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Review Article

Acacetin and Chrysoeriol: A Short Review of the Chemistry, Plant Sources, Bioactivities and Structure-Activity Relationships of these Methylated Flavones

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ABSTRACT

Flavonoids are plant secondary metabolites that are well-known for their bioactivities. In this article, the chemistry, plant sources, bioactivities and structure-activity relationships of acacetin (ACT) and chrysoeriol (CSE) are reviewed. Of these two flavones, only ACT has been reviewed but not CSE. Sources of information cited were from Google Scholar, PubMed, PubMed Central, Science Direct, Web of Science, J-Stage, PubChem and Directory of Open Access Journals (DOAJ). The criteria used for selection of articles are based on topics rather than period of coverage, although recent references accord higher priority. Flavones, a class of flavonoids, have a C2–C3 double bond and a 4-carbonyl group but lack the C3 hydroxyl group at ring C. ACT and CSE are lesser-known methylated flavones with hydroxyl groups at C5 and C7 of ring A. The methoxy group of ACT is at C4' while that of CSE is at C3'. Found in many plant species, ACT and CSE have generated much research interest because of their diverse pharmacological activities, notably, their anti-cancer properties. The anti-cancer effects and molecular mechanisms of ACT towards lung, liver, gastric, prostate, breast and squamous cancer cells including leukaemia have been reported. Studies have shown that CSE inhibited breast, lung and pancreatic cancer cells including myeloma. Other bioactivities and structure-activity relationships of ACT and CSE are also briefly mentioned. Some areas for further research are suggested.

***Keywords*:** Acacetin, Chrysoeriol, Methylated Flavones, Cytotoxicity, Structure-Activity Relationships.

Introduction

Flavonoids are the largest family of phenolic secondary metabolites, found in almost all herbs, fruits and vegetables.[1-3] Their molecular structures consist of two benzene rings A and B that are joined by a heterocyclic pyran ring C forming the benzo-pyrone (C6–C3–C6) moiety.[4,5] Rings A and C compose of the chroman (C6–C3) nucleus.[6] Flavonoids can be divided into classes such as flavones, flavonols, flavanones and flavanols.[4,5,7] Flavones (examples: apigenin and luteolin) have a C2–C3 double bond and a 4-carbonyl group, but lack the C3 hydroxyl group at ring C. Flavonols (e.g., fisetin, quercetin, morin and myricetin) possess all the three functional moieties. Flavanones (e.g., naringenin, hesperitin and taxifolin) lack the C2–C3 double bond while flavanols (e.g., catechin and epicatechin) lack the C2–C3 double bond and the 4-carbonyl group.[1,2] Flavonoids have been reported to possess broad bioactivities such as anticancer, immunomodulation and antioxidant activities, that can be enhanced, to a certain extent, by methylation.[8] Methylated flavones containing only one or two methoxy groups are metabolically more stable than polymethoxylated flavones and have more superior chemopreventive properties.[9] Investigations on the structure-activity relationship of polymethoxylated flavones such as nobiletin and tangeretin showed a correlation between the number/position of methoxy group and their antiproliferative activity.[10,11]

In this short review, the chemistry, plant sources, bioactivities and structure-activity relationships of acacetin (ACT) and chrysoeriol (CSE) are reviewed. These methylated flavones are found in many plant species and have been reported to exhibit diverse pharmacological properties notably anti-cancer activities. To date, only ACT has been reviewed,[12,13] while CSE has not been reviewed.

Chemistry

Acacetin

ACT (5,7-dihydroxy-4'-methoxyflavone) is a natural methylated flavone.[12] Its molecular formula is $C_{16}H_{12}O_5$ and its molecular weight is 284 g/mol. Being a flavone, ACT has a C2–C3 double bond, a 4-carbonyl group but lacks the C3 hydroxyl group of ring C (Figure 1).

