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Acacetin—A simple flavone exhibiting diverse pharmacological activities

Ruchi Badoni Semwal[a,b], Deepak Kumar Semwal[a,c], Sandra Combrinck[a,d], Jeanne Trill[e], Simon Gibbons[e], Alvaro Viljoen[a,d,*]

[a] Department of Pharmaceutical Sciences, Faculty of Science, Tshwane University of Technology, Private Bag X680, Pretoria, 0001, South Africa
[b] Department of Chemistry, Pt. Lalit Mohan Sharma Govt. Post Graduate College, Rishikesh, 249201, India
[c] Department of Phytochemistry, Faculty of Biomedical Sciences, Uttarakhand Ayurved University, Harrawala, Dehradun, 248001, India
[d] SAMRC Herbal Drugs Research Unit, Faculty of Science, Tshwane University of Technology, Private Bag X680, 3 Pretoria, 0001, South Africa
[e] Research Department of Pharmaceutical and Biological Chemistry, UCL School of Pharmacy, 29-39 Brunswick Square, London, WC1N 1AX, UK

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ABSTRACT

Acacetin (5,7-dihydroxy-4-methoxyflavone) is a naturally occurring flavonoid, known to possess numerous pharmacological properties, including neuroprotective, cardioprotective, anticancer, anti-inflammatory, anti-diabetic, and antimicrobial activities. The molecule is widespread throughout the Plant Kingdom, but is particularly abundant in the Asteraceae, Euphorbiaceae, Passifloraceae, Lamiaceae and Malvaceae families. It has been shown to exhibit strong inhibitory effects against glutathione reductase, cyclo-oxygenase, acetylcholinesterase, aldose reductase and xanthine oxidase enzymes. A comprehensive overview of the potential therapeutic applications of acacetin was prepared after collating selected peer-reviewed papers, accessed from online scientific databases, specifically PubMed, Web of Science and Scopus. The mechanism of action, dose forms and structure-activity relationships of the molecule are some of the aspects discussed in the review, to facilitate further research and use of this molecule.

1. Introduction

Acacetin (5,7-dihydroxy-4′-methoxyflavone; Fig. 1 synonym linarigenin), a plant-derived flavonoid, has recently gained attention worldwide due to its diverse biological activities, including *in vitro* neuroprotective, cardioprotective, anti-ageing, anticancer and antimicrobial properties (Zhou et al., 2014). The molecule has been reported to inhibit several important and clinically-relevant enzymes, including monoamine oxidase B (Han et al., 1987), human topoisomerase-I (Boege et al., 1996), glutathione reductase (Zhang et al., 1997), cyclo-oxygenase (COX) I/II (Liao et al., 1999), acetylcholinesterase (Lim et al., 2007), aromatase (Zhao et al., 2008), aldose reductase (Manivannan et al., 2015) and xanthine oxidase (Rauf et al., 2016). A number of pharmacological studies has also confirmed its potential role in the treatment of viral diseases, inflammatory conditions, oxidative stress, malaria and cell proliferation, with few toxic reactions (Pan et al., 2005; Kim et al., 2015). Acacetin efficiently inhibited platelet-activating factor receptor-binding to rabbit platelets using ^{3}H-platelet-activating factor as a ligand (Jalil et al., 2012), and exhibited low anti-P-glycoprotein activity without suppressing P-glycoprotein (Katayama et al., 2007).

Acacetin occurs throughout the Plant Kingdom in its free form, or in the form of a glycoside (Abdallah et al., 2016; Li et al., 2015). This bioactive flavone has been reported to be a major constituent of various plants, including *Carthamus tinctorius* L. (Roh et al., 2004), *Tanacetum sinaicum* (Fresen.) Delile ex K.Bremer & Humphries (Marzouk et al., 2016a), *Chrozophora tinctoria* (L.) Raf. (Marzouk et al., 2016b), *Wissadula periplocifolia* (L.) C.Presl (Teles et al., 2015), *Agastache mexicana* (Kunth) Lint & Epling (Flores-Flores et al., 2016) and *Turnera diffusa* (dnapharma.net/product/acacetin/). Robinson and Venkataraman (1926) synthesized the molecule almost a century ago. Since then, many modifications have been proposed, including a recently developed synthetic route by Hanamura et al. (2016).

Several products containing acacetin as active ingredient, alone or in combination with other compounds or plant extracts, are available as health supplements online (dnapharma.net/product/acacetin; consumerhealthdigest.com/testosterone-booster/acacetin-99.html; steroidbulks.com/acacetin.html; anabolicwarfare.com/products/eshred). Most of these so-called “natural testosterone boosters” contain acacetin derived from *Turnera diffusa* leaf (50 mg per capsule). These products are purported to have anti-aromatase activity, implying that they restore the healthy balance of testosterone and estrogen in the body,

* Corresponding author at: Department of Pharmaceutical Sciences, Faculty of Science, Tshwane University of Technology, Private Bag X680, Pretoria, 0001, South Africa.

E-mail address: viljoenam@tut.ac.za (A. Viljoen).

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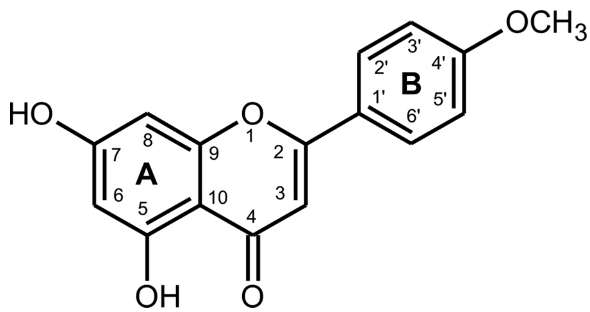

Fig. 1. Chemical structure of acacetin (5,7-dihydroxy-4′-methoxyflavone).

encouraging optimal muscle building and fat loss. Additional claims made include appetite suppression, the treatment of prostate cancer, as well as anti-allergy and anti-inflammatory activities. A search of Google patents (bing.com/search?q = google + patents&pc = MOZI&form = MOZTSB) revealed the existence of more than 1000 patents mentioning acacetin, although only 20 of these mentioned acacetin in the title. The majority were filed with regard to the prevention and treatment of cancer, ulcerative colitis, skin ageing and neurodegenerative diseases (Alzheimer's and Parkinson's diseases). Acacetin-containing products are freely available online, yet, this review will show that all of the claims made are based solely on *in vitro* data. In fact, very little information is available on *in vivo* experiments, while clinical data are lacking, even in the patents filed. Moreover, there are no reports on the bioavailability of the compound and data on safety is sparse.

