Kaempferol	[634]
Potentilla argentea	Rosaceae	Kaempferol 3-O-β-D-(6"-E-p-coumaroyl)-glucopyranoside	[168]
Primula spp	Primulaceae	Kaempferol 3-O-(2-O-α-L-rhamnopyranosyl-6-O-β-D-xylopyranosyl-β-D-glucopyranoside)	[635]
Prunus amygdalus	Rosaceae	Kaempferol 3-O-α-L-rhamnopyranosyl-(1→6)-β-D-glucopyranoside	[636]
Prunus davidiana	Rosaceae	Kaempferol and kaempferol 7-O-β-D-glucoside	[637]
Prunus serotina	Rosaceae	Kaempferol 3-O-α-L-arabinofuranoside (juglanin)	[638]
Prunus serrulata	Rosaceae	Kaempferol 3-O-α-arabinofuranoside, kaempferol 3-O-β-xylopyranoside, kaempferol 3-O-β-glucopyranoside and kaempferol 3-O-β-xylopyranosyl-(1→2)-β-glucopyranoside	[639]
Prunus spinosa	Rosaceae	Kaempferol, kaempferol 3-O-α-L-arabinofuranoside, kaempferol 3-O-α-L-ramnopyranoside, kaempferol 7-O-α-L-ramnopyranoside, kaempferol 3-O-β-D-xylopyranoside, kaempferol 3,7-di-O-α-L-rhamnopyranoside and kaempferol 3-O-(2"-E-p-coumaroyl)-α-L-arabinofuranoside	[640, 641]
Prunus tomentosa	Rosaceae	Kaempferol, kaempferol 3-O-α-L-rhamnopyranoside, kaempferol 3-O-β-D-(6-acetyl)-glucopyranosyl-(1→4)-α-L-rhamnopyranoside (multiflorin A) and kaempferol 3-O-β-D-glucopyranosyl-(1→4)-α-L-rhamnopyranoside (multiflorin B)	[104]
Psidium guajava	Myrtaceae	Kaempferol	[642]
Pteridium aquilinum	Dennstaedtiaceae	Kaempferol 3-O-β-D-glucopyranoside	[643]
Pterogyne nitens	Caesalpiniaceae	Kaempferol and kaempferol 3,7-O-α-di-rhamnoside (kaempferitrin)	[644]
Punica granatum	Punicaceae	Kaempferol	[645]
Pyrenacantha staudtii	Icacinaceae	Kaempherol 3-O-β-rhamnopyranosyl-(1→6)-β-D-glucopyranoside	[646]
Pyrrosia petiolosa	Polypodiaceae	Kaempferol 3-O-β-D-glucopyranoside-7-O-α-L-arabinofuranoside	[647]

(Table 1). Contd…..

Species	Family	Compounds	Reference
Pyrus communis	Rosaceae	Kaempferol 3-O-β-D-glucopyranoside, 8-methoxykaempferol 3-O-β-D-(2"-O-α-D-glucopyranosyl)-glucopyranoside and 8-methoxykaempferol 3-O-β-D-(2"-O-α-L-rhamnopyranosyl)-glucopyranoside	[648]
Quercus dentata	Fagaceae	Kaempferol 3-O-β-D-glucopyranoside, kaempferol 3-O-(6"-trans-p-coumaroyl)-β-D-glucopyranoside, kaempferol 3-O-(2",6"-di-trans-p-coumaroyl)-β-D-glucopyranoside and kaempferol 3-O-(2",4"-di-acetyl-3"-cis-p-coumaroyl-6"-trans-p-coumaroyl)-β-D-glucopyranoside	[649]
Randia formosa	Rubiaceae	Kaempferol 3-O-rutinoside	[650]
Reseda muricata	Resedaceae	Kaempferol 3-O-β-D-glucopyranosyl-(1'"→2")-O-α-L-rhamnopyranoside 7-O-β-D-glucopyranoside and kaempferol 3-O-β-D-glucopyranosyl-(1'"→2")-O-α-L rhamnopyranoside 7-O-β-D-(6""-O-E-coumarylglucopyranoside)	[651]
Rhamnus nakaharai	Rhamnaceae	Kaempferol	[652]
Rhamnus nipalensis	Rhamnaceae	Kaempferol 4'-methylether	[653]
Rhamnus petiolaris	Rhamnaceae	Kaempferol 3-rhamninoside	[654]
Rhamnus procumbens	Rhamnaceae	Kaempferol	[655]
Rhamnus thymifolius	Rhamnaceae	Kaempferol 3-O-α-L-rhamnopyranosyl-(1→3)-(4-O-acetyl)-O-α-L-rhamnopyranosyl-(1→6)-O-β-D-galactopyranoside and kaempferol 4'-O-α-L-rhamnopyranosyl-(1→3)-O-α-L-rhamnopyranosyl-(1→6)-O-β-D-galactopyranoside	[656]
Rheum nobile	Polygonaceae	Kaempferol glycoside	[657]
Rhodiola rosea	Crassulaceae	Kaempferol	[217]
Rhodiola sachalinensis	Crassulaceae	Kaempferol, kaempferol 3-O-β-D-xylofuranosyl-(1→2)-β-D-glucopyranoside, kaempferol 7-O-α-L-rhamnopyranoside and kaempferol 3-O-β-D-glucopyranosyl-(1→2)-β-D-glucopyranoside	[658-660]
Rhus verniciflua	Anacardiaceae	Kaempferol and kaempferol 3-O-glucoside	[91]
Ribes nigrum	Grossulariaceae	Kaempferol 3-O-(6"-malonyl)glucoside	[661]
Rodgersia podophylla	Saxifragaceae	Kaempferol 3-O-α-L-5"-acetyl-arabinofuranoside and kaempferol 3-O-α-L-3"-acetyl-arabinofuranoside	[662]
Rosa spp	Rosaceae	Kaempferol	[663]
Rosa canina	Rosaceae	Kaempferol 3-O-β-D-(6"-E-p-coumaroyl)-glucopyranoside (tiliroside)	[664]
Rosa damascena	Rosaceae	Kaempferol, kaempferol 3-O-glucoside and other kaempferol glycosides	[219, 665]
Rosa hybrids	Rosaceae	Kaempferol	[438]
Rosmarinus officinalis	Lamiaceae	Kaempferol	[666]
Rubus idaeus	Rosaceae	Kaempferol, kaempferol 3-O-β-D-galactosides, kaempferol 3-O-β-L-arabinopyranoside and kaempferol 3-O-β-D-(6"-E-p-coumaroyl)-glucoside (tiliroside)	[667, 668]
Rubus sanctus	Rosaceae	Kaempferol 3-O-(6"-O-galloyl)-(4)C(1)-β-D-galactopyranoside	[669]
Rubus ulmifolius	Rosaceae	Kaempferol 3-O-β-D-glucuronide	[670, 671]
Rumex chalepensis	Polygonaceae	Kaempferol 3-rhamnosyl-(1→6) galactoside	[672]

(Table 1). Contd…..

Species	Family	Compounds	Reference
Rumex japonicus	Polygonaceae	Kaempferol 3-O-β-D-glucoside	[673]
Sageretia theezans	Rhamnaceae	Kaempferol 3-O-α-L-rhamnopyranoside	[674]
Salix raddeana	Salicaceae	Kaempferol 3-O-glucoside	[675]
Sambucus nigra	Caprifoliaceae	Kaempferol	[676]
Sanguisorba minor	Rosaceae	Kaempferol 3-O-[2'''-galloyl-O-β-glucosyl-(1'''→2'')-O-β-glucoside)] and kaempferol 3-O-mono-glycosides	[677]
Sauropus androgynus	Euphorbiaceae	Kaempferol and 3-O-β-D-glucosyl-(1→6)-β-D-glucosyl-kaempferol	[23, 244]
Scabiosa hymettia	Dipsacaceae	Kaempferol 3-O-[3- O-acetyl-6-O-(E)-p-coumaroyl]-β-D-glucopyranoside and kaempferol 3-O-β-D-glucopyranoside (astragallin)	[678]
Scopolia carniolica	Solanaceae	Kaempferol 3-O-(2-glucosyl)-galactoside-7-O-glucoside	[679]
Scopolia caucasica	Solanaceae	Kaempferol 3-O-(2-glucosyl)-galactoside-7-O-glucoside and kaempferol 3-O-(2-glucosyl)-galactoside	[680]
Scopolia lurida	Solanaceae	Kaempferol glycosides	[679]
Scopolia sinensis	Solanaceae	Kaempferol 3-O-(2-glucosyl)-galactoside-7-O-glucoside	[679]
Scrophularia ilwensis	Scrophulariaceae	Kaempferol 3-O-rutinoside	[681]
Sebastiania brasiliensis	Euphorbiaceae	Kaempferol	[682]
Securigera securidaca	Leguminosae	Kaempferol	[683]
Securinega virosa	Euphorbiaceae	Kaempferol 3-O-(4-galloyl)-β-D-glucopyranoside	[684]
Sedum dendroideum	Crassulaceae	Kaempferol 3-α-O-rhamnopyranosyl-(1→2)-β-glucopyranoside-7-O-α-glucopyranoside, kaempferol 3-O-α-rhamnopyranosyl-(1→2)-β-glucopyranoside-7-O-α-rhamnopyranoside, kaempferol 3,7-O-α-di-rhamnoside (kaempferitrin) and kaempferol 3-O-β-glucopyranoside-7-O-α-rhamnopyranoside	[302]
Sedum sarmentosum	Crassulaceae	Kaempferol 3-α-arabinopyranoside	[233]
Senecio scandens	Asteraceae	Kampferol 3-O-rhamnoside	[685]
Silphium perfoliatum	Asteraceae	Kaempferol 3-O-β-D-apiofuranoside 7-O-α-L-rhamnosyl-(1''''→6''')-O-β-D-galactopyranoside and kaempferol 3-O-β-D-apiofuranoside-7-O-α-L-rhamnosyl-(1''''→6''')-O-β-D (2'''-O-E-caffeoylgalactopyranoside)	[686]
Simarouba versicolor	Simaroubaceae	Kaempferol	[687]
Siparuna apiosyce	Monimiaceae	Kaempferol glycosides	[688, 689]
Siraitia grosvenori	Cucurbitaceae	Kaempferol 7-O-α-L-rhamnopyranoside and kaempferol 3,7-di-O-α-L-rhamnopyranoside	[690]
Smilax bockii	Smilacaceae	Kaempferol and kaempferol 7-O-β-D-glucopyranoside	[691]
Smilax china	Smilacaceae	Kaempferol 7-O-β-D-glucoside	[182, 187]
Solanum lycopersicum	Solanaceae	Kaempferol, kaempferol 3-O-sophoroside and kaempferol 3-O-rutinoside	[692-694]
Solanum nigrum	Solanaceae	Kaempferol	[695]
Solenostemma argel	Asclepiadaceae	Kaempferol 3-O-α-rhamnopyranosyl-(1→2)-β-glucopyranoside	[696]
Solidago altissima	Asteraceae	Kaempferol 3-O-β-D-apiofuranosyl-(1→6)-β-D-glucopyranoside	[697]
Solidago virga-aurea	Asteraceae	Kaempferol and kaempferol 3-O-rutinoside	[698]

(Table 1). Contd…..