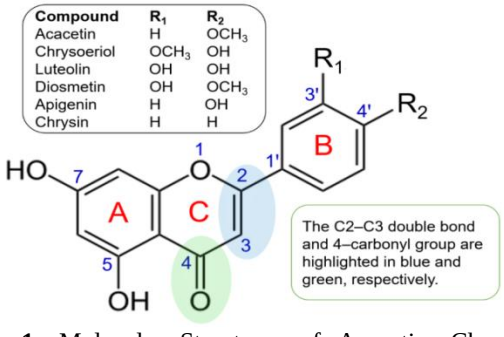

Figure 1: Molecular Structures of Acacetin, Chrysoeriol, Luteolin, Diosmetin, Apigenin and Chrysin

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The molecule has two hydroxyl groups at C5 and C7, and one methoxy group at C4'. ACT is also known as apigenin-4'-methyl ether because it is structurally similar to apigenin which lacks the 4'-methoxy group. ACT is also similar to diosmetin, another methoxyflavone with hydroxyl groups at C3', C5 and C7, and a C4'-methoxy group.[14]

Chrysoeriol

CSE (4',5,7-trihydroxy-3'-methoxyflavone) is another natural methylated flavone. Its molecular formula is $C_{16}H_{12}O_6$ and its molecular weight is 300 g/mol. Being a flavone, CSE has a C2–C3 double bond, a 4-carbonyl group but lacks the C3 hydroxyl group of ring C (Figure 1). The molecule has three hydroxyl groups at C5, C7 and C4', and one methoxy group at C3'. CSE is also called luteolin-3'-methyl ether because it is structurally similar to luteolin which lacks the 3'-methoxy group. CSE is similar to diosmetin in that they both have a methoxy group and a hydroxyl at the B ring i.e., C3' and C4' for CSE and C4' and C3' for diosmetin.

Plant Sources

Acacetin

ACT is found in the aerial parts of *Chrysanthemum zawadskii* (*Zawadskii* chrysanthemum),[15] *Agastache mexicana* (Mexican giant hyssop),[16] *Potentilla evestita* (cinquefoil),[17] *Ziziphora clinopodioides* (blue mint bush),[18] *Robinia pseudoacacia* (black locust tree),[19] *Artemisia* species (mugworts),[20] and *Saussurea involucrata* (snow lotus);[21] flowers of *Chromolaena odorata* (Siam weed),[22] and *Chrysanthemum morifolium* (florist's daisy);[23] seeds of *Carthamus tinctorius* (safflower);[24] and *Acacia* honey.[25] In the review on the therapeutic potential of ACT,[13] plant sources of ACT consist of 80 plant species, commonly reported in the genera of *Artemisia* (five species) and *Chrysanthemum* (four species).

Chrysoeriol

CSE is found in various plant species including the flowers of *Lonicera japonica* (Japanese honeysuckle),[25] tea of *Aspalathus linearis* (rooibos),[27,28] aerial parts of *Medicago sativa* (alfafa),[29] leaves of *Eurya ciliata* (no common name),[30,31] and flowers of *C. morifolium* (florist's daisy).[32]

Anti-Cancer Properties

Acacetin

ACT inhibited the growth of A549 lung and MCF-7 breast cancer cells with IC_{50} values of 9.46 μM[33] and 26.4 μM,[34] respectively. ACT from the aerial parts of *C. zawadskii* showed strong cytotoxic activity against HCT116 colon and UO-31 renal cancer cells with IC_{50} values of 2.44 and 2.89 μg/mL, respectively.[15] Luteolin, the other compound isolated, displayed no activity against the tested cancer cells. Tested against Jurkat T leukaemia and HSC-3 oral squamous carcinoma cells, the IC_{50} values of ACT were 25.8 μM[35] and 25.0 μg/mL,[36] respectively. The anti-cancer effects and molecular mechanisms of ACT towards different lung (A549), liver (HepG2), gastric (AGS), prostate (LNCaP and DU145), breast (MCF-7), oral squamous (HSC-3), head and neck squamous (UM-SCC-22A), and colon (SW480 and HCT-116) cancer cells including leukaemia (Jurkat T and B-lymphocytes), FaDu pharyngeal carcinoma, and U87 glioblastoma are shown in Table 1.