Over the past few decades, acacetin has been investigated mainly for its inhibitory effect towards various enzymes *i.e.* aromatase, topoisomerase and acetylcholinesterase, which are pivotal endogenous enzymes and targets in disease states. This systematic review was undertaken to highlight the potential of this simple flavone as a potential healthcare product of commercial importance, but also to reveal important gaps in the available knowledge on the compound.

2. Pharmacological activities

Earlier research revealed that acacetin has the potential to inhibit many important and clinically-relevant enzymes that are responsible for a variety of human diseases, including neuro, cardiac and pulmonary disorders. In addition to its neuroprotective effects, various *in vitro* and/or *in vivo* studies confirmed its role in viral infections, inflammation, acute lung injury, oxidative stress and cancer (Pan et al., 2005; Kim et al., 2015). Various pharmacological activities exhibited by acacetin are discussed in the following sections.

2.1. Neuroprotective activity

Acacetin was reported to have activity against disorders of the central nervous system by protecting it from neuronal damage. The inhibitory effect of the molecule was recorded against depolarization-evoked glutamate release and cytosolic-free Ca^{2+} concentration in the hippocampal nerve terminals (synaptosomes) in rats, although, no change was observed in the potential of the synaptosomal membrane (Lin et al., 2014). Intraperitoneal administration to rats at 10 and 50 mg/kg decreased kainic acid (15 mg/kg, i.p.)-induced neuronal cell death and microglia activation in the CA3 subsection of the *cornu ammonis*, a part of the hippocampus responsible for memory processes. The CA3 is, however, susceptible to seizures and undergoes neuro-degeneration. Acacetin could be considered an efficient agent for the treatment of excitotoxicity-associated neurological disorders. Kim et al. (2012) proposed that the compound is able to protect dopaminergic neurons against neurotoxicity associated with Parkinson's disease. Patients suffering from this debilitating condition have difficulty in turning. They found that intraperitoneal administration of acacetin at 10 mg/kg per day for 3 days decreased turning time and locomotor activity in a 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (30 mg/kg)-induced mice model for Parkinson's disease. It further inhibited the degeneration of dopaminergic neurons and the depletion of dopamine levels induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine toxicity in the *substantia nigra* and *striatum*.

Acacetin inhibited LPS-induced neuro-inflammatory reactions. Intraperitoneal injection of 25 mg/kg into C57BL/6 mice caused a reduction in their neurological function scores and cerebral infarction volumes, when studied in a cerebral ischemia-reperfusion injury model. Mechanistically, acacetin treatment lowered the expression of Iba1, TNF, pro-IL-1β, IL-1β and IL-6, toll-like receptor 4, NFkB, NLRP3, procaspase-1 and caspase-1 in experimental mice (Bu et al., 2019).

An *in vitro* study by Kim et al. (2017) found that this molecule, at a concentration of 10 μM, has potential for preventing human dopaminergic neuronal death *via* inhibition of 6-hydroxydopamine-induced neuronal cell death in SH-SY5Y cells. The compound also inhibited neurotoxicity and neuronal cell death through ROS production and MMP dysfunction. The mechanism of action of acacetin involves the reduction of phosphorylation of JNK, p38 MAPK, PI3K/Akt, and GSK-3β. The researchers suggested that acacetin should be considered as a therapeutic agent to slow the progression of Parkinson's disease.

2.2. Anti-Alzheimer activity

Various studies have confirmed the inhibitory effect of acacetin against acetylcholinesterase (AChE), an enzyme that catalyzes the rapid breakdown of acetylcholine and other choline esters that function as neurotransmitters. Inhibition of the enzyme has been proven to slow down the progression of Alzheimer's Disease, a chronic neurodegenerative disease that causes dementia, particularly in the elderly. Active AChE inhibitors were identified from *Chrysanthemum indicum* following a bioassay-guided approach (Lim et al., 2007). The strong activities of the isolated acaciin and acacetin-7-O-β-D-galactopyranoside were compared to that of luteolin, apigenin and acacetin. The results revealed that the methoxy groups at C-4′ in ring B and a sugar at *O*-7 in the B-ring may be essential for the structure-activity relationship. However, a later *in vitro* experiment by Rashed et al. (2015) revealed that acacetin derivatives (acacetin-7-O-α-rhamnoside, -7-O-β-glucoside and -4′-methoxy apigenin), isolated from the methanol extract of *A. brevipedunculata* were not able to inhibit acetylcholinesterase.

The acacetin glycoside demonstrated potential for mitigating AD, since at 1 μM it was able to reduce amyloid-induced mitochondrial dysfunction, by restoring altered matrix metalloproteinase (MMP), reactive oxygen species (ROS) production and adenosine triphosphate (ATP) levels in neuroblastoma cells expressing mutant amyloid-β protein precursor (Dragicevic et al., 2011). It was also reported that acacetin inhibited the production of nitric oxide (NO), as well as prostaglandin-E (PGE2), and the expression of inducible nitric oxide synthase (iNOS) and COX-2 in lipopolysaccharide (LPS)-stimulated BV2 cells at 10 μM. Moreover, it decreased the pro-inflammatory cytokines (TNF-α and IL-1b), and blocked the activation of NF-kB and p38-MAPK (Ha et al., 2012). The same report indicated that acacetin at 20 mg/kg/day for 3 days decreased neuronal cell death in an *in vivo* ischemia model, whilst at 25 mg/kg/day, neuronal cell death was completely inhibited. This study revealed that acacetin could hold some potential for disorders involving neuro-inflammation, including AD.

The human β-amyloid-cleaving enzyme (BACE1) is a relatively new target for the treatment of AD. Acacetin tested at three concentrations (100, 300, and 500 μM) was effective at preventing the development of eye and motor abnormalities in *Drosophila melanogaster* expressing amyloid precursor protein/BACE1. The compound also effectively regulated the transcription of human BACE1 and amyloid precursor protein, and caused a reduction in β-amyloid production, by interfering with BACE1 activity and amyloid precursor protein synthesis (Wang et al., 2015).

Both AD and Parkinson's disease are associated with elevated levels of monoamine oxidase B in the brain. An *in vitro* study revealed that acacetin was able to inhibit monoamine oxidase B, but the IC_{50} value (2.46 mM) reported (Han et al., 1987), was so high that it can be considered an irrelevant test concentration. A later study (Chaurasiya et al., 2016) yielded far more promising IC_{50} values of 0.121 and 0.049 μM for acacetin, isolated from the leaves of *Calea urticifolia*, towards human monoamine oxidase A and B, respectively. These enzymes play a vital role in the deactivation of neurotransmitters. In addition, IC_{50} values of 0.19 and 0.17 μM were reported (Lee et al., 2017a).for the inhibition of recombinant human monoamine oxidase A and B, respectively.