Species	Family	Compounds	Reference
Sophora japonica	Leguminosae	Kaempferol, kaempferol 3-O-α-L-rhamnopyranosyl-(1→6)-β-D-glucopyranosyl-(1→2)-β-D-glucopyranoside, kaempferol 3-O-[α-L-rhamnopyranosyl-(1→6)]-[β-D-glucopyranosyl-(1→2)]-β-D-glucopyranoside, kaempferol 3-O-β-D-glucopyranosyl-(1→2)-β-D-glucopyranoside-7-O-α-L-rhamnopyranoside, kaempferol 3-O-β-rutinoside and kaempferol 3-O-α-L-rhamnopyranosyl(1→6)-β-D-glucopyranosyl(1→2)- β-D-glucopyranoside-7-O-α-L rhamnopyranoside	[699-703]
Spiraea canescens	Rosaceae	6'-O-(4''-methoxy-trans-cinnamoyl)-kaempferol-3-β-D-glucopyranoside	[704]
Spiranthes australis	Orchidaceae	Kaempferol 3-O-[[O-β-D-xylopyranosyl]-(1→2)-β-D-glucopyranosyl]-8-(p-hydroxy-benzyl) and kaempferol 3-O-[O-[2-O-(E)-p-coumaroyl-β-D-xylopyranosyl]-(1→2)-β-D-glucopyranosyl]- 8-(p-hydroxy-benzyl)	[705]
Stenochlaena palustris	Blechnaceae	Kaempferol 3-O-(3''-O-E-p-coumaroyl)-(6''-O-E-feruloyl)-β-D-glucopyranoside, kaempferol 3-O-(3'',6''-di-O-E-p-coumaroyl)-β-D-glucopyranoside, kaempferol 3-O-(3''-O-E-p-coumaroyl)-β-D-glucopyranoside, kaempferol 3-O-(6''-O-E-p-coumaroyl)-β-D-glucopyranoside and kaempferol 3-O-β-D-glucopyranoside	[706]
Stocksia brauhica	Sapindaceae	Kaempferol 3-O-[(α-L-rhamnopyranosyl)oxy]-7-O-[(acetyl)-β-D-glucopyranosyl-(1 → 4)]-[6-O-(4-hydroxy-E-cinnamoyl)-β-D-glucopyranosyl-(1→2)-α-L-rhamnopyranosyl-oxy], 3-O-{[2-O-β-D-glucopyranosyl]-3-[O-β-D-glucopyranosyl]-4-[(6-O-p-coumaroyl) -O-β-D-glucopyranosyl]}-α-L-rhamnopyranosyl-kaempferol-7-O-α-L-rhamnopyranoside and 3-O-{2-[(6-O-p-coumaroyl)-O-β-D-glucopyranosyl]-3-[O-β-D-glucopyranosyl]-4-[(6-O-p-coumaroyl)-O-β-D-glucopyranosyl]}-α-L-rhamnopyranosyl-kaempferol-7-O-α-L-rhamnopyranoside	[707, 708]
Sutherlandia frutescens	Leguminosae	Kaempferol 3-O-β-D-xylopyranosyl-(1→2)-[6- O-(3-hydroxy-3-methylglutaroyl)]-β-D-glucopyranoside and kaempferol 3-O- β- D-apiofuranosyl-(1→2)-[6-O-(3-hydroxy-3-methylglutaroyl)]-β-D-glucopyranoside	[709]
Symplocarpus renifolius	Araceae	Kaempferol 3-O-β-D-glucopyranosyl-(1→2)-β-D-glucopyranosyl-7-O-β-D-glucopyranoside	[710]
Syzygium aromaticum	Myrtaceae	Kaempferol	[711]
Tadehagi triquetrum	Leguminosae	Kaempferol	[712]
Tamarix nilotica	Tamaricaceae	Kaempferol 4'-methyl ether	[713]
Taxus baccata	Taxaceae	Kaempferol and 7-O-glucosides kaempferol	[22]
Tephrosia calophylla	Leguminosae	Kaempferol 3-O-β-D-glucopyranoside	[714]
Terminalia myriocarpa	Combretaceae	Kaempferol 3-O-β-D-rutinoside	[715]
Ternstroemia japonica	Theaceae	Kaempferol derivative	[716]
Tetrapanax papyriferus	Araliaceae	Kaempferol 7-O-(2-E-p-coumaroyl-α-L-rhamnoside) and kaempferol 7-O-(2,3-di-E-p-coumaroyl-α-L-rhamnoside)	[717]
Theobroma grandiflorum	Sterculiaceae	Kaempferol	[718]
Thesium chinense	Santalaceae	Kaempferol and kaempferol 3-O-glucoside	[719]
Thevetia peruviana	Apocynaceae	Kaempferol 3-glucosyl-(1→4)-[6'''-sinapoylglucosyl]-(1→2)-galactoside and 3-[2''''-sinapoylglucosyl]-(1→4)-[6'''-sinapoylglucosyl]-(1→2)-galactoside, kaempferol 3-[6'''-sinapoylglucosyl]-(1→2)-galactoside and kaempferol 3-glucosyl-(1→2)-galactoside	[720]

(Table 1). Contd…..

Species	Family	Compounds	Reference
Thyrocarpus glochidiatus	Boraginaceae	Kaempferol 3-O-β-D-glucoside	[721]
Tilia americana	Tiliaceae	Kaempferol glycosides	[289]
Tilia argentea	Tiliaceae	Kaempferol 3,7-O-α-di-rhamnoside and kaempferol 3-O-β-D-(6"-E-p-coumaroyl)-glucopyranoside (tiliroside)	[86, 722]
Tilia petiolaris	Tiliaceae	Kaempferol 3-O-glucoside-7-O-rhamnoside	[292]
Tilia tomentosa	Tiliaceae	Kaempferol	[723]
Tribulus terrestris	Zygophyllaceae	Kaempferol 3-gentiobioside	[724]
Trifolium alexandrinum	Leguminosae	Kaempferol	[725]
Trifolium resupinatum	Leguminosae	Kaempferol glycosides	[726]
Trigonella foenum-graecum	Leguminosae	Kaempferol 3-O-β-D-glucosyl-(1→2)-β-D-galactoside, kaempferol 3-O-β-D-glucosyl-(1→2)-β-D-galactoside 7-O-β-D-glucoside and kaempferol 3-O-β-D-glucosyl-(1→2)-(6"-O-acetyl)-β-D-galactoside-7-O-β-D-glucoside	[727]
Tulipa gesneriana	Liliaceae	Kaempferol 7-O-glucuronides	[728]
Ullucus tuberosus	Basellaceae	Kaempferol 3-O-(2",6"-di-O-α-L-rhamnopyranosil)-β-D-glucopyranoside	[729]
Uvaria tonkinensis	Annonaceae	Kaempferol 3,7-O-α-L-di-rhamnoside	[730]
Vaccinium vitis-idaea	Ericaceae	Kaempferol-pentoside, kaempferol-deoxyhexoside and kaempferol 3-O-[4"-(3-hydroxy-3-methylglutaroyl)]-α-rhamnose	[731]
Vahlia capensis	Vahliaceae	Kaempferol	[732]
Vernonia ferruginea	Asteraceae	Kaempferol 3-O-β-D-apiofuranosyl-(1→4)-β-D-glucopyranoside and kaempferol 4'-methyl ether 3-O-β-D-xylopyranoside	[733]
Vernonia travancorica	Asteraceae	Kaempferol 3-O-β-[β-(6'"-acetyl)-D-glucopyranosyl-(1→2)]-D-glucopyranosyl, 4'-methoxykaempferol, 3-O-β-D-glucopyranoside and kaempferol	[734]
Vicia faba	Leguminosae	Kaempferol 3-O-galactoside,7-O-rhamnoside	[735]
Vinca minor	Apocynaceae	Kaempferol glycosides	[736]
Viola tricolor	Violaceae	Kaempferol glycosides	[737]
Vismia laurentii	Clusiaceae	Kaempferol	[738]
Vitis rotundifolia	Vitaceae	Kaempferol glycosides	[739]
Vitis vinifera	Vitaceae	Kaempferol, kaempferol 3-glucoside, kaempferol 3-galactoside and kaempferol 3-glucuronide	[740]
Waltheria indica	Sterculiaceae	Kaempferol 3-O-β-D-(6"-O-coumaroyl)glucopyranoside (tiliroside)	[741]
Warburgia stuhlmannii	Canellaceae	Kaempferol, kaempferol 3-O-α-L-rhamnopyranoside and kaempferol 7-O-β-D-glucopyranoside	[742]
Warburgia ugandensis	Canellaceae	Kaempferol 3-O-α-rhamnoside-7,4'-di-O-β-galactoside, kaempferol 3,7,4'-tri-O-β-glucoside, kaempferol, kaempferol 3-rhamnoside, kaempferol 3-rutinoside, kaempferol 3-arabinoside, kaempferol 3-rhamnoside-4'-galactoside and kaempferol 3-glucoside	[743]
Zelkova oregoniana	Ulmaceae	Kaempferol	[744]
Zingiber aromaticum	Zingiberaceae	Kaempferol 3-O-(2,3-di-O-acetyl-α-L-rhamnopyranoside), kaempferol 3-O-(2,3,4-tri-O-acetyl-α-L-rhamnopyranoside) and kaempferol 3-O-methylether	[745, 746]

(Table 1). Contd…..