Table 1: Anti-Cancer Effects and Molecular Mechanisms of Acacetin towards Different Cancer Cell Lines

Cancer cell line & type	Anti-cancer effect and molecular mechanism of ACT	Reference
A549 lung	Induced cell cycle arrest at G1 phase and cell apoptosis involving the expression of p53 and activity of the Fas/Fas ligand.	33
MCF-7 breast	Induced apoptosis *via* caspase cascade, mitochondria-mediated death signalling and SAPK/JNK1/2-c-Jun activation.	34
Jurkat T leukaemia	Induced apoptosis *via* up-regulation of Bax, down-regulation of Bcl-2, and possibly by activation of the Fas-mediated pathway.	35
HSC-3 oral squamous	Induced apoptosis through activation of a MAPK-mediated pathway followed by induction of a mitochondria- and caspase-dependent mechanism.	36
HepG2 liver	Inhibited cell proliferation by arresting cell cycle progression and induced apoptosis involving the activity of p53 and Fas/Fas ligand.	37
AGS gastric	Triggered apoptosis was mainly associated with ROS production, mitochondrial dysfunction, and Fas activation.	38
LNCaP & DU145 prostate	Inhibited cell proliferation and cell cycle progression, and induced apoptotic cell death accompanied by PARP cleavage.	39
A549 lung	Inhibited cell proliferation by reducing MMP-2 and u-PA expressions *via* reduced phosphorylation of JNK, and reducing NF-κB and AP-1 binding activities.	40
DU145 prostate	Inhibited cell invasion and migration *via* inactivation of the p38 MAPK signalling pathway.	41
A549 lung	Inhibited cell invasion and migration *via* inactivation of p38α and involvement of the MKK and/or MLK signalling pathways.	42
DU145 prostate	Exhibited *in vitro* and *in vivo* anti-cancer activity *via* the suppression of NF-κB/Akt signalling.	43
B-lymphocytes leukaemia	Induced apoptosis by targeting mitochondria, through increased ROS formation, MMP collapse, increased MPT, release of cytochrome c and caspase 3 activation.	44
UM-SCC-22A head & neck squamous	Induced apoptosis *via* cytochrome c release, activation of caspase-3, and possibly involving the muscarinic M3R pathway.	45
FaDu pharyngeal carcinoma	Inhibited cell growth and induced apoptosis *via* the death receptor-mediated and the mitochondria-mediated apoptotic pathways.	46
SW480 & HCT-116 colon	Induced mitochondrial ROS-mediated cell death by inducing AIF.	47
U87 glioblastoma	Induced Cdk-cyclin mediated G2/M phase arrest and triggered ROS-mediated apoptosis.	48

Abbreviations: AIF = apoptosis-inducing factor, AP-1 = activator protein 1, Bax = Bcl-2 associated X protein, Bcl-2 = B-cell lymphoma 2, JNK = c-jun N-terminal kinase, M3R = M3 receptor, MAPK = mitogen-activated protein kinase, MKK = mitogen-activated protein kinase kinase, MLK = mixed-lineage protein kinase, MMP = matrix metallopeptidase, MPT = mitochondrial permeability transition, NF-κB = nuclear factor-kappa B, PARP = poly-(ADP-ribose) polymerase, ROS = reactive oxygen species, SAPK = stress-activated protein kinase, and u-PA = urokinase-type plasminogen activator.