2.3. Role in cardiovascular diseases

Atrial fibrillation (AF) is associated with a wide-range of cardiac and extra-cardiac complications and contributes expressively to morbidity and mortality (Jost et al., 2011). Acacetin has been shown to be an atrium-selective molecule, with potential for treating AF. It was found to suppress human atrial ultra-rapid delayed rectifier K^+-current and transient outward K^+-current with IC_{50} values of 3.2 and 9.2 μM/L, respectively. In addition, the compound prolonged the action potential duration in human atrial myocytes, but blocked acetylcholine-activated K^+-current in guinea pig cardiac monocytes. Intraduodenal administration of acacetin at 5 mg/kg to anesthetized dogs was found to prolong the atrial effective refractory period in both atria to 4 h. This was without prolonging corrected QT (QTc) interval – QTc is determined by electrocardiogram, and is considered a risk factor for sudden cardiac death. In contrast, the positive control, sotalol (5 mg/kg), prolonged both the atrial effective refractory period and the QTc interval (Li et al., 2008).

Liu et al. (2016) designed a water-soluble prodrug in the form of a phosphate sodium salt that is rapidly converted to acacetin in plasma. The intravenous administration of this prodrug at three doses (3, 6 and 12 mg/kg) was found to inhibit atrial fibrillation without increasing the QTc interval in dogs. The intravenous LD_{50} of the prodrug was reported as 721 mg/kg in mice.

A preliminary *in vitro* study by Yang et al. (2014) revealed that acacetin at 5, 10 and 25 μg/mL reduced the concentration of malondialdehyde in neonatal rat cardiomyocytes with injury induced by hypoxia/reoxygenation. The molecule protected the cardiomyocytes from this form of stress-induced damage, by decreasing lipid peroxidation and increasing the anti-oxidant effect. An *in vivo* study in mice suggested that the compound improves cardiac dysfunction and ameliorate cardiomyocyte apoptosis following myocardial infarction *via* MAPK and PI3K/Akt signaling pathways (Chang et al., 2017).

An *in vitro* study demonstrated that acacetin could effectively attenuate xanthine oxidase (IC_{50} 11.92 μM). Inhibition of the enzyme was proposed as a mechanism for improving cardiovascular activity (Rauf et al., 2016). Acacetin also caused a potent endothelium-independent vaso-relaxing effect, which was attributed to the hydroxy group at position 5. This finding suggests a possible interaction with large-conductance, calcium-activated potassium channels (Calderone et al., 2004). Senejoux et al. (2012) found that acacetin is one of the active principles of *Ziziphora clinopodioides* Lam., an antihypertensive plant in traditional Uighur medicine. In this study, acacetin and other flavonoids demonstrated hypotensive effects in an *in vitro* model using thoracic aortic rings isolated from rats.

Acacetin has been found to inhibit transient outward potassium (hKv4.3) current in human atrial myocytes by binding to both closed and open channels. At 0.2, 0.5, 1, and 3.3 Hz the channels were blocked, with IC_{50} values determined as of 7.9, 6.1, 3.9 and 3.2 μM, respectively. However, the compound acted as an antagonist towards the hKv4.3 mutants T366 A, T367 A, V392 A, I395 A and V399 A, with IC_{50} values of 44.5, 25.8, 17.6, 16.2 and 19.1 μM, respectively. This action may contribute to the management of atrial fibrillation (Wu et al., 2013). Acacetin in the concentration range 0.3–3 μM caused a decrease in the apoptosis and ROS production induced by hypoxia/reoxygenation injury in cardiomyocytes and H9C2 cardiomyoblasts by reducing Bax and cleaved-caspase-3, and increasing Bcl-2. It was not only found to suppress the release of TLR-4 and IL-6 induced by hypoxia/reoxygenation injury, but also increased the secretion of IL-10 (Wu et al., 2018a).

2.4. Anti-inflammatory activity

The anti-inflammatory property of this bioflavonoid is considered of major importance, due to its effect on neuro-inflammation. Various studies have reported the anti-inflammatory activity in both *in vitro* and *in vivo* models. Acacetin at 25 mg/kg, p.o was reported to reduce airway hyper-responsiveness, eosinophil infiltration and goblet cell hyperplasia in lung tissue of ovalbumin-sensitized asthmatic mice (Huang et al., 2012). It further inhibited eotaxin-1- and Th2-associated cytokines in bronchoalveolar lavage fluid, and suppressed the level of ovalbumin-IgE in serum. Furthermore, acacetin decreased the concentrations of IL-6, IL-8, intercellular adhesion molecule-1, and eotaxin-1 in activated human bronchial epithelial cells *in vitro*, and prevented eosinophils from adhering to inflammatory cells. Moreover, the *in vitro* inhibitory effects towards 5-hydroxyeicosatetraenoic acid, leukotriene-B4 formation and 5-lipoxygenase also indicate potential benefits of acacetin in the treatment of inflammatory disorders (Fan et al., 2012).

The intraperitoneal administration of acacetin inhibited acetic acid-induced writhing in mice with an ED_{50} value of 20 mg/kg (Carballo-Villalobos et al., 2014). In addition, licking and shaking associated with nociceptive behaviour was also inhibited in a mouse model. The compound reduced visceral and inflammatory nociception, and inhibited formalin-induced oedema, involving 5-HT_{1A}, GABA/BZD and opioid receptors. This action indicates that acacetin could be an agent for the treatment of pain-related disorders.

The flavone exhibited activity against the arachidonate cascade enzymes using elicited rat peritoneal leukocytes. These results indicated that acacetin is able to block eicosanoid synthesis by inhibiting cyclooxygenase with an IC_{50} value of 77.5 μM (Liao et al., 1999). It also produced a marked inhibitory effect against LPS-stimulated NO and pro-inflammatory cytokines. A study by Srisook et al. (2015) supported the findings that acacetin may inhibit NO production stimulated by LPS, after the compound was isolated from the leaves of *Clerodendrum inerme* (L.) Gaertn., a traditional Thai medicine used to treat inflammatory disorders. Moreover, Pan et al. (2006) found that acacetin prevented the transcriptional activation of iNOS and COX-2 in LPS-induced murine macrophages. It further blocked the protein and mRNA expression of iNOS and COX-2 in LPS-induced macrophages, and reduced the translocation of the NFκB subunit, as well as its dependent transcriptional activity. Nguyen et al. (2016) also reported the *in vitro* anti-inflammatory effect of acacetin against LPS-induced NO production in RAW 264.7 cells. They found that the compound has potential for treating inflammation, as reflected by a very low IC_{50} value (14 μM).