Species	Family	Compounds	Reference
Zingiber zerumbet	Zingiberaceae	Kaempferol 3,4',7-O-trimethylether, kaempferol 3-O-methylether, kaempferol 3,4'-O-dimethylether, 4''-O-acetylafzelin, kaempferol 3-O-(2,4-O-diacetyl-α-L-rhamnopyranoside) and kaempferol 3-O-(3,4-O-diacetyl-α-L-rhamnopyranoside)	[747, 748]
Zollernia ilicifolia	Leguminosae	Kaempferol 3-O-α-L-rhamnopyranosyl-(1→2)-O-[α-L-rhamnopyranosyl-(1→6)]-O-β-D-galactopyranoside-7-O-α-L-rhamnopyranoside	[749]

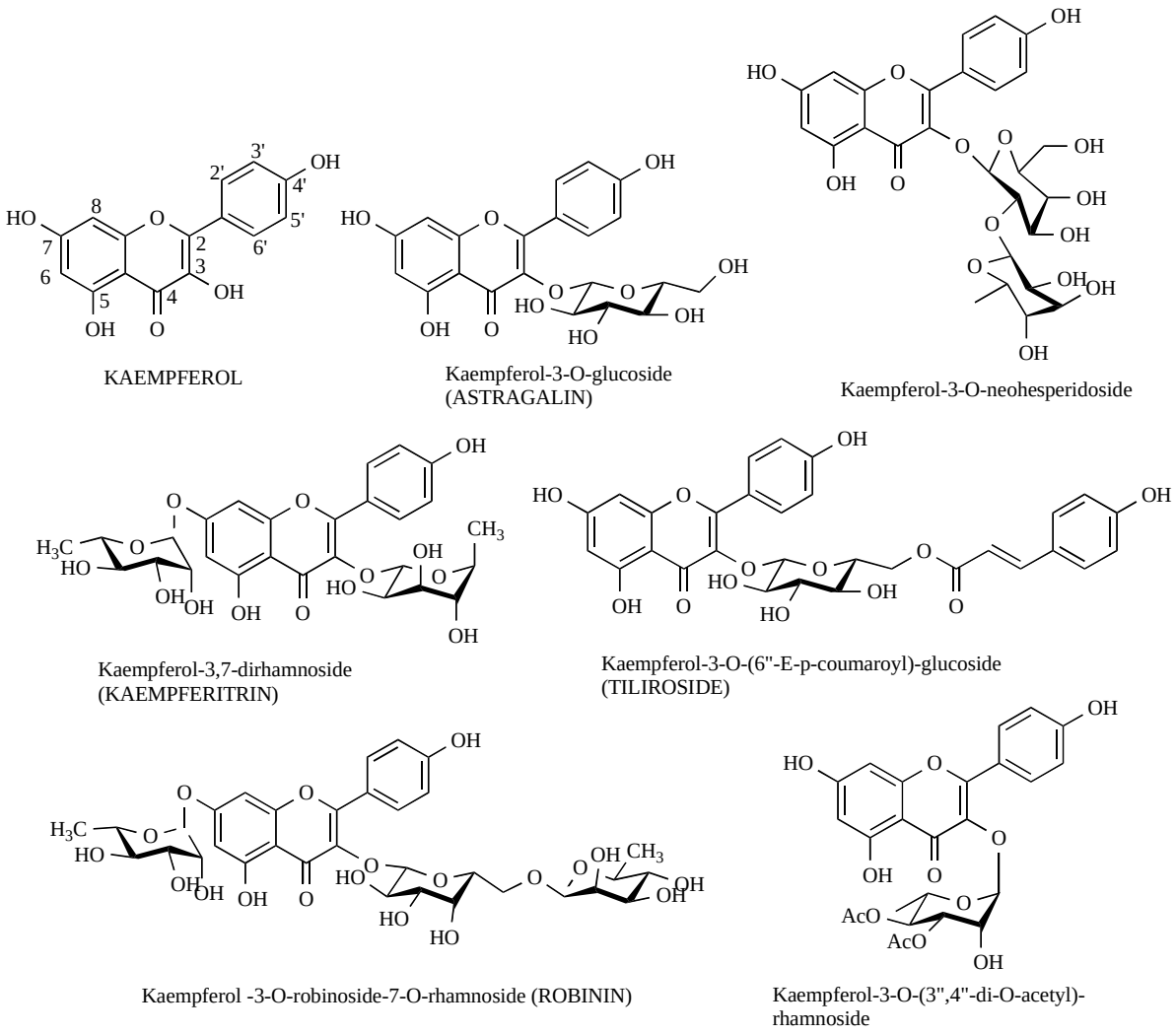

Fig. (2). Estructures of kaempferol and selected glycosides of kaempferol.

Liliaceae, Musaceae, Orchidaceae, Poaceae, Smilacaceae and Zingiberaceae (see Table **1** for references). In Dicotyledons, kaempferol has been identified in numerous families, including Actinidiaceae, Alangiaceae, Amaranthaceae, Anacardiaceae, Annonaceae, Apiaceae, Apocynaceae, Aquifoliaceae, Araliaceae, Asclepiadaceae, Asteraceae, Balsaminaceae, Basellaceae, Berberidaceae, Bignoniaceae, Boraginaceae, Brassicaceae, Cactaceae, Caesalpiniaceae, Campanulaceae, Canellaceae, Cannabaceae, Capparaceae, Caprifoliaceae, Caryophyllaceae, Celastraceae, Chenopodiaceae, Chloranthaceae, Chrysobalanaceae, Cistaceae, Clusiaceae, Combretaceae, Convolvulaceae, Cornaceae, Corylaceae, Crassulaceae, Crypteroniaceae, Cucurbitaceae, Daphniphyllaceae, Dipsacaceae, Ebenaceae, Elaeagnaceae, Epacridaceae, Ericaceae, Euphorbiaceae, Fagaceae, Frankeniaceae, Gentianaceae, Geraniaceae, Grossulariaceae, Hydrangeaceae, Lamiaceae, Lauraceae, Lecythidaceae, Leguminosae, Loranthaceae, Lythraceae, Magnoliaceae, Malvaceae, Melastomataceae, Meliaceae, Monimiaceae,

Moraceae, Moringaceae, Myrsinaceae, Myrtaceae, Nelumbonaceae, Nepenthaceae, Nyctaginaceae, Nymphaeaceae, Ochnaceae, Oleaceae, Paeoniaceae, Papaveraceae, Phytolaccaceae, Platanaceae, Polygalaceae, Polygonaceae, Primulaceae, Punicaceae, Ranunculaceae, Resedaceae, Rhamnaceae, Rhizophoraceae, Rosaceae, Rubiaceae, Rutaceae, Salicaceae, Santalaceae, Sapindaceae, Saxifragaceae, Scrophulariaceae, Simaroubaceae, Solanaceae, Staphyleaceae, Sterculiaceae, Tamaricaceae, Theaceae, Thymelaeaceae, Tiliaceae, Ulmaceae, Vahliaceae, Violaceae, Vitaceae and Zygophyllaceae (see Table **1** for references).

Kaempferol has been identified in many edible plants. It has been found in *Allium ampeloprasum* (leek), *Allium cepa* (onion), *Allium schoenoprasum* (chives), *Amaranthus lividus* (amaranth), *Angelica keiskei* (ashitaba), *Armoracia rusticana* (horseradish), *Artemisia dracunculus* (tarragon), *Atriplex hortensis* (orach), *Brassica campestris* (Chinese cabbage), *Brassica juncea* (mustard), *Brassica napobrassica* (rutabagas), *Brassica oleracea* (broccoli, brussels sprouts, green cabbage and kale), *Brassica rapa* (turnip greens), *Bunias orientalis* (Turkish rocket), *Camellia sinensis* (tea), *Capparis spinosa* (capers), *Celosia argentea* (feather cockscomb), *Cichorium endivia* (endive), *Citrus paradisi* (grapefruit), *Cnidoscolus aconitifolius* and *C. chayamansa* (tree spinach), *Coccinia grandis* (ivy gourd), *Cucumis sativus* (cucumber), *Cucurbita maxima* (squash), *Cyamopsis tetragonoloba* (cluster bean), *Diplotaxis erucoides* (wall rocket), *Diplotaxis tenuifolia* (wild rocket), *Eruca sativa* (rocket-salad), *Foeniculum vulgare* (fennel), *Fragaria vesca* (strawberry), *Houttuynia cordata* (fishwort), *Ipomoea batatas* (sweet potato), *Lactuca sativa* (lettuce), *Lepidium sativum* (cress), *Levisticum officinale* (lovage), *Lycium barbarum* and *L. chinense* (goji berries), *Malus domestica* (apple), *Momordica cochinchinensis* (gac), *Morinda citrifolia* (Indian mulberry), *Nasturtium officinale* (watercress), *Olea europaea* (olive oil), *Petroselinum crispum* (parsley), *Phaseolus vulgaris* (green beans), *Pistacia vera* (pistachio), *Prunus persica* (peach), *Raphanus sativus* (radishes), *Ribes uva-crispa* (gooseberries), *Rubus fruticosus* (blackberries), *Rubus idaeus* (raspberry), *Sambucus nigra* (elderberry), *Sauropus androgynus* (star gooseberry), *Sesbania grandiflora* (sesbania), *Solanum lycopersicum* (tomatoes), *Solanum nigrum* (nightshade), *Solanum tuberosum* (potatoes), *Spinacia oleracea* (spinach), *Vaccinium erythrocarpum, V. acrocarpon, V. microcarpum* and *V. oxycoccos* (cranberries), *Vaccinium vitis-idaea* (cowberries), *Vicia faba* (broadbeans) *Vigna unguiculata* (cowpea), *Vitis rotundifolia* (muscadine grapes) and *Vitis vinífera* (grapes) (for references, see Table **1**, "USDA database for the flavonoid content of selected foods" or ref. [23, 24]).

Kaempferol has been identified in many plant species commonly used in traditional medicine. It has been found in *Acacia nilotica, Adansonia digitata, Albizia lebbeck, Aloe vera, Amburana cearensis, Ammi majus, Angelica keiskei, Ardisia japonica, Bauhinia forficata, Bauhinia microstachya, Bunium persicum, Capparis spinosa, Cassia alata, Centella asiatica, Chromolaena odorata, Cissus sicyoides, Coccinia grandis, Crassocephalum crepidioides, Crocus sativus, Cynanchum acutum, Cynanchum chinense, Dicliptera chinensis, Equisetum arvense, Euphorbia pekinensis, Ficaria verna, Foeniculum vulgare, Galega officinalis, Ginkgo biloba, Glycine max, Grindelia robusta, Gymnema sylvestre, Helleborus niger, Hippophae rhamnoides, Houttuynia cordata, Hypericum perforatum, Impatiens balsamina, Lamium album, Laurus nobilis, Lonicera japonica, Lycium barbarum, Lycium chinense, Lysimachia vulgaris, Malva parviflora, Peumus boldus, Phyllanthus emblica, Ribes nigrum, Rosmarinus officinalis, Sambucus nigra, Sanguisorba minor, Siraitia grosvenori, Solanum nigrum, Solenostemma argel, Solidago virga-aurea, Sutherlandia frutescens, Symphytum officinale, Syzygium aromaticum, Tilia americana, Toona sinensis, Trigonella foenum-graecum, Tropaeolum majus, Vaccinium vitis-idaea, Warburgia ugandensis and Wedelia trilobata* (for references, see Table **1** or ref. [23]).