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Chrysoeriol

CSE inhibited the proliferation of RPMI 8226 and KM3 multiple myeloma cells at IC_{50} values of 26 and 35 μmol/L, respectively.[49] Against leukaemia HL-60 cells, growth inhibitory effects of CSE were dose-dependent with IC_{50} value of 29 μM[50] and 15 μM against A549 lung cancer cells.[51] Against MRC-5 normal lung cells, cytotoxicity of CSE was significantly weaker with IC_{50} value at 93 μM.[51] Earlier, the anti-proliferative activity of CSE, tested against MCF-7 breast, DMS-114 lung, HT-29 colon, SL-MEL5 melanoma, DU-145 prostate cancer cells displayed IC_{50} values of 7, 17, 20, 23 and 30 μM, respectively.[52] In comparison, luteolin (CSE without the methoxy group) exhibited IC_{50} values of 3, 11, 21, 32 and 32 μM, respectively.

In recent years, several studies reported on the anti-cancer properties of CSE by testing different cancer cell lines. CSE significantly inhibited cell proliferation and regulated cell cycle of RPMI 8266 and KM3 multiple myeloma cells by suppression of the PI3K-AKT-mTOR pathway.[49] CSE promoted cell cycle arrest at G2/M and inhibited migration and invasion of MDA-MB-231 cells by down-regulation of matrix metallopeptidase 9 (MMP-9) and cyclooxygenase-2 (COX-2) expression.[53] CSE exerted *in vitro* and *in vivo* cytotoxic effects on A549 lung cancer cells *via* the activation of autophagy, sub-G1 cell cycle arrest, cell migration and invasion inhibition, and modulation of the mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) signalling pathway.[51] 8-CSE triggered apoptosis of SW1990 pancreatic cancer cells *in vitro* by inhibiting B-cell lymphoma 2 (BCL-2), the anti-apoptotic protein.[54]

Related to anti-cancer activities, CSE inhibited DNA adduct formation with benzo[α]pyrene[55] and inhibited the formation of a carcinogenic estrogen metabolite[56] in MCF-7 breast cancer cells. In addition, CSE inhibited the efflux transporter breast cancer resistance protein (BCRP/ABCG2) more strongly than ACT with IC_{50} values of 0.01 and 0.14 μM, respectively.[57] The anti-cancer effects and molecular mechanisms of CSE towards different breast (MCF-7 and MDA-MB-231), pancreas (SW1990), lung (A549) cancer cells including myeloma (RPMI 8226 and KM3) are shown in Table 2.

Other Bioactivities

Acacetin

In this short review, the bioactivities of ACT are updated based on recent reviews.[12,13] ACT possesses antibacterial,[59] antiviral,[60] anti-diabetic,[61] anti-neuroinflammatory,[62,63] anti-arthritic,[64] anti-aging,[65] anti-Alzheimer[66] and antinociceptive[67] properties (Table 3).

Chrysoeriol

The bioactivities of CSE have been briefly described in recent reviews.[68,69] CSE displays lipase inhibitory,[70] antibacterial,[71] anti-inflammatory,[72-74] anti-diabetic[75] and neuroprotective[76] activities (Table 3).

Structure-Activity Relationships

Acacetin

Results of a structure-activity relationship (SAR) study showed that ACT had no 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical scavenging activity (IC_{50} value > 500 μM) while luteolin displayed strong activity (IC_{50} value of 17.8 μM).[77] ACT and luteolin are flavones with hydroxyl groups at C5 and C7 of ring A (Figure 1). ACT has a methoxy group at C4′ while luteolin has hydroxyl groups at C3′ and C4′ of ring B. This indicated that the methoxy group of ACT attributed to its effective cytotoxic activity against cancer cells. A SAR study showed that linarin and linarin acetate with a rhamnose substitution at C7 displayed much weaker induction of apoptosis than ACT with a hydroxyl group at C7.[39]