Acacetin (20, 40, and 80 mg/kg bw) attenuated sepsis-induced acute lung injury and lung oedema in mice. It decreased protein and inflammatory cytokine concentration, infiltrated inflammatory cells and pulmonary myeloperoxidase activity. This study indicated that acacetin has protective activity towards sepsis related to the regulation of iNOS, COX-2, SODs and heme oxygenase 1 (Sun et al., 2018). It also had a protective effect against LPS-induced acute lung injury in BALB/c mice, by attenuating inflammation and oedema, and by reducing TNF-α and IL-1β in lung tissues. In addition, it suppressed LPS-induced ROS generation and elevated pulmonary heme oxygenase-1 and Nrf2 activities (Wu et al., 2018b).

2.5. Anti-arthritic activity

This molecule was found to be potentially effective in the treatment of rheumatoid arthritis (RA), an autoimmune disorder of the joints. Chen et al. (2015) reported that acacetin reduced the activation of fibroblast-like synoviocytes (FLSs), which are a major factor in the development of RA. Investigation into the mechanism of action revealed that the compound inhibits p38 and JNK phosphorylation and decreases the expression of MMP-1, -3 and -13 in IL-1β-induced FLSs.

The results of an *in vivo* study suggests that acacetin represses the incidence of collagen-induced arthritis, prevents the pathological alteration, and reduces type II collagen-specific IgG and IgG1 levels in mice. In addition, the expansion of Treg cells and the decreasing Th17 cells in spleen and inguinal lymph nodes, after the initiation of collagen-induced arthritis, were noted. The study also found that acacetin inhibits T-cell proliferation and the expression of the transcriptional coactivator with PDZ-binding motif (Liu et al., 2018).

2.6. Anticancer activity

The results of various *in vitro* studies suggest that acacetin may potentially have a role in the treatment of different cancers, including cancers of the prostate, liver, cervix, mouth and blood (Jaganathan and Mandal, 2012). The *in vitro* activity of the compound against various cancer cell lines is summarised in Table 1. Several researchers (Costa-Lotufo et al., 2005; Kamatou et al., 2008) used an IC_{50} of less than 30 μg/mL for the test compound as a measure to reflect anticancer potential. However, the lower value of 20 μg/mL is also applied (Fadeyi et al. (2013).

Acacetin is considered a CYP1 family inhibitor, because of its association with the activity of the human cytochrome P450 enzymes, CYP1A1 and CYP1B1, which have been linked to the occurrence of cancer. Hence, in view of the possible role of human cytochrome P450 enzymes in activating carcinogens, acacetin may afford protection against certain types of cancer (Doostdar et al. (2000).

Mechanism-of-action studies have reported that the methoxy group at C-4′ on the B-ring and the 5,7-dihydroxy moieties on the A-ring of the molecule play a key role in ethoxyresorufin-*O*-deethylase inhibition (Androutsopoulos et al., 2009, 2011). Acacetin was shown to be a promising agent for chemoprevention, by inhibiting ATP-competitive PI3-K. An *in vivo* study by Jung et al. (2014) demonstrated that the compound could potentially reduce the growth of SK-MEL-28 tumours. In addition, it was found to block the phosphorylation of Akt, a group of enzymes involved in processes, such as signal transfer, related to cell growth and survival. Acacetin suppressed EGF-induced cell transformation, attenuated phosphorylation of Akt and p70S6K, and inhibited PI3-K activity. Moreover, it also inhibited both anchorage-dependent and anchorage-independent growth of cells expressing PI3-K activity, and was found to inhibit tyrosine phosphorylation of stat-(signal transducer and activator of transcription) signalers, Stat-1 and -3. Its ability to inhibit Stat-signaling and suppress angiogenesis has been confirmed through *in vitro*, *ex vivo*, and *in vivo* experimental models, including the effective suppression of angiogenesis in Matrigel plugs implanted in mice (Bhat et al., 2013). All these experiments indicate that acacetin may inhibit tumour growth.

Acacetin has been shown to inhibit the Tumor Necrosis Factor-related apoptosis-inducing ligand (TRAIL)-R1 death receptor expression level in RAW264.7 macrophages (Warat et al., 2014). Liu et al. (2011) reported that acacetin reduced the steady level of vascular endothelial growth factor (VEGF) mRNA and inhibited VEGF transcriptional activation - VEGF plays a key role in angiogenesis and tumour growth. Through inhibition of the expression of VEGF and HIF-1α, this study also confirmed that acacetin can effectively inhibit ovarian cancer cell-induced angiogenesis and tumour growth in animal models. Acacetin was reported to activate mitogen-activated protein kinases, extracellular signal-regulated kinase (ERK)-1 and ERK-2, in cultured osteoblastic ROS 17/2.8 cells. Compound concentrations ranging from 10^{-14} to 10^{-6} M, induced rapid and transient activation of ERK-1/2 through phosphorylation (Park et al., 2002).

Acacetin was found to alleviate telomere position effect (TPE) in human cells, and also deprotected telomeres against DNA damage response. The telomere uncapping and anti-TPE activities of acacetin have been found to contribute to its anticancer effect (Boussouar et al., 2013).

In spite of a multitude of studies investigating the *in vitro* anticancer activity of acacetin, very few studies have focused on the *in vivo* effects. Topical administration of acacetin reduced the number of papillomas in 12-*O*-tetradecanoylphorbol 13-acetate-induced tumor promotion in mice at 20 weeks (Pan et al., 2006). Oral administration of acacetin resulted in anticancer activity in a chronic lymphocytic leukemia xenograft mouse model. The compound, at a concentration of 10 μM, was found to induce apoptosis in chronic lymphocytic leukemia B-lymphocyte (25% at 24 h) *via* increased ROS formation, MMP collapse, MPT, release of cytochrome c, caspase 3 activation, and apoptosis (Salimi et al., 2016). In contrast, normal healthy B-lymphocytes were unaffected at similar concentrations.

2.7. Anti-ageing activity

The development of age-related disorders is partially associated with elevated intracellular reactive oxygen species (ROS) and oxidative stress levels. The mean lifespan of Caenorhabditis elegans (worms) was increased by 27.31%, when compared to the untreated control, after exposure to acacetin at a dose of 25 μM (Asthana et al., 2016). They also demonstrated greater oxidative and thermal stress resistance. Under similar experimental conditions, acacetin also reduced the level of intracellular ROS, aggregation of lipofuscin (an age-pigment), and elevated the mean survival in a stress hypersensitive *mev-1* mutant by 40.5%. Furthermore, it was found to decrease the aggregation of α-synuclein in a transgenic worm model of Parkinson's disease.

The possible mechanism of action of acacetin against age-related pathology is associated with increased levels of the stress-modulatory enzymes, superoxide dismutase and catalase (Asthana et al., 2016). In addition, its anti-ageing and neuromodulatory activities are mediated by the up-regulation of the stress-response genes *sod-3* and *gst-4*.