3. BIOLOGICAL ACTIVITIES OF KAEMPFEROL

3.1. Epidemiological Studies

The possible association between the consumption of foods containing kaempferol and a reduced risk of developing several disorders, including cancer and cardiovascular diseases, has been evaluated in several epidemiological studies. Some case-control (retrospective) and cohort (prospective) studies have evaluated the relationship between consumption of kaempferol-rich foods and the risk of developing several types of cancer. Cui *et al.* [25] conducted a case-control study of 558 lung cancer cases and a group of 837 controls, and observed that the consumption of kaempferol-rich foods (i.e. tea, beans, broccoli, spinach, apples and strawberries; approximately 2 mg kaempferol/day) was inversely associated with lung cancer risk (OR= 0.68; 95% CI: 0.51-0.90); this association was less clear among non-smokers. A case-control study conducted in Spain with 103 cases and 206 hospital controls also reported a positive association between high intake of kaempferol and a lower incidence of lung cancer (OR = 0.51; 95% CI: 0.22-1.17), although this association was not significant [26]. García-Closas *et al.* carried out a case-control study with 354 cases of gastric cancer and 354 controls and found that consumption of kaempferol-containing foods (i.e. onions, cruciferous, green beans, apples, grapes and strawberries) was associated with a reduced gastric cancer risk (OR = 0.48; p for trend = 0.04) [5]. Nöthlings *et al.* [27] conducted a cohort study to evaluate the possible association between consumption of kaempferol-containing foods (i.e. onions, tea, apples, cruciferous and other vegetables) and pancreatic cancer risk in 183518 people. After a follow-up period of 8 years, the authors found that kaempferol consumption was inversely associated with pancreatic cancer risk (RR = 0.78; 95% CI: 0.58-1.05; p trend: 0.017; the median intake of kaemmperol was 3.89 mg/day). The correlation between intake of kaempferol-rich foods (i.e. broccoli, kale and tea) and incidence of epithelial ovarian cancer was evaluated in a cohort study in 66940 women. The study found that kaempferol was associated with a significant 40% decrease in epithelial ovarian cancer incidence (RR = 0.60; 95% CI: 0.42-0.87; p for trend: 0.002; median intake was 11 mg kaempferol/day) [28]. This association between kaempferol

intake and ovarian cancer risk, however, was not observed in a recent case-control study with 1141 cases and 1183 controls [29].

Other epidemiological studies did not find a positive correlation between consumption of kaempferol-containing foods and the risk of several other types of cancer. A case-control study carried out with 497 cases, 547 neighborhood controls and 566 hospitals controls did not find a reduced bladder cancer risk in people consuming kaempferol-containing foods [30]. Likewise, McCann *et al.* [31] conducted a case-control study with 433 prostate cancer cases and 538 population-based controls and did not find a significant association between the consumption of kaempferol-containing foods (i.e. coffee, tea, green peppers, green beans, turnip greens, orange juice and apple juice) and a reduced prostate cancer risk (OR = 0.83; 95% CI: 0.58-1.18; p for trend: 0.80). A prospective study evaluated the association between flavonol-rich foods intake and breast cancer risk in 90630 women [32] and found a similar relative risk of developing breast cancer in the lower (0.80 mg kaempferol/day) and higher (12.9 mg kaempferol/day) quintile (MV RR = 1.01; 95% CI: 0.80-1.27; p for trend: 0.91). Lin *et al.* [33] evaluated the possible correlation between consumption of kaempferol-containing foods and the risk of colorectal cancer in a prospective study (71976 women and 35425 men) and found no association between increased intake of kaempferol and reduced colorectal cancer risk (RR = 1.12; 95% CI: 0.90-1.39; p for trend 0.25).

Several case-control and cohort studies have evaluated the relationship between consumption of kaempferol-rich foods and the risk of cardiovascular diseases. The possible correlation between flavonoid consumption (quercetin, kaempferol, myricetin, apigenin and luteolin) and mortality from coronary heart disease was studied in a cohort study in 805 men aged 65-84 years [1]. The study found that the consumption of flavonoid-containing foods (i.e. black tea, onions and apples) was associated with a reduced mortality from coronary heart disease (RR = 0.42; 95% CI; p for trend: 0.015) and with a reduced incidence of myocardial infarction (p trend: 0.08). Geleijnse *et al.* [34] conducted another cohort study in 4807 people followed-up for 5,6 years and observed that a high intake of tea (source of kaempferol) was inversely associated with myocardial infarction (RR = 0.57; 95% CI: 0.33-0.98). The correlation between intake of kaempferol-rich foods and the risk of coronary heart disease was also analyzed in a cohort study in 66360 women followed-up for 12 years [35]. This study found a weak risk reduction for coronary heart disease death among women with a higher intake of kaempferol-containing foods (i.e. broccoli, onions, grapes, apples and tea; RR = 0.66; 95% CI: 0.48-0.93; p trend: 0.04). In a cohort study with 361 men and 394 women aged 65-99 years and followed up for up to 10 years, kaempferol consumption was also associated with a significant decreased relative risk of acute myocardial infarction (RR = 0.481, 95% CI: 0.3-0.77; p trend: 0.002) [36]. The association between flavonoid-containing foods intake (i.e. apples, grapefruit, onions, white cabbage, berries, juices and oranges) and risk of several chronic diseases was assessed in a cohort study in 10054 people [37]. This study showed that the incidence of cerebrovascular disease was lower at higher kaempferol intakes (RR = 0.70; 95% CI: 0.56-0.86; p: 0.003; median intake was 0.5 mg kaempferol/day). These data suggest that consumption of foods containing kaempferol may reduce the risk of developing some cardiovascular disorders.

The correlation between the consumption of kaempferol-containing foods and the occurrence of type 2 diabetes has been studied in a cohort study [38]. This study included 38018 women aged ≥45 and free of cardiovascular disease, cancer and diabetes. Although the authors found that none of the tested flavonoids (including kaempferol) was significantly associated with risk of type 2 diabetes, they observed a reduced relative risk of type 2 diabetes in people with an increased intake of the kaempferol-containing foods apples (RR: 0.72; p for trend: 0.006) and tea (RR: 0.73; p for trend: 0.06; 95% CI).

In summary, epidemiological data suggest that a high intake of kaempferol-containing foods may reduce the risk of developing several types of cancers (e.g. lung, gastric, pancreatic and ovarian cancer) and cardiovascular diseases. But the relatively low number of studies and the possible presence of other bioactive constituents in kaempferol-containing foods (e.g. vitamins, minerals and other phytochemicals) make these data insufficient to draw any conclusion regarding the possible protective effect of kaempferol in these diseases. Numerous experimental data have shown, however, that kaempferol possesses a wide range of biological activities involved in the prevention and treatment of these and other diseases. The biological activities of kaempferol are summarized and analyzed in the following sections.

3.2. Antioxidant Activity

We breathe because our cells need oxygen to generate energy in a mitochondrial process called oxidative phosphorylation (oxphos). In this process, the generation of energy in the form of ATP is coupled with a reaction in which oxygen (O_2) is reduced to H_2O. In this reaction, 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 and peroxynitrite. The controlled production of ROS has an important physiological role [39]. A high production of ROS that is not counterbalanced by the cellular antioxidant defense, however, increases the cellular levels of ROS and 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, rheumatoid arthritis, and ageing [40, 41]. Antioxidant agents can reduce oxidative stress and may therefore play a protective role in the development of these processes.

The antioxidant properties of flavonoids are widely acknowledged [42-44]. Numerous reports have shown that kaempferol, some glycosides of kaempferol, and several

kaempferol-containing plants have antioxidant activity not only *in vitro*, but also *in vivo* [45-50]. Several studies have shown that the presence of a double bond at C2-C3 in conjugation with an oxo group at C4, and the presence of hydroxyl groups at C3, C5 and C4', are important structural features involved in the antioxidant activity of kaempferol [42, 58].

Kaempferol has been found to be a potent superoxide scavenger, with an IC_{50} of 0.5 μM [51]. The ability of kaempferol to decrease superoxide levels at low concentrations may play an important role in its antioxidant activity, as the formation of superoxide anion is required for the normal production of most reactive oxygen and nitrogen species involved in oxidative stress [52]. Superoxide anion is commonly converted into H_2O_2 by the enzymes superoxide dismutases. In the presence of reduced transition metals (e.g., ferrous or cuprous ions), H_2O_2 can be converted into the highly reactive hydroxyl radical. Superoxide anion can also react with nitric oxide to form peroxynitrite. Hydroxyl radical and peroxynitrite are highly reactive species known to cause damage to DNA, proteins and lipids. Interestingly, low concentrations of the flavonol kaempferol have been found to scavenge these two highly reactive species. Wang *et al.* [51] evaluated the antioxidant activity of several flavonoids and found that kaempferol was one of the strongest scavengers for the Fenton-generated hydroxyl radical, with an IC_{50} of 0.5 μM. Likewise, Heijnen *et al.* [53] observed that kaempferol was a potent peroxynitrite scavenger, with an IC_{50} of 0.35 ± 0.5 μM.

The ability of kaempferol to decrease superoxide anion, hydroxyl radical and peroxinitrite levels at submicromolar concentrations may play a key role in its antioxidant activity. Kaempferol has also been found to exert antioxidant effects through other mechanisms of action, although most of these effects have been observed at higher concentrations. Kaempferol can inhibit the activity of enzymes that generate ROS, such as the enzyme xanthine oxidase [51, 54, 55]. Like other flavonoids, kaempferol can also reduce the formation of hydroxyl radical through the Fenton's reaction by chelating ferrous or cuprous ions [56-58]. Kaempferol may also induce antioxidant effects by increasing the expression or activity of antioxidant enzymes such as superoxide dismutase, catalase, and heme oxygenase-1 [59-61]. Other studies have revealed that kaempferol and some glycosides of kaempferol prevent lipid peroxidation [58, 62-69]; the activity of kaempferol is higher than that of its glycosides because kaempferol has a higher lipophilia and capacity to penetrate into lipid bilayers to exert this activity. Kaempferol can also prevent the oxidation of low-density lipoprotein (LDL), which may play a protective role in atherosclerosis [70-74].