Chrysoeriol

Unlike luteolin that displayed strong DPPH radical scavenging activity (IC_{50} value = 17.8 μM), CSE showed no such activity (IC_{50} value > 500 μM).[77] Results of a SAR study for inhibition of matrix metallopeptidase-9 (MMP-9) and cyclooxygenase-2 (COX-2) activity by the flavonoids showed that flavones had better inhibitory activities when compared to flavonols.[53] CSE was found to be the most active followed by ACT, diosmetin and luteolin and apigenin (Figure 1). CSE with substitutions such as 5,7-dideoxychrysoeriol (lacking OH groups at C5 and C7) and 2,3-dihydrochrysoeriol (lacking the C2–C3 double bond), showed weaker inhibition of MMP-9 and COX-2 activity than CSE.[53] With regard to proliferation of HL-60 leukaemia cells by 5,7-dihydroxyflavones, diosmetin and CSE induced ~80% inhibition.[50] The inhibitory effects of chrysin, apigenin, acacetin and luteolin were weaker. It was suggested that the combinations of hydroxyl and methoxy groups at the B ring influenced the inhibitory effects of the compounds on HL-60 cell proliferation. A recent study on CSE and its analogues showed that they inhibited both mesenchymal–epithelial transition factor (c-Met) and vascular endothelial growth factor receptor 2 (VEGFR2) that are involved in tumorigenesis of certain types of cancer.[78] To address cancer drug resistance, further SAR analyzes are needed to guide structural optimizations.

Table 2: Anti-Cancer Effects and Molecular Mechanisms of Chrysoeriol towards Different Cancer Cell Lines

Cancer cell line & type	Anti-cancer effect and molecular mechanism of CSE	Reference
RPMI 8226 & KM3 myeloma	Inhibited cell proliferation by regulation of cell cycle and inhibition of the PI3K-AKT-mTOR pathway.	49
A549 lung	Exerted *in vitro* and *in vivo* cytotoxic effects through activation of autophagy, sub-G1 cell cycle arrest, cell migration and invasion inhibition *via* inhibition of the MAPK/ERK signalling pathway.	51
MDA-MB-231 breast	Promoted cell cycle arrest at G2/M, and inhibited migration and invasion of cells by by down-regulation of MMP-9 and (COX-2) expression *via* the NF-κB pathway.	53
SW1990 pancreas	Triggered cell apoptosis by inhibiting BCL-2, the anti-apoptotic protein.	54
MCF-7 breast	Inhibited DNA adduct formation with benzo[α]pyrene in cancer cells.	55
MCF-7 breast	Inhibited the formation of carcinogenic estrogen metabolite in cancer cells.	56
MCF-7 breast	Inhibited TNFα-induced CYP19 expression through the inhibition of ERK1/2-mediated EGR-1 expression.	58

Abbreviations: BCL-2 = B-cell lymphoma 2, COX-2 = cyclooxygenase-2, CYP19 = cytochrome P450 19, EGR-1 = early growth response gene 1, ERK1/2 = extracellular signal-regulated kinase 1/2, MAPK = mitogen-activated protein kinase, MMP-9 = matrix metallopeptidase 9, mTOR = mechanistic target of rapamycin, NF-κB = nuclear factor-kappa B, PI3K = phosphoinositide 3-kinases, and TNFα = tumor necrosis factor alpha.

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Table 3: Other Bioactivities and Mechanisms of Acacetin (ACT) and Chrysoeriol (CSE)