2.8. Anti-oxidant activity

A study of superoxide anion-scavenging by acetacin, conducted by generating the anions in a phenazin methosulphate-NADH system and subsequent assay by reduction of nitroblue tetrazolium, indicated a poor scavenging ability compared to several other flavonoids (Chen et al., 1990). An investigation of the anti-oxidant activity revealed that acacetin moderately inhibited lipid peroxidation of mouse liver homogenate with an IC_{50} value of 10^{-5} M. Liu et al. (2004) reported that the hydroxyl groups present in the structure are possibly responsible for its anti-oxidant effect, through protecting erythrocytes against free radical-induced peroxidation.

Acacetin exhibited 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical-scavenging activity with an IC_{50} of 2.39 μg/mL, compared to that of Vitamin C (1.22 μg/mL) (More et al., 2012). In contrast, a quantitative structure-activity relationship study revealed that acacetin did not produce any anti-oxidant effects below an IC_{50} of 200 mM (Scotti et al., 2011). This was substantiated by Ahn et al. (2009), who reported that acacetin demonstrated very poor anti-oxidant activity in DPPH free radical-scavenging and ferric reducing/anti-oxidant power assays. These findings indicate that, compared to other widely available flavonoids, acacetin is not a good anti-oxidant.

2.9. Activity against diabetes and diabetic retinopathy

The use of *Anoda cristata* (L.) Schltdl. in the treatment of diabetes was partly attributed to the presence of acacetin (Juárez-Reyes et al., 2015). Shin et al. (1995) reported that acacetin inhibited *in vitro* rat lens aldose reductase activity, which has been associated with diabetic

Table 1
Effect of acacetin against different cancer cell lines.

Cell line	Significant findings	Positive/ negative control	Reference
HepG2 (a human liver cell line)	1. Moderate activity at IC_{50} 89.22 μM	Pacletaxel (IC_{50} 7.2 μM)	Rauf et al., 2016
A498 (Human renal carcinoma cell line)	1. Poor activity at IC_{50} > 200 μM	Pacletaxel (IC_{50} 7.2 μM)	Rauf et al., 2016
A549 (human lung cancer cell line)	1. Inhibition of proliferation by inducing apoptosis and blocking cell cycle progression in the G1 phase at IC_{50} 9.46 μM. 2. Increased the expression of p53 and p21/WAF1 protein, contributing to cell cycle arrest.	DMSO (0.1%)	Hsu et al., 2004a; 2004b
	1. Inhibited 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced abilities of the adhesion, invasion, and migration. 2. Inhibited phosphorylation of c-Jun N-terminal kinase 1 and 2 (JNK1/2) involved in the down-regulating protein expressions and transcriptions of MMP-2 and urokinase-type plasminogen activator induced by TPA. 3. Inhibited TPA-stimulated nuclear levels of NF-κB, c-Fos, and c-Jun.		Fong et al., 2010
	1. Cytotoxic at an IC_{50} value of > 40 μg/mL.	Cisplatin (IC_{50} 10.1 μg/mL)	Rahman and Moon, 2007
	1. Inhibited the abilities of the adhesion, morphology/ actin cytoskeleton arrangement, invasion, and migration at 10-30 μM for 24-48 hours. 2. Effect was mediated *via* sustained inactivation of the phosphorylation of mixed-lineage protein kinase 3, MAPK kinases 3/6, and p38α MAPK signal involved in the downregulation of the expressions of MMP-2, MMP-9 and u-PA. 3. Decreased the phosphorylation and degradation of IκBα and the nuclear levels of NFκB, c-Fos, and c-Jun. 4. Inhibited the binding abilities of NFκB and activator protein-1.	DMSO (0.2%)	Chien et al., 2011
	1. A combined treatment of acacetin (25 μM) with doxorubicin (10 μM) decreased the cell viability. 2. The combination caused G2/M arrest by downregulating CDK-cyclin complex in A549 cells. 3. The combination decreased the clonogenic potential of A549 and H1299 cells by up to 82%.	Tubulin and β-actin	Punia et al., 2017
H1299 (non-small-cell lung carcinoma cells)	1. A combined treatment of acacetin (25 μM) with doxorubicin (10 μM) decreased the cell viability. 2. The combination decreased the clonogenic potential of A549 and H1299 cells up to 59%.	Tubulin and β-actin	Punia et al., 2017
HL-60 (human promyelocytic leukemia cells)	1. Nitro blue tetrazolium reducing cells by > 40% at a concentration of 40 μM. 2. Structure-activity relationship revealed that ortho-catechol moiety in ring B and C2-C3 double bond play an important role for induction of differentiation of HL-60.	DMSO (0.4%)	Kawaii et al., 1999
V79 (hamster embryo cell line)	1. Inhibited the B[a]P-induced mutagenesis in a hamster embryo cell-mediated V79 cell mutation assay without showing cytotoxicity. 2. Acacetin can be considered as a chemopreventive agent.	DMSO (0.1%)	Young et al., 1992
PC-3 (human prostate cell line)	1. Cytotoxic against solid human tumor cell line with ED_{50} at < 4 μg/mL.	Adriamycin (0.0024 μg/mL)	Tian and McLaughlin, 2000
AGS (human gastric carcinoma cell line)	1. Inhibited cell proliferation and induced apoptosis at 30-100 μM. 2. Induced caspase-3 activity, and degradation of DNA fragmentation factor (DFF-45) and poly-(ADP-riobse) polymerase. 3. Caused a rapid loss of mitochondrial transmembrane potential, stimulated ROS, released mitochondrial cytochrome c into cytosol, and induced procaspase-9 processing.	DMSO (0.05%)	Pan et al., 2005
HSC-3 (human oral squamous carcinoma cell line)	1. Inhibited the growth with an IC_{50} value of 25 μM. 2. Maximum caspase-3 activity observed with 100 μg/mL for 24 h. 3. Induced apoptosis of cancer cells, which is closely related to its ability to activate the MAPK-mediated signaling pathways.	Pyrrolidine dithiocarbamate (25 μM)	Kim et al., 2015
HeLa (human cervical cancer cell line)	1. Cytotoxic with an IC_{50} value of 174 μM.	Curcumin (30 μM)	Nath et al., 2015
MDA-MB-231 (human breast cancer cell line)	1. Inhibited the activation of NF-κB, and the expression of MMP-9 and COX-2 in cancer cells at 25 μM.	Serum free media	Amrutha et al., 2014
	Treatment of acacetin (50, 100 and 150 μM) resulted in increase in percentage of cells at G2/M phase and decrease in percentage of cells at G1 and S phase.	GAPDH	Zhang et al., 2018
T-47D (human breast cancer cell line)	1. Acacetin (0.001-10 μmol/L) promoted the proliferation and increased the number of cells arrested in S and G2/M phase. 2. Ki67 mRNA levels and the ERa protein levels in T47D cells were remarkably upregulated.	PHTPP	Si et al., 2017
DU145 (human prostate cancer cell line)	1. Suppressed cell viability *in vitro* at 50 μM. 2. Acacetin-treated nude mice bearing DU145 tumor xenografts exhibited significantly reduced tumor size and weight, due to the effects of acacetin on cancer cell apoptosis. 3. Exerted antitumor effect by targeting the Akt/NF-kB signaling pathway.	β-Actin	Kim et al., 2014
	1. Acacetin exerted cytotoxicity, and clearly suppressed constitutive STAT3 activation, and induced apoptosis in DU145 cells at 50 μM.	β-Actin	Kim et al., 2013