The antioxidant activity of kaempferol has been observed in several *in vivo* studies [45-50]. For instance, kaempferol was found to decrease intracellular ROS accumulation and increase the survival of *Caenorhabditis elegans* [45]. An extract of *Capparis spinosa*, which contained kaempferol derivatives, showed a significant antioxidant activity when applied topically in healthy human volunteers [46]. Sanz *et al.* [47] treated mice with kaempferol-3-O-galactoside after bromobenzene intoxication and observed that this flavonoid reduced hepatic lipid peroxidation products and increased the levels of reduced glutathione. The intraperitoneal injection of an extract of *Crassocephalum crepidioides* that contained kaempferol glycosides showed a strong antioxidant effect and prevented galactosamine- and lipopolysaccharide-induced hepatotoxicity in rats [50]. A *Ginkgo biloba* extract, containing kaempferol and quercetin derivatives, has also been reported to exert antioxidants effects *in vivo* [48].

3.3. 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 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 [75]. Like other flavonoids [76], kaempferol has anti-inflammatory properties. Numerous reports have shown that kaempferol, kaempferol glycosides and/or kaempferol-containing plants have anti-inflammatory activity not only *in vitro* but also *in vivo* [77-88].

The anti-inflammatory activity of kaempferol may be mediated by several mechanisms of action. The activation of the nuclear factor kappa B (NF-κB) increases the expression of pro-inflammatory cytokines, chemokines and enzymes (e.g. TNF-α, IL-1, IL-6, IL8, COX-2, iNOS), and several works have shown that kaempferol inhibits NF-κB activity [51, 77, 78, 90-93]. Several studies have also shown that kaempferol can inhibit TNF-α activity [94-99] and IL-1β and IL-8 expression [94, 100]. Activator protein 1 (AP-1) is a transcriptional regulator composed of members of the Fos and Jun families that participates in the inflammatory response, and kaempferol has been shown to inhibit the activation of AP-1 [96, 101]. The enzymes cyclooxygenases (COX), lipoxygenases (LOX) and inducible nitric oxide synthase (iNOS) are known to play important roles in inflammation by participating in the synthesis of eicosanoids (e.g. prostaglandins, leukotrienes) and in the production of reactive species. Some reports have shown that kaempferol can inhibit COX-2 [90, 102-107], LOX [108, 109] and iNOS [89, 90, 105, 106, 110]. ROS are also known to participate in the inflammatory process and, as shown in the previous section, kaempferol can reduce the cellular levels of ROS. In summary, numerous *in vitro* and *in vivo* studies have revealed that kaempferol has anti-inflammatory activity and have shown several mechanisms that may participate in this activity.

3.4. Anticancer Activity

Epidemiological evidence (case-control and cohort studies) suggests that the consumption of kaempferol-rich

foods may reduce the risk of developing some types of cancer, including lung cancer [25, 26], gastric cancer [5], pancreatic cancer [27] and ovarian cancer [28]. Although few studies have evaluated the anti-carcinogenic activity of kaempferol in animal models [111], numerous preclinical studies have shown that this flavonoid has cancer preventive and therapeutic properties.

The most accepted view of carcinogenesis (the somatic mutation theory of cancer) considers that cancer is caused by DNA alterations [112], and several reports suggest that low concentrations of kaempferol may protect DNA from damage induced by different carcinogens [113-116]. It is widely accepted that the formation of a malignant tumor requires that tumor cells acquire several capabilities (the so-called hallmarks of cancer), such as apoptosis resistance, increased angiogenesis, or capacity of invasion and metastasis [118, 119]. The formation of a cancer requires that tumor cells develop apoptosis resistance, and it has been observed that kaempferol can induce apoptosis [120-127]. Angiogenesis (the generation of new blood vessels) 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 kaempferol has been shown to inhibit angiogenesis *in vitro* [128-130]. It is recognized that the metastatic spread of primary tumors accounts for approximately 90% of all cancer deaths; the process by which cells from a localized tumor invade adjacent tissues and metastasize to distant organs may therefore be the most clinically relevant process involved in carcinogenesis [131]. Experimental data have revealed that kaempferol may inhibit this process *in vitro* and/or *in vivo* [93, 132-134].

Accumulating evidence suggests that reactive oxygen species (ROS) have an important role in the development of cancer. The key role of ROS in carcinogenesis is supported by experimental data showing that cancer cells commonly have increased levels of ROS, that ROS can induce cell malignant transformation and that the malignant phenotype of cancer cells can be reversed by reducing the cellular levels of ROS [135-138]. Because antioxidant agents can prevent the accumulation and/or reduce excessive cellular levels of ROS, they may play a protective role in cancer development. For instance, experimental data revealed that the expression of antioxidant enzymes in malignant cells decreased their cellular levels of ROS; these cells reverted to a normal appearance, their growth rate normalized, and they were no longer capable of producing tumors in athymic mice [137]. These data suggest that the extensively reported antioxidant activity of kaempferol may be a key mechanism by which this dietary flavonoid prevents cancer.

Several lines of research suggest that inflammation plays a significant role in cancer [139]. It is recognized that inflammatory diseases increase the risk of developing many types of cancer, including bladder, cervical, gastric, intestinal, esophageal, ovarian, prostate and thyroid cancer. Inflammatory cells, chemokines and cytokines are also present in the microenvironment of all tumors 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 tumors. In addition, the targeting of inflammatory mediators (chemokines and cytokines, such as TNF-α and IL-1β), transcription factors involved in inflammation (such as NF-κB and STAT3) or inflammatory cells decreases the incidence and spread of cancer. Non-steroidal anti-inflammatory drugs are also known to reduce the risk of developing certain cancers (such as colon and breast cancer) and reduce the mortality caused by these cancers [139]. These data suggests that the anti-inflammatory properties of kaempferol may play an important role in the cancer preventive activity of this flavonoid.

Most chemical carcinogens need to be enzymatically activated to become genotoxic, and the cytochrome P450 (P450) enzymes are the most prominent enzymes involved in such activation [140]. Some studies have shown that kaempferol may inhibit P450 [141, 142] and therefore prevent the activation of carcinogenic agents. Kaemferol has been found to decrease the activation of the naturally occurring mycotoxin aflatoxin in rats [143]. This flavonoid has also been found to act as a potent inhibitor of the aryl hydrocarbon receptor (AhR); this receptor is activated by human carcinogens present in air pollution and cigarette smoke [144]. The authors observed that kaempferol also inhibited the ability of cigarette smoke condensate to induce growth of immortalized lung epithelial cells [144]. Mukai *et al.* found that oral administration of kaempferol or *Ginkgo biloba* extract (EGb) containing 24% flavonol at 100 mg/kg body weight suppressed AhR transformation induced by 3-methylcholanthrene in the liver of mice [145]. Kaempferol has also been described as a potent non-competitive inhibitor of sulfotransferase 1A1, an enzyme capable of bioactivating procarcinogens to reactive electrophiles [146]. In addition to inhibiting several phase I enzymes, kaempferol may induce phase II detoxifying enzymes, such as quinone reductase [147]. Kaempferol has also been found to reduce the cellular levels of the carcinogen 7,12-dimethylbenz(a)-anthracene by potently stimulating the P-glycoprotein-mediated efflux of this carcinogen [148].

Hypoxia-inducible factor 1 (HIF-1) is a key regulator of O_2 homeostasis. The activation of HIF-1 is known to play a vital role in the most relevant aspects of carcinogenesis, including cell survival, angiogenesis, invasion, metastasis, cellular immortalization and metabolic reprogramming [149-151]. HIF-1 activation is observed in most human cancers and has been associated with increased patient mortality. For instance, Zhong *et al.* [152] identified increased HIF-1 expression (relative to adjacent normal tissue) in 13 tumor types, including lung, prostate, breast, and colon carcinoma, which are the most common cancers in developed countries. These data suggest that HIF-1 activation is a key event in carcinogenesis and may therefore represent a key target for cancer chemoprevention [153]. Mylonis *et al.* [154] investigated the effect of kaempferol on activity, expression levels and localization of HIF-1 in hepatoma cancer cells and found that this dietary flavonoid inhibited this transcription factor in the low micromolar range. HIF-1 was also down-regulated by kaempferol in ovary cancer cells [155].

Kaempferol has shown other activities that may be relevant to cancer chemoprevention. The ribosomal S6 kinase 2 (RSK2), a member of the p90(RSK) family of proteins, is a widely expressed serine/threonine kinase that is activated by extracellular signal-regulated kinase 1/2 and phosphoinositide-dependent kinase 1 in response to many growth factors and peptide hormones. Its activation is known to be involved in proliferation and cell transformation induced by carcinogens. Kaempferol 3-*O*-(3″,4″-di-*O*-acetyl-α-L-rhamnopyranoside), also known as compound SL0101 (Fig. **2**), was identified as the first specific inhibitor of this kinase (IC_{50} = 89 nM) and was also found to suppress proliferation of MCF-7 breast cancer cells [156]. The related compound 3Ac-SL0101 also inhibited this kinase in LNCaP prostate cancer cells [157]. This activity has also been shown by its aglycone kaempferol [158, 159]. Kaempferol can also act as a weak estrogen receptor agonist and may cause estrogenic or antiestrogenic effects mainly depending on the concentration of endogenous estrogens. The antiestrogenic (and weak estrogenic) activity of kaempferol may result in inhibition of the growth of hormone-dependent cancers such as breast and prostate cancers [160-163]. Kaempferol may also induce differentiation in colon cancer cells by re-establishing gap junctional intercellular communications, which are commonly impaired in cancer [164].