Flavone	Bioactivity	Effect and mechanism	Reference
ACT	Antibacterial	ACT inhibited *in vitro* and *in vivo* virulence factor of Gram-positive *Streptococcus pneumoniae* by targeting spore-forming activity or pneumolysin.	59
	Antiviral	ACT is a potent inhibitor of replication of HSV1.	60
	Anti-diabetic	ACT enhanced glucose uptake through insulin-independent GLUT4 translocation in L6 myotubes.	61
	Anti- neuroinflammatory	ACT attenuated LPS-induced neuroinflammation in mice by suppressing microglial activation and reducing neuronal cell death.	62
		ACT protected dopaminergic cells against MPTP-induced neuroinflammation *in vitro* and *in vivo*.	63
	Anti-arthritic	ACT displayed anti-arthritic effects in FLS cells.	64
	Anti-aging	ACT promoted healthy aging in *Caenorhabditis elegans* by altering stress response.	65
	Anti-Alzheimer	ACT protected against Aß production (target of Alzheimer's disease treatment) by reducing APP protein expression and BACE-1 activity, and inhibited APP synthesis that resulted in a decrease in the number of amyloid plaques.	66
	Antinociceptive	ACT decreased visceral and inflammatory nociception, and prevented formalin-induced oedema in pain-related diseases.	67
CSE	Anti-diabetic	CSE exhibited anti-diabetic properties by inhibition of the activity of lipase.	70
		CSE ameliorated hyperglycaemia in streptozotocin-induced diabetic rats by regulating carbohydrate metabolic enzymes.	71
	Antibacterial	CSE exhibited antibacterial activity against nine pathogens at 40 µg per disc, and had a MIC value of 1.25 µg/mL against MRSA.	72
	Anti-inflammatory	The inhibitory effects of CSE on AP-1 activation may be associated with its potent NO blocking and anti-inflammatory activity.	73
		CSE ameliorated TPA-induced skin inflammation in mice by inhibiting NF-κB and STAT3 pathways.	74
		CSE ameliorated COX-2 expression in LPS-stimulated murine macrophages through NF-κB, AP-1 and MAPK regulation.	75
	Neuroprotective	CSE mediated mitochondrial protection in MPP^+-treated SH-SY5Y cells (a typical *in vitro* PD model) *via* PI3K/Akt pathway.	76

Abbreviations: Aß = ß-amyloid, AD = Alzheimer's disease, AP-1 = activator protein 1, APP = amyloid precursor protein, BACE-1 = amyloid precursor cleaving enzyme, COX-2 = cyclooxygenase-2, FLS = fibroblast-like synoviocyte, GLUT-4 = glucose transporter type 4, HSV1 = herpes simplex virus type-1, LPS = lipopolysaccharide, MAPK = mitogen-activated protein kinase, MIC = minimum inhibitory concentration, MPP^+ = 1-methyl-4-phenylpyridinium iodide, MPTP = 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine, MRSA = methicillin-resistant *Staphylococcus aureus*, NF-κB = nuclear factor-kappa B, NO = nitric oxide, PD = Parkinson's disease, PI3K = phosphoinositide 3-kinases, STAT3 = signal transducers and activators of transcription 3, and TPA = 12-*O*-tetradecanoylphorbol-13-acetate.

Conclusion

Flavonoids are a very large plant family of phenolic secondary metabolites. These compounds have a molecular structure consisting of two benzene rings A and B joined by a pyran ring C to form a benzo-pyrone (C6–C3–C6) moiety. The majority of flavonoids have the B ring linked in position 2 to the C ring, and they can be further divided into classes such as flavones, flavonols, flavanols and flavanones. Among the flavones, SAR studies have shown that the presence of the C2–C3 double bond and the 4-carbonyl group at ring C, the absence of the C3 hydroxyl group at ring C, and the pattern of hydroxylation at ring B are associated with enhanced cytotoxicity towards cancer cells. ACT and CSE are methylated flavones with hydroxyl groups at C5 and C7 of ring A. ACT has a methoxy group at C4' while CSE has a hydroxyl group at C4' and a methoxy group at C3'. Further research on the structural modifications of ACT and CSE is needed to synthesis novel derivatives with enhanced anti-cancer properties. Clinical research on ACT and CSE is warranted to evaluate their safety and chemopreventive efficacy when used alone or in combination with other chemotherapy agents.

Conflict of Interest

The authors had no conflict of interest.

Authors' Declaration

The authors hereby declare that this short review is original and that any liability for claims relating to the contents will be borne by them.

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