(*continued on next page*)

Table 1 (*continued*)

Cell line	Significant findings	Positive/ negative control	Reference
	1. Inhibited the abilities of the adhesion, invasion, and migration of cancer cells at various concentrations up to 60 μM for 24 and 48 h. 2. Inhibit the phosphorylation of p38 MAPK involved in the downregulation of the expressions of MMP-2, MMP-9, and urokinase-type plasminogen activator. 3. Decreased the nuclear levels of NF-κB, c-Fos, and c-Jun.	β-Actin	Shen et al., 2010
	1. Showed cell growth inhibition by 25-62%, 29–68% and 45–83% at 25, 50 and 100 μM doses, respectively. 2. Showed G1 and/or G2-M arrest. 3. Induced cell death associated with significant increase in apoptosis induction.	DMSO (0.1%)	Singh et al., 2005
K562 (human immortalized myelogenous leukemia cell line)	1. Acacetin potentiated the cytotoxicity of 7-ethyl-10-hydroxycamptothecin (SN-38) and mitoxantrone in BCRP-transduced K562 (K562/BCRP) cells at 3 μM. 2. Overcome the breast cancer resistance protein-mediated drug resistance in tumor cells.	α-Tubulin	Imai et al., 2004
SW480 (human colonic carcinoma cell line)	1. Showed cell-cycle arrest at the G2/M phase with 80 μM concentration for 48 h. 2. Cell number was significantly decreased. 3. Combined with apigenin (20 μM), acacetin at 30 μM increased the proportion of G2/M cells by 22%. However, the interaction became antagonistic with doses higher than 40 μM.	DMSO (0.2%)	Wang et al., 2004
Jurkat (human T cell leukemia cell line)	1. Inhibited the proliferation of Jurkat cells by inducing apoptosis at IC_{50} of 25.77 μM. 2. Induced caspase-3, -8 and -9 activities. 3. Promoted the expression of FAF1, phosphor-FADD, Apaf-1 and cytochrome c. 4. Acacetin simultaneously induced apoptosis and cytoprotective autophagy in Jurkat T cells 1.	β-Actin	Watanabe et al., 2012; Lee et al., 2017b
HUVECs (human umbilical vein endothelial cell line)	1. Inhibited TNF-α-induced E-selectin expression, a good target for therapeutic intervention in cancer metastasis. 2. Suppressed TNF-α-induced phosphorylation of p38. 3. Inhibited the activation of NF-κB by stimulation with TNF-α.	β-Actin	Tanigawa et al., 2013
B16 (murine skin tumor cell line)	1. Inhibited cancer cells with IC_{50} value of < 50 μM at 48 h. 2. Cytotoxicity due to C2-C3 double bond and 3',4'-dihydroxylation.	DMSO (1%)	Touil et al., 2009
	1. Inhibited the proliferation at IC_{50} 7.5-21.2 μg/mL.	DMSO (1%)	Gadelha Militão et al., 2005
Lewis (mouse lung cancer cell line)	1. Inhibited cancer cells with IC_{50} value of < 50 μM at 48 h. 2. Cytotoxicity due to C2-C3 double bond and 3',4'-dihydroxylation.		Touil et al., 2009
B16F1 (mouse skin cancer cell line)	1. Cytotoxic at an IC_{50} value of > 40 μg/mL.	Cisplatin (IC_{50} 7 μg/mL)	Rahman and Moon, 2007
SK-Mel-2 (human skin cancer cell line)	1. Cytotoxic at an IC_{50} value of 39 μg/mL.	Cisplatin (IC_{50} 5 μg/mL)	Rahman and Moon, 2007
LNCaP (human prostate cancer cell line)	1. Showed cell growth inhibition by 30-63%, 45–77% and 50–80% at 25, 50 and 100 μM doses, respectively, for 24–72 h. 2. Showed G1 and/or G2-M arrest. 3. Induced cell death associated with significant increase in apoptosis induction.	DMSO (0.1%)	Singh et al., 2005
MCF-7 (human breast cancer cell line)	1. Inhibited the proliferation at IC_{50} 7.5-21.2 μg/mL.	DMSO (1%)	Gadelha Militão et al., 2005
	1. Caused growth inhibition at IC_{50} of 26.4 μM for 24 h. 2. Apoptosis characterized by DNA fragmentation and an increase of sub-G1 cells and involved activation of caspase-7 and PARP. 3. Reduced Bcl-2 expression leading to an increase of the Bax:Bcl-2 ratio.	DMSO (1%)	Shim et al., 2007
	At a low dose of 10^{-3} to 1 μM, it promoted cell proliferation and increased the expression of cell cycle-related molecules, ERK1/2 and PI3K/AKT.	DMSO (1%)	Ren et al., 2018
CEM (human T-lymphoblastoid cancer cell line)	1. Inhibited the proliferation at IC_{50} 7.5-21.2 μg/mL.	DMSO (1%)	Gadelha Militão et al., 2005
NCI-H187 (human lung cancer cell line)	1. Cytotoxic with the MIC value of 24.6 μM	DMSO (1%)	Suksamrarn et al., 2004

retinopathy. The flavonoid showed anti-hyperglycemic activity in streptozotocin-induced diabetic mice at oral doses of 3 and 31.6 mg/kg, by decreasing blood glucose levels in healthy and hyperglycemic mice when compared to an untreated group (Juárez-Reyes et al., 2015). Additionally, acacetin showed stable binding to the active site of aldose reductase, a primary mediator of diabetes-induced oxidative stress in retinopathy. It can interrupt the proton donation mechanism by forming a hydrogen bond with Tyr48 of this enzyme. The study suggested that acacetin, derived from natural sources, could be used as an aldose reductase inhibitor (Manivannan et al., 2015).