In addition to having cancer chemopreventive properties, kaempferol has shown activities that may have relevance to cancer therapy. Numerous reports have shown that kaempferol and/or some kaempferol glycosides induce cell death in a variety of cancer cells from different tissues, including lung [124, 165-167], breast [120, 122, 127, 161, 168, 169], colon [159, 165, 170, 171], prostate [120, 172, 173], liver [154, 174], pancreas [126], blood/lymph [117, 123, 175-181], skin [159, 165, 167, 176, 182, 183], esophagus [184, 185], brain [125, 165, 186], uterus [182, 187], ovary [155, 165, 188, 189], thyroid [190] and bone [121]. Many of these reports have shown that kaempferol induces cell death through apoptosis, and the possible mechanisms involved in this process have been elucidated. Caspases are a family of cysteine proteases involved in the initiation and execution of apoptosis, and kaempferol has been found to induce the activation of caspase-3 [123, 125, 166, 170, 179, 184-186, 191], caspase-7 [122, 124] and caspase-9 [122, 123, 179, 184, 185]. This flavonoid can also activate the apoptosis-inducing factor (AIF), which is involved in the initiation of a caspase-independent pathway of apoptosis [166]. Several studies have shown that kaempferol can decrease the antiapoptotic proteins Bcl-2 [123-125, 191] and Bcl-Xl [124] and increase the proapoptotic proteins Bax and Bad [122-124]. This dietary agent can also down-regulate the antiapoptotic protein X-linked inhibitor of apoptosis protein (XIAP) [186]. Poli-ADP-ribose polymerase (PARP) activation, cytochrome c release and loss of mitochondrial membrane potential are important events in the induction of apoptosis, and kaempferol has been found to stimulate PARP [123, 125, 127, 179] and induce mitocondrial cytochrome c release and loss of mitochondrial membrane potential [123, 125, 170, 179, 186]. Filomeni *et al*. [192] have recently reported that kaempferol induces energetic failure due to inhibition of both glucose uptake and complex I of the mitochondrial respiratory chain; this results in the activation of autophagy, which may prevent to some extent the capacity of kaempferol to induce apoptosis.

Several other mechanisms may participate in kaempferol-induced cancer cell death. Kaempferol-induced apoptosis in cancer cells has been associated with its ability to inhibit the activity of fatty acid synthase (FAS), a lipogenic enzyme that is activated in cancer cells [120, 193]. The enzymes DNA topoisomerases I and II are the target of several anticancer drugs commonly used in the clinic (e.g. etoposide, doxorubicin, topotecan and irinotecan), and kaempferol has been found to inhibit topoisomerase I [194] and topoisomerase II [195, 196]. Kaempferol can induce cell cycle arrest at G2/M [117, 122, 172, 183, 185, 191, 197], which may be mediated, for instance, by the inhibition of the activity of the cyclin-dependent kinase CDK1 [183]. Proteasomes are large protein complexes that degrade unneeded or damaged proteins by proteolysis; these complexes play an important function in regulating protein levels and are necessary for cell survival. Proteosoma inhibitors are a new class of anticancer agents (e.g. bortezomib) and kaempferol has been found to act as a proteasome inhibitor in human leukemia cells [198]. The antiproliferative effects of kaempferol in cancer cells may also be mediated by the inhibition of the MAPK/ERK pathway [124, 127, 186]. Finally, although low concentrations of kaempferol can reduce the cellular levels of ROS and induce antioxidant effects, higher concentrations of this flavonoid are known to generate ROS [123, 125, 179, 186]. The induction of ROS in cancer cells is emerging as an important anticancer strategy [138, 199-201] and may play an important role in the cytotoxic effects of kaempferol [123, 125, 127].

Evidence suggests that kaempferol could be used in combination with several anticancer drugs to improve their therapeutic effects. It has been reported that kaempferol can sensitize cancer cells to the cytotoxic effects of cisplatin [189], 5-fluorouracil [126], cytarabine [202], doxorubicin [125], mitoxantrone and the active metabolite of irinotecan (SN-38) [203]. This flavonoid can also enhance the cytotoxic effects of tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) [204, 205]. These investigations suggest that kaempferol may have clinical applications as adjuvant therapy in the treatment of some cancers.

3.5. Antimicrobial Activity

Flavonoids are known to play a protective role against microbial invasion in plants that synthesize these polyphenols. This protective role involves the presence of flavonoids in plants as constitutive agents as well as their accumulation as phytoalexins in response to microbial attack [206]. It is not surprising, therefore, that plants rich in flavonoids have been used for many years in traditional medicine to treat infectious diseases [207]. Kaempferol and its glycosides have been isolated from plants used in popular medicine for their antimicrobial properties. Numerous papers have reported that kaempferol, its glycosides, or plants containing kaempferol have antibacterial, antiviral, antifungal and antiprotozoal activities.

The antibacterial activity of kaempferol has been widely reported. Table **2** shows bacteria species inhibited by kaempferol and/or by glycosides of kaempferol. The antibacterial activity of this flavonol has been observed *in vivo*. Four weeks after inoculating Mongolian gerbils with *Helicobacter pylori* orally, Kataoka *et al.* administered kaempferol orally twice a day for 10 days and observed that this flavonoid significantly decreased the number of *Helicobacter pylori* colonies in the stomach of the gerbils [208]. Habbu *et al.* [209] observed that the oral administration of kaempferol-7-O-methyl-3-sulphate (2 mg/Kg, daily for 7 days) significantly increased the survival of mice infected with the bacteria *Klebsiella pneumoniae* ($p < 0.001$). Kaempferol and its glycosides can also act synergistically with antibiotics (e.g. rifampicin, vancomycin, methicillin, erythromycin and clindamycin) against antibiotic-resistant bacteria [210-212], therefore suggesting that kaempferol could be used in combination with these drugs in cases of resistance.

Kaempferol has shown anti-viral activity against several viruses, including herpes simplex virus [213-215], cytomegalovirus [216], influenza virus [217], and human immunodeficiency virus (HIV) [218, 219]. Kaempferol can inhibit the enzyme reverse transcriptase [218, 220] and it has been suggested that the hydroxyl groups at C3 and C4' are necessary for the inhibition of this enzyme [220]. This activity, along with its ability to inhibit viral proteases and binding of gp120 to lymphocytes CD4, may account for the anti-HIV activity of this flavonoid [219]. Jeong *et al.* [217] observed that some compounds isolated from *Rhodiola rosea*, including kaempferol, inhibited neuraminidase activity and showed high inhibitory activity against the influenza viral strains H1N1 and H9N2. Mitrocotsa *et al.* [216] evaluated the antiviral activity of seven kaempferol derivatives against human cytomegalovirus and observed that the presence of acyl substituents markedly increased the activity; the most active compound was kaempferol-3-O-α-L-(2",3"-di-E-p-acetylcoumaroyl)-rhamnopyranoside.

Some studies have found that kaempferol interferes with enzymes that are vital for growth or virulence of certain fungi [221-224]. Chitin is a structural polysaccharide of fungal cell walls, which is vital for its integrity and is synthesized by chitin synthase. Hwang *et al.* [221] carried out an *in vitro* study with several flavonoids and found that kaempferol and kaempferol-3-O-(2"-O-galloyl)- β-D-glucoside inhibited chitin synthase II and prevented fungal cell division. It has also been shown that kaempferol is able to inhibit melanin synthesis [223]; melanin is a virulence factor in pathogenic fungi and a known target for antimycotic compounds. Yordanov *et al.* [222] found that kaempferol affected extracellular enzymes of *Candida albicans*, which are claimed to be virulence factors responsible for penetration of the yeast into host cells. Kaempferol administration to animals with systemic *Candida albicans* infection was found to increase the number of survivors. The authors also showed that the application of kaempferol in cutaneous infection suppressed the symptoms and accelerated the elimination of the yeast from the site of inoculation [222].

Kaempferol has also been described as an antiprotozoal agent [225-228]. This flavonoid has shown activity against *Leismania* spp [229, 230] and is also active against *Entamoeba histolytica* and *Giardia lamblia* [227], which are known to cause diarrhea. The antigiardial activity of kaempferol has been observed *in vivo* in female CD-1 mice infected with *Giardia lamblia* [225].

3.6. Other Biological Activities

Several case-control and cohort studies evaluated the relationship between consumption of kaempferol-rich foods and the risk of developing or dying of cardiovascular diseases. These studies revealed that the consumption of kampferol-containing foods was associated with a reduced mortality from coronary heart disease [1] , with a weak risk reduction for coronary heart disease death [35], with a reduced incidence of myocardial infarction [1, 34, 36], and with a lower incidence of cerebrovascular disease [37]. The protective role of kaempferol in cardiovascular diseases may be mediated by different mechanisms. Because oxidative stress [231] and inflammation [232] are known cardiovascular risk factors, it makes sense to think that the known antioxidant and anti-inflammatory properties of kaempferol may play a critical role in this protective effect. The ability of kaempferol to prevent atherosclerosis may be mediated, for instance, by its capacity to prevent the oxidation of the lipoproteins LDL [70-74]. Kaempferol has also been shown to inhibit angiotensin converting enzyme (which converts angiotensin I to angiotensin II and causes an elevation of blood pressure) [233-236], to induce vasodilator effects [237-239], and to cause antiplatelet and antithrombotic effects [240, 241]. Kaempferol and some glycosides of kaempferol may also decrease triglycerides levels, cholesterol levels and/or reduce body weight [242-244].

Evidence suggests that some kaempferol glycosides and several kaempferol-containing plants have antidiabetic activity [245-254] and may prevent diabetic complications [255, 256]. For instance, studies with kaempferol-3,7-O-α-dirhamnoside (kaempferitrin) and kaempferol 3-neohesperidoside (Fig. **2**), isolated from *Cyathea phalerata* stems, showed a significant hypoglycemic effect in diabetic rats [257]. This antidiabetic effect may be mediated by stimulation of glycogen synthesis, and Cazarolli *et al.* found that the phosphatidylinositol 3-kinase (PI3K)-glycogen synthase kinase 3 (GSK-3) pathway and the MAPK-protein phosphatase 1 (PP1) pathway were involved in the stimulatory effect of kaempferol 3-neohesperidoside on glycogen synthesis in rat soleus muscle [258]. This flavonoid was also found to induce a stimulatory effect on glucose uptake when the rat soleus muscle was incubated with very low concentrations of this kaempferol glycoside (1 and 100 nM) [259]. The authors also showed that 100 mg/kg of kaempferol 3-neohesperidoside administered by oral gavage was able to increase glycogen content in the muscle, and suggested that this flavonoid stimulates glucose uptake in the rat soleus muscle *via* the PI3K and PKC pathways [259]. The oral administration of kaempferitrin has also been found to induce a significant hypoglycemic effect in normal and in alloxan-induced diabetic rats [246]. A single oral administration of two extract from the aerial parts of

Table 2. Antibacterial Activity of Kaempferol and Glycosides of Kaempferol

Species	Compound	Reference
Staphylococcus aureus	Kaempferol 3-O-[3-O-acetyl-6-O-(E)-p-coumaroyl]-β-D-glucopyranoside and kaempferol 3-O-β-D-glucopyranoside (astragalin)	[678]
	Kaempferol 7-O methyl 3- sulphate	[209]
	Kaempferol 3-O-α-L-(2",4"-di-E-p-coumaroyl)-rhamnoside and kaempferol 3-O-α-L-(2"-Z-p-coumaroyl-4"-E-p-coumaroyl)-rhamnoside	[211]
	Kaempferol 3-O-rutinoside	[577]
	Kaempferol	[212, 750]
	Kaempferol 3,7-O-α-L-di-rhamnoside	[224]
Staphylococcus epidermidis	Kaempferol 3-O-[3-O-acetyl-6-O-(E)-p-coumaroyl]-β-D-glucopyranoside and kaempferol 3-O-β-D-glucopyranoside (astragalin)	[678]
Pseudomonas aeruginosa	Kaempferol 3-O-[3-O-acetyl-6-O-(E)-p-coumaroyl]-β-d-glucopyranoside	[678]
Enterococcus faecalis	Kaempferol 7-O methyl 3- sulphate	[209]
	Kaempferol	[751]
	Kaempferol 3,7-O-α-L-di-rhamnoside	[224]
Enterobacter cloacae	Kaempferol 3-O-[3- O-acetyl-6-O-(E)-p-coumaroyl]-β-D-glucopyranoside and kaempferol 3-O-β-D-glucopyranoside (astragalin)	[678]
Escherichia coli	Kaempferol 3-O-[3-O-acetyl-6-O-(E)-p-coumaroyl]-β-D-glucopyranoside	[678]
	Kaempferol 7-O methyl 3- sulphate	[209]
	Kaempferol 3-O-(2"-O-β-D-glucopyranosyl)-α-L-rhamnopyranoside	[16]
	Kaempferol 3,7-O-α-L-di-rhamnoside	[224]
Klebsiella pneumoniae	Kaempferol 3-O-[3- O-acetyl-6-O-(E)-p-coumaroyl]-β-D-glucopyranoside and kaempferol 3-O-β-D-glucopyranoside (astragalin)	[678]
	Kaempferol 7-O methyl 3-sulphate	[209]
	Kaempferol 3,7-O-α-L-di-rhamnoside	[224]
Mycobacterium tuberculosis	Kaempferol 7-O methyl 3-sulphate	[209]
Acinetobacter baumannii	Kaempferol 3,7-O-α-L-di-rhamnoside	[224]
Bacillus subtilis	Kaempferol 3,7-O-α-L-di-rhamnoside	[224]
Porphyromonas gingivalis	Kaempferol	[711]
Prevotella intermedia	Kaempferol	[711]
Helicobacter pylori	Kaempferol	[208, 671]
Clostridium perfringens	Kaempferol 3-O-α-(6'"-p-coumaroylglucosyl-β-1,4-rhamnoside)	[16]
Vibrio cholerae	Kaempferol	[751]
Propionibacterium acnes	Kaempferol	[210]

Equisetum myriochaetum also reduced blood glucose levels in diabetic rats; the authors proposed that kaempferol-3-sophoroside-4'-O-β-D-glucoside was responsible for this activity [248]. The hypoglycemic effect of a water extract from the aerial parts of *Equisetum myriochaetum* was later evaluated in eleven type 2 diabetic patients [249]. The authors found that the oral administration of the extract (0.33 g/kg) significantly reduced blood glucose levels in these diabetic patients without significantly affecting insulin levels [249]. Fang *et al.* observed that kaempferol improved insulin-stimulated glucose uptake in mature adipocytes and suggested that this flavonoid could potentially act on multiple targets to ameliorate hyperglycemia, including the peroxisome proliferator-agonist receptor γ (PPAR γ) [260].

Kaempferol may also prevent the onset of diabetes by preventing oxidative damage in pancreatic β cells [261]. All these studies support the idea that kaempferol, several glycosides of kaempferol and/or some kaempferol-containing plants have potential to be developed as antidiabetic agents.

Phytoestrogens are a group of compounds from plant origin that share a similar structure with the estrogenic compound estradiol. These compounds can bind to the estrogen receptors and produce estrogenic effects, although these effects are weaker than those of 17β-estradiol. Because phytoestrogens compete with estrogens for the same receptors, phytoestrogens can act as estrogenic or antiestrogenic compounds mainly depending on the concentration of endogenous estrogens. When the levels of estrogens are low (e.g. after menopause), phytoestrogen act as estrogenic compounds and may relieve the menopause symptoms and cause beneficial effects on cardiovascular disease, osteoporosis, Alzheimer's disease, etc. When the levels of estrogens are not decreased, phytoestrogens act as antiestrogenic compounds and may be beneficial for preventing the development of some cancers that need estrogens for their growth, such as some breast and prostate cancers. Several reports have shown that kaempferol is a phytoestrogen that cause both estrogenic and antiestrogenic effects [161, 162, 262]. This flavonoid can bind to both subtypes of the estrogen receptor (ER), ER-α and ER-β, although it has been observed that the affinity of kaempferol for the ER-β receptor is higher than for the ER-α receptor [161, 162, 262-265]. The hydroxyl group at C-4' seems crucial for the estrogenic activity of kaempferol [266]. The antiestrogenic (and weak estrogenic) activity of kaempferol may result in inhibition of the growth of homone-dependent cancers such as breast and prostate cancers [160-163]. The estrogenic effects of kaempferol may be beneficial for women after menopause, when estrogen levels fall. It has been reported that kaempferol potentiated the uterotrophic effect of 17β-estradiol in immature and ovariectomized rats [267] and increased sensitivity of the uterus to estrogens in immature female mice [268].

Kaempferol may exert a protective effect against post-menopausal bone loss, as it has been found to promote osteoblast mineralization *in vitro* and bone formation *in vivo* [269-274]. Wattel *et al.* [269] observed that kaempferol, at concentrations ranging from 100 nM to 100 μM reduced bone resorption in a time and dose-dependent manner. The authors observed significant inhibitory effects at concentrations as low as 100 nM and reported data suggesting that the estrogenic activity of kaempferol could be involved in the inhibition of bone resorption [269]. Trivedi *et al.* [270] reported that kaempferol increased mineralized nodules in rat primary osteoblasts at concentrations from 0.2 to 5 μM. Daily oral administrations of kaempferol (5 mg/kg body weight) for 10 weeks to ovariectomized rats resulted in significantly higher bone mineral density (BMD) in the trabecular regions (femur neck, proximal tibia and vertebrae) and lower serum ALP (a bone turnover marker). Kaempferol treatment also caused an increase in osteoprogenitor cells as well as a reduction of adipocyte differentiation from bone marrow cells. The authors concluded that kaempferol exerts bone anabolic activity with attendant inhibition of bone marrow adipogenesis [270]. An extract of *Ginkgo biloba*, which contains kaempferol glycosides, was also found to restore bone mass in aged ovariectomized rats [271].

Some *in vitro* and *in vivo* studies suggest that kaempferol, some glycosides of kaempferol and plants containing this flavonoid may have neuroprotective activity and play a protective role in the development of Alzheimer's disease, Parkinson's disease or Huntington's disease [275-283]. For instance, Lopez-Sanchez *et al.* [275] carried out an *in vivo* study to evaluate the neuroprotective effect of kaempferol and found that the intravenous administration of this dietary agent decreased ischemia-induced brain damage in rats. This protective effect was associated with the capacity of kaempferol to reduce metalloproteinase activation, to prevent protein nitrotyrosines accumulation and to protect against apoptotic cell death caused by oxidative stress [275]. Because oxidative stress is known to play an important role in some neurodegenerative disorders [40, 41] it makes sense to think that the antioxidant activity of kaempferol participates in its neuroprotective activity [284]. Other mechanisms, such as reduction in amyloid β protein, may participate in the possible protective effect of kaempferol against Alzheimer's disease [279, 285-287].

Several reports suggest that kaempferol, glycosides of kaemperol such as tiliroside (Fig. **2**) and several kaempferol-containing plants (e.g. *Tilia* species) have anxiolytic activity *in vivo* [288-292]. *In vitro* and *in vivo* studies have also reported that kaempferol have antiallergic and antiasthmatic activity [84, 97, 293-298], which may be mediated, at least in part, by inhibition of histamine release [97, 293, 294]. Analgesic activity has also been observed with several kaempferol glycosides and kaempferol-containing plants in numerous *in vivo* studies [79, 83, 85-88, 299-302].

Okamoto *et al.* [303] reported data suggesting that kaempferol could be useful for the treatment of cell mediated immune diseases, such as acute graft-versus-host disease (GVHD). The authors found that kaempferol acted directly on T cells and inhibited Th1 cytokine production, thus suppressing the expansion and generation of $CD8^+$ cytotoxic T-lymphocytes *in vitro*. They also observed that C57BL/6-into-BDF1 mice treated with kaempferol for 1 week after acute GVHD induction showed reduced GVHD-associated anti-host CTL activity, induction of Th2 cell development, and host repopulation with donor lymphocytes, resulting in early restoration of body weight and increased survival [303]. Cortés *et al.* found that kaempferol inhibited IL-4-induced STAT6 activation by specifically targeting the tyrosine kinase JAK3 [304]. The authors discussed that this inhibitory effects of kaempferol could be useful in controlling T cell-dependent responses mediated by JAK3-dependent cytokines, and that the specific inhibition of JAK3 would result in a T cell immune suppression that could be useful in lymphoproliferative diseases with JAK3 abnormalities and in transplant rejection [304].

4. PHARMACOKINETICS

Numerous *in vitro* studies have revealed that kaempferol has a wide range of biological activities. Some of these

activities, however, may not be relevant in an *in vivo* setting if this flavonoid does not reach the target tissues at specific concentrations for a particular period of time. In other words, a low bioavailability and/or a high metabolism of kaempferol may be an obstacle for kaempferol to induce some bioactivities *in vivo*. Since kaempferol is a common dietary constituent and since the oral route is the preferred route of administration for most drugs, it is important to understand the fate of this flavonoid in the body when taken orally.

The pharmacokinetics of kaempferol has been studied *in vitro* and *in vivo*, both in rats and humans. An overview of the pharmacokinetics of kaempferol is illustrated in Fig. (**3**). Flavonols such as kaempferol are commonly ingested as glycosides. It is recognized that the high polarity of glycosides hinders their absorption, whereas the intermediate polarity of aglycones facilitates it. Although this suggests that the absorption of glycosides needs the previous hydrolysis to absorbable aglycones, studies have shown that glycosides can be absorbed without hydrolysis [305-307]. Like other flavonoids, kaempferol is mainly absorbed in the small intestine. The lipophilicity of kaempferol facilitates its absorption by passive diffusion, but evidence suggests that it can also be absorbed by facilitated diffusion or active transport [308]. Kaempferol can be metabolized in the small intestine (to glucuronides and sulfoconjugates) by intestinal conjugation enzymes [308]. Like other flavonoids, kaempferol glycosides and kaempferol are extensively metabolized by the colon microflora. The colonic bacteria can both hydrolyze the glycosides to aglycones and break the C3 ring of aglycones to form simple phenolic compounds such as 4-hydroxyphenylacetic acid, phloroglucinol and 4-methylphenol, which can either be absorbed or excreted in feces [307, 309-314]. After absorption, kaempferol is extensively metabolized in the liver to form glucurono- and sulfo-conjugated forms [308, 315, 316]. These conjugated forms of kaempferol, some phenolic compounds produced by the colon microflora, kaempferol and some kaempferol glycosides can reach systemic circulation and tissues and are then excreted in urine [270, 317-323]. The percentage of kaempferol excreted in urine has been found to be 1.9% [318] and 2.5% [321] of the total amount of kaempferol ingested.