2.10. Antipyretic and anti-nociceptive activity

Intraperitoneal injection of acacetin at 5 and 10 mg/kg into yeast-induced febrile mice caused a 33% and 55% reduction in pyrexia, respectively (Rauf et al., 2014). This method of administration also resulted in a reduction in rectal temperature of the treated mice. They also reported that the compound at 5 and 10 mg/kg exhibited anti-nociceptive activity, with a 44.77% and a 67.03% reduction, respectively, in abdominal constriction as determined in an acetic acid-induced writhing test conducted in mice. The researchers proposed that the mode of action of the observed antinociceptive activity of acacetin could be the inhibition of the release of endogenous compounds such as arachidonic acid metabolites, which excite nerve endings responsible for pain. The intraperitoneal administration of acacetin in the formalin-induced flinching behaviour model caused a dose-dependent reduction in noxious stimulation, with a 42.07% and 64.57% reduction in pain attenuation at 5 and 10 mg/kg i.p., respectively.

In a separate study (González-Trujano et al., 2012), acacetin derived from *Agastache mexicana*, a Mexican traditional medicinal plant used to reduce pain, anxiety and insomnia, also demonstrated antinociceptive activity. It generated a significant spasmolytic response in isolated guinea pig ileum rings, when compared to ursolic acid and papaverine. In addition, its antinociceptive response was established in the writhing test in mice *via* intraperitoneal, as well as oral routes, with diclofenac, a standard analgesic drug, used as a control.

2.11. Hepatoprotective activity

Intraperitoneal administration of acacetin was found to protect against D-galactosamine/ lipopolysaccharide-induced liver injury in mice by suppressing TLR4-signaling, and enhancing autophagic flux (Cho et al., 2014). It potentially reduced D-galactosamine (800 mg/kg) and lipopolysaccharide (40 μg/kg)-induced mortality and serum aminotransferase activity at 25, 50, and 100 mg/kg i.p. Furthermore, the compound reduced the levels of TNF-α, while increasing the concentrations of IL-6 in experimental mice. Acacetin was found to be an inhibitor of the human UDP-glucuronosyl-transferase 1A1 (UGT1A1), a key enzyme in detoxification of endogenous harmful compounds, such as bilirubin. The structure-activity relationship study revealed that the hydroxyl group at C-7 is possibly responsible for this activity (Liu et al., 2019).

2.12. Anti-allergic and immunomodulatory activities

Pearce et al. (1984) reported the antihistaminic activity of acacetin in an *in vitro* study using cultured *Nippostrongylus brasiliensis*-infected intestinal mast cells of rats. The results from the study indicated possible inhibition of the anaphylactic release of histamine in mast cells by acacetin.

Acacetin also exhibited immunomodulatory activity *in vitro* by blocking Kv1.3 channel and inhibiting human T-cell activation with IC_{50} values at + 40 mV of 21.09 and 3.63 μM/L, respectively. Throughout the treatment, acacetin inhibited the expression of Kv1.3 protein, Ca^{2+} influx, Ca^{2+}-activated transcription factors, NF-κB p65/p50 activity and proliferation, as well as IL-2 production (Zhao et al., 2014).

2.13. Antimicrobial activity

Acacetin displayed moderate antimicrobial activities against several Gram-positive bacteria (*Actinomyces naeslundii*, *Actinomyces israelii*, *Streptococcus mutans*), as well as against a variety of Gram-negative bacteria (*Prevotella intermedia*, *Porphyromonas gingivalis*, *Aggregatibacter actinomycetemcomitans*), as reflected by the minimum inhibitory concentrations (MICs), which ranged from 0.25 and 1.0 mg/mL (More et al., 2012). The compound was also active against *Candida albicans*. Further antimicrobial assays were conducted against other *Candida* species (Rahman and Moon, 2007), to establish the antifungal activity of acacetin. Instead of determining MICs, the inhibition zone diameters (IZD) of the fungal growth were measured. Application of 40 mg acacetin/disc resulted in IZDs of 9 and 12 mm for *C. glabrata* and *C. tropicalis*, respectively, compared to the IZDs of 10.5 and 11 mm for the positive control (amphotericin B). As a bioactive constituent of *Combretum vendae* (Combretaceae), acacetin exhibited strong activity against *Staphylococcus aureus, Enterococcus faecalis, Escherichia coli* and *Pseudomonas aeruginosa*, with MIC values ranging from 0.16 to 0.35 mg/mL (Komape et al., 2014).

Gomes et al. (2011) reported a similar MIC value (0.256 mg/mL) for acacetin towards *S. aureus*. It was found to enhance the antimicrobial activities of the antibiotics, norfloxacin and ethidium bromide, as reflected by a two-fold reduction in their MICs, at a starting concentration of 0.064 mg/mL. The compound was also found to inhibit the activity of sortase A in the bacterium, with an IC_{50} value of 36.46 μg/mL (Bi et al., 2016). Sortase A catalyses at least 25 surface proteins that covalently bind to cell wall peptidoglycans The anti-mycobacterial activity of acacetin against *Mycobacterium tuberculosis* was poor, with an MIC of 704.2 μM reported (Suksamrarn et al., 2004).

As part of an investigation into *Scoparia dulcis*, acacetin, one of the major metabolites, was found to inhibit the replication of Herpes simplex virus type 1 (HSV-1) in a dose-dependent manner (Hayashi et al., 1993). Nevertheless, at higher doses, it displayed only weak virucidal activity. In the same study, it effectively inhibited protein synthesis in virus-infected cells.

Notably, the flavone inhibited HIV expression in TNF-α-treated OM-10.1 cells, and demonstrated a potent effect against HIV activation (therapeutic index 5–10). The molecule did, however, not effectively inhibit NF-κB activation, following TNF-α treatment (Critchfield et al., 1996). Xu et al. (2000) reported that the molecule exhibited inhibitory activity towards HIV-1 protease. In addition to the above effects, acacetin has also shown inhibitory activity against influenza viruses, when compared to that of ribavirin (Wu et al., 2010).

2.14. Anti-parasitic activity

Anti-Leishmania studies on acacetin revealed that the compound produced a moderate effect against *Leishmania donovanii*, with IC_{50} and IC_{90} values of 18 and 40 μg/mL obtained, respectively. These values indicate considerably lower activity than for the positive controls, pentamidine (IC_{50}, 1.9 and IC_{90}, 8.5 μg/mL) and amphotericin B (IC_{50}, 0.7 and IC_{90}, 1.7 μg/mL). With regard to *Plasmodium falciparum*. the compound was found to be inactive at 1.59 μg/mL when compared to artemisinin (IC_{50}, 0.014 μg/mL) (Filho et al., 2009). However, the IC_{50} of 55.14 μM indicated some degree of activity against the parasite when compared to the antimalarial drug chloroquine (IC_{50} 0.11 μM), suggesting moderate antimalarial efficacy (Rauf et al., 2016).