Several human studies have demonstrated that, after oral ingestion, kaempferol is detected in plasma at nanomolar concentrations. Eight healthy volunteers received endive as a source of kaempferol (246 mg kaempferol/kg endive) [318]. A portion of endive, which contained 8.65 mg kaempferol in the form of kaempferol-3-glucuronide (79%), kaempferol-3-glucoside (14%) and kaempferol-3-(6-malonyl)-glucoside (7%), led to a mean maximum plasma concentration of 100 nM 5.8 h after oral ingestion. Radket *et al.* [322] measured the plasma concentrations of several flavonoids in 48 healthy women and found that the mean intake of kaempferol was 4.7 mg/day and that the corresponding mean plasma concentration was 10.7 nM. Cao *et al.* [324] undertook a dietary intervention study and reported that an estimated intake of 14.97 mg kaempferol/day led to a plasma concentration of 57.86 nM. An intake of 27 mg kaempferol from tea has also been reported to lead to a plasma concentration of 15 ng/ml (52 nM) [321].

Some studies have found interconversions between kaempferol (3,5,7,4'-tetrahydroxyflavone) and the flavonoids galangin (3,5,7-trihydroxyflavone) and quercetin (3,5,7,3',4'-pentahydroxyflavone). Galangin can be transformed to kaempferol by rat cytochrome P450 (CYP) *via* hydroxylation of the B-ring at C3' [325]. Nielsen *et al.* [326] found that kaempferol was metabolized to quercetin and that this effect was probably mediated by the enzymes CYP1A. Similar findings were reported by Breinholt *et al.* [327]. These data suggest that the biological activities of kaempferol could be observed after galangin ingestion, and that some of the effects induced by kaempferol *in vivo* might be mediated in part by quercetin, which is known to have a wide rage of biological activities [328, 329].

As discussed previously, rodent and human studies have shown that the concentrations of kaempferol achieved in plasma and tissues after oral ingestion are in the nanomolar range. Although kaempferol has shown biological activities in this range, most of the effects described in the literature come from *in vitro* studies in which kaempferol was tested at micromolar concentrations. This suggests that, outside of the gastrointestinal tract, these effects may not be relevant in an *in vivo* setting when kaempferol is taken orally. Many *in vivo* studies discussed in this review have found, however, that kaempferol has different biological activities outside of the gastrointestinal tract when administered orally (e.g. antioxidant, anti-inflammatory, analgesic, antidiabetic, anticancer, etc). For instance, a recent study by Huang *et al.* [121] found that kaempferol inhibited the growth and induced apoptosis in human osteosarcoma U-2 OS cells *in vitro*, with an IC_{50} of approximately 150 μM. The authors then observed that the oral administration of 25 or 50 mg/kg of kaempferol significantly reduced tumor weights and volumes in BALB/c (nu/nu) mice subcutaneously injected with U-2 OS cells [121]. Because the oral bioavailability of kaempferol is low, it is unlikely that the oral administration of kaempferol can lead to a concentration close to 150 μM in the U-2 OS cancer cells placed under the skin of the mice. This suggests that the tumor growth inhibition observed in mice after the oral administration of kaempferol [121] may be caused by metabolites of kaempferol or by an unknown indirect effect. The low oral bioavailability of kaempferol may be overcome by using alternative routes of administration, such as the i.v. route [275].

5. SAFETY

There are conflicting reports regarding the safety of kaempferol. For example, although some studies have shown kaempferol to induce antimutagenic activity [114, 115, 330-332], other reports have revealed that this flavonoid may induce genotoxic effects [117, 333-341]. The prooxidant activity of kaempferol may play an important role in these genotoxic effects. Although flavonoids are known antioxidants, these compounds can also act as prooxidant agents under specific conditions [56]. By hydrogen atom donation, a flavonoid can reduce a free radical and be transformed in a phenoxyl radical. This phenoxyl radical may either react with a second radical becoming stable (antioxidant effect), or interact with oxygen resulting in the generation of ROS (prooxidant effect) [44]. The prooxidant effects of flavonoids have also been attributed to their

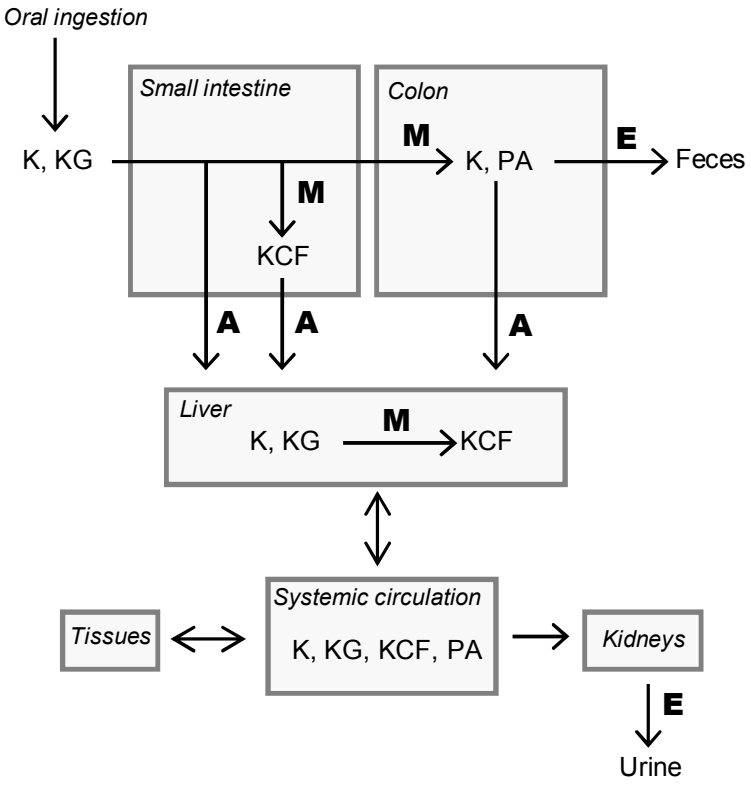

Fig. (3). Overview of the pharmacokinetics of kaempferol (see text for details). K: kaempferol; KG: kaempferol glycosides; KCF: kaempferol conjugated forms; PA: phenolic acids; **A**: absorption, **M**: metabolism; **E**: excretion.

capacity of reducing iron and copper ions; these reduced metals may participate in the formation of hydroxyl radicals (e.g. Fenton reaction) and in lipid peroxidation [56, 66, 339]. Although the prooxidant effects of flavonoids have also been attributed to their capacity to autooxidize when they are dissolved in aqueous buffers, kaempferol did not show this capacity in a study performed by Canada *et al.* [342]. The prooxidant activity of kaempferol may also be mediated by its ability to modulate the levels or activity of antioxidant and prooxidant enzymes [340, 343]. Some reports suggest that the mutagenicity of kaempferol may also be caused by its transformation, by CYP 1A1 enzymes, to the more potent genotoxicant quercetin [337, 338]. Although numerous *in vitro* studies suggest that kaempferol and quercetin may be genotoxic and carcinogenic, these effects have not been demonstrated in animal studies [344-346]. For instance, Takanashi *et al.* [346] observed that the oral administration of quercetin (0.1%) and kaempferol (0.04%) in the diet for 540 days did not increase the incidences of tumors in rats [346]. The low oral bioavailability of kaempferol may prevent this flavonoid from reaching genotoxic concentrations *in vivo*.

Several reports suggest that kaempferol may cause other unwanted effects under specific conditions. Kaempferol can react with iron and reduce its bioavailability [347] or may decrease the cellular uptake of folic acid [348]; these effects may cause problems in people with iron or folic acid deficiency. Kaempferol may also increase the bioavailalability of the anticancer drug etoposide and increase its toxicity [349] or reduce the anticancer activity of cisplatin [350]. It is important to mention that, like other antioxidant/prooxidant polyphenols [351], kaempferol can potentially increase or decrease the activity and toxicity of anticancer drugs with a prooxidant mechanism of action. At low concentrations, kaempferol may exert an antioxidant effect and reduce the activity of drugs that need to generate ROS to kill cancer cells efficiently. At high concentrations, kaempferol may generate ROS and increase the activity and toxicity of anticancer agents with a prooxidant mechanism. Because kaempferol has a low oral bioavailability, the ingestion of relatively high amounts of kaempferol leads to low concentrations of this flavonoid in plasma and tissues. These concentrations of kaempferol may cause antioxidant effects and can potentially reduce the activity of anticancer agents that need to generate ROS to exert their therapeutic effect.

6. CONCLUSIONS

Kaempferol is a flavonoid widely distributed in the plant kingdom. Numerous edible plants contain kaempferol, and it has been estimated that the human dietary intake of this polyphenol may be up to approximately 10 mg/day [28, 32, 352]. Epidemiological studies have found a positive association between the consumption of kaempferol-containing foods and a reduced risk of developing cardiovascular diseases and some types of cancer. Numerous *in vitro* and some animal studies support a role of kaempferol in the prevention and/or treatment of these and other diseases, such as neurodegenerative diseases, infectious diseases, diabetes, osteoporosis, anxiety, allergies,

inflammation and pain. However, many of these studies have been conducted at doses higher than those documented in humans and, therefore, it is difficult to predict from these results the effects of kaempferol intake on the prevention of these diseases. Likewise, most *in vitro* studies have been carried out at concentrations far beyond those achieved in plasma and tissues after the oral administration of kaempferol. This means that some biological effects induced by kaempferol *in vitro*, including some toxic effects, may not be relevant *in vivo* when this flavonoid is taken orally. The low oral bioavailability and high metabolism of kaempferol in humans should be overcome (e.g. by using alternative routes and forms of administration) to maximize some therapeutic properties of kaempferol. Additional animal studies and clinical trials are needed to better understand the possible health effects of kampferol and to further evaluate its potential as a new drug.

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