2.15. Hypouricemic activity

Acacetin, isolated from the flowers of *Chrysanthemum sinense* Sabine, demonstrated hypouricemic activity in rats pretreated with the uricase inhibitor, potassium oxonate (Nguyen et al., 2005). An oral administration of 20 and 50 mg/kg decreased the concentration of serum uric acid in rats by 49.9 and 63.9%, respectively, whereas intraperitoneal administration with similar doses reduced uric acid by 63 and 95%, respectively. This study also further indicated that acacetin inhibits xanthine oxidase activity in rat liver as reflected by the *in vitro* IC_{50} value of 2.22 μM. This finding suggests that the hypouricemic activity of this molecule is associated with its xanthine oxidase inhibitory effect.

2.16. Melanogenesis inhibitory activity

Acacetin inhibited melanin production by *Streptomyces bikiniensis* with an IZD value of 11 mm at 30 mg/paper disk (Roh et al., 2004). The molecule further inhibited tyrosinase with an IC_{50} value of 0.779 mM compared to the known melanogenesis inhibitor arbutin (IC_{50} = 0.223 mM). Acacetin inhibited melanin synthesis in B16 melanoma cells at an IC_{50} value of > 20 mM, and displayed toxicity towards cultured B16 cells, with an IC_{50} of 0.423 mM. However, arbutin was considerably more active demonstrating melanin inhibition activity and cytotoxicity against B16 cells, with IC_{50} values of 0.122 and > 20 mM, respectively.

3. Toxicity

Considering the many studies conducted on the pharmacological activities of acacetin, very little information is available on the toxicity of the compound. The brine shrimp lethality test did not indicate any toxicity on the part of acacetin, although the positive control, ampicillin trihydrate, was lethal (Rahman and Moon, 2007). An *in vitro* study also indicated that acacetin did not exert cytotoxicity against normal human lung cells (WI-38) at concentrations up to 50 μM, however, the compound was effective against the human non-small cell cancer cell line A549 (Chien et al., 2011).

Furthermore, this molecule did not display any significant insecticidal activity against *Aedes atropalpus* mosquito larvae (Pereda-Miranda et al., 1997). A separate study investigating the suppressive effects of acacetin on gene expression, revealed that it suppressed the furylfuramide-induced SOS response in *Salmonella typhimurium* TA1535/pSK1002 in the umu test by 60.2% after exposure to 0.70 μM/mL. An ID_{50} value of 0.62 μM/mL was reported (Miyazawa and Hisama, 2003). Acacetin exerted antifeedant activity against striped leaf beetles, but the activity was only moderate since exposure to a high concentration (2 mg/mL) of acacetin for 24 h yielded an antifeedant index of 51.22 (Xu et al., 2009).

Hiremath and Rao (1990) investigated the endocrine and contraceptive effects of the compound in the pre-implantation stage of pregnancy using a rat model. They found that oral administration of the molecule has an anti-implantation effect at 5–25 mg/kg/day from Days 1–4 of pregnancy. In addition, the compound prevented complete implantation at an oral dose of 10 mg/kg on Days 1, 2 and 3. However, acacetin did not produce anti-estrogenic effects in pregnant rats.

As far as could be ascertained, the bioavailability of the compound has not been investigated. Compounds that are well absorbed and rapidly metabolised may exert toxicity in specific organs.

4. Structure-activity relationship

Structure-activity relationship studies revealed that the hydroxy groups at C-5/C-7, the double bond at C-2/3 and the methoxy group at C-4′are the key components in the biological activity of acacetin (Fig. 1). Androutsopoulos et al. (2009) found that the ethoxyresorufin-*O*-deethylase inhibitory activity of the molecule was due to both the 5,7-dihydroxy moieties of the A-ring and the methoxy group of the B-ring. Furthermore, the *ortho*-catechol moiety in Ring B, as well as the C-2/3 double bond, were found to play a key role in the induction of differentiation of HL-60 cells (Kawaii et al., 1999). A double bond at C-2/3 and hydroxy groups in ring A have been associated with tracheal relaxant activity (Ko et al., 2003).

5. Concluding remarks

Studies carried out on acacetin suggest that the flavone may be safe to incorporate in commercial nutraceuticals. However, the question of bioavailability in humans has not been addressed and the existing data on toxicity is too sparse to recommend the commercialization of preparations containing acacetin at highly enriched dosages. A critical gap for further research to investigate safety, relying on the use of a variety of animal models, has been identified.

A review of the literature revealed that the compound has a modulating effect on the concentrations of various enzymes such as aromatase, which is responsible for converting testosterone to estrogen. The molecule is currently available on the market as an aromatase and estrogenic antagonist. Evidence indicates that one of the most important applications of acacetin in the human diet could potentially be to prevent and halt the development of AD. Not only have some researchers reported that the molecule inhibits acetylcholinesterase (Lim et al., 2007), but it also regulates the transcription of human BACE1 and amyloid precursor protein, and reduces β-amyloid production, by interfering with BACE1 activity and the synthesis of amyloid precursor protein (Wang et al., 2015). The compound may also be beneficial in the prevention of atherosclerosis, since, according to Cho et al. (2004), acacetin was able to efficiently reduce the cholesterol content of cultured HepG2 cells at a concentration of 0.1 μM. Intake of acacetin could therefore improve blood lipid status by increasing HDL-cholesterol formation and cholesterol excretion. Results of several *in vitro* studies indicate anti-inflammatory activity, providing further impetus towards investigating the beneficial role of the compound in treating heart conditions. There is plenty of *in vitro* evidence to suggest that the compound has anticancer activity, yet appears to be non-toxic towards normal cells. An *in vitro* study by Androutsopoulos et al. (2008) found that the molecule is not toxic towards normal cells, since it had no effect on cell proliferation of MCF-10 A, a cell line derived from normal mammary tissue, at a concentration of 1.5 μM.

The anti-inflammatory activity of the compound was verified both *in vitro* (Fan et al., 2012) and *in vivo* (Carballo-Villalobos et al., 2014). However, it was disappointing to find that, despite promising *in vitro* results obtained when other pharmacological effects were investigated, very few animal studies were carried out to evaluate the benefits of acacetin in heart disease, cancer, and the progression of dementia. Once the results of such studies have been evaluated, clinical trials should be initiated to conclusively prove beneficial effects and rule out safety concerns. This review has collated the existing data on a very interesting metabolite in the hope that researchers will take on the challenge of proving the worth of this simple molecule as a health supplement.

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