Synthesis and Structure–Activity Relationship Analysis of the Natural Flavone Acacetin as a Promising Anticancer Agent

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Abstract:

Flavonoids are diverse group of phytochemicals that are found in fruits, vegetables, and medicinal plants and exhibit wide range of pharmacological activities, including antioxidant, anti-inflammatory, antiviral, cardioprotective, neuroprotective, and anticancer activities. Among the subclasses of flavonoids, flavones have gained a lot of attention because of their therapeutic potential in solving problems associated with oxidative stress. A 2-phenylchromen-4-one skeleton structurally defines these compounds, and representative flavones such as apigenin and acacetin exhibit significant biological actions that can be attributed to their specific hydroxyl and methoxy substitution patterns. Acacetin (5,7-dihydroxy-4'-methoxyflavone) is naturally occurring flavone which may be isolated from such species as Turnera diffusa, Saussurea involucrata, and Robinia pseudoacacia. The compound exhibits unique physicochemical properties and high lipophilicity, which enable it to exert powerful anticancer action on various human cancer cell lines through the induction of apoptosis and cell cycle arrest. Mechanistic studies have shown that acacetin regulates both mitochondrial (intrinsic) and death receptor (extrinsic) apoptotic pathways, as well as p53-mediated signaling, which inhibit the proliferation, migration, angiogenesis, and metastasis of the cells. Structure-activity relationship studies have established the importance of a free hydroxyl group on the A-ring and a methoxy group on the B-ring for the maintenance of the cytotoxicity of acacetin. Alterations to these functional groups frequently result in diminished biological activity, underscoring the importance of maintaining the native substitution pattern for optimal therapeutic potential. Future research should focus on elucidating the detailed molecular interactions of acacetin with its cellular targets, characterizing its metabolic profile, and developing clinically viable derivatives.

Key words: Flavonoids, Flavone, Acacetin, Synthesis, SAR, and Mechanisms of Anticancer Activity.

1. INTRODUCTION:

1.1. Flavonoids:

Flavonoids are Phytochemicals that are found in numerous plants, fruits, vegetables, and leaves, and may be used in medicinal chemistry. Flavonoids are known to have a number of medical advantages, including anticancer, antioxidant, anti-inflammatory, and antiviral effects [1]. They are also neuroprotective and cardioprotective. Such biological processes require reliance on the nature of flavonoid, mode of action (possibly), and bioavailability. These are cost-effective medicinal components which possess considerable biological activities, and their usefulness has been demonstrated against many diseases. The latest research is dedicated to their isolation, synthesis of their analogues, and their impact on human health with the help of numerous methods and animal models. It has managed to isolate thousands of flavonoids, with the number rising continuously [1]. We have thus attempted to compile the isolated flavonoids with helpful activities with the aim of having a better insight into their impact on human health. Flavonoids are reported to suppress cell proliferation and are an anticancer agent. Chemoprevention involves the administration of natural or artificial chemicals to prevent carcinogens [2].

The skeleton of the basic flavonoid structure is the flavan nucleus, or 15 carbon atoms that are a result of the C6-C3-C6 skeleton, as illustrated in Figure 1. The skeleton of a flavonoid consists of 2 aromatic rings (usually denoted by A and B) connected with the help of a three-carbon chain. The linking carbon chain reacts with some oxygen to form a heterocyclic central or C-ring of most flavonoids except chalcones, where the carbon backbone between the A and B ring is linear [3]. Flavonoids may further be subclassified into different groups based on the level of unsaturation and oxidation of the C ring and the carbon of the C ring to which the B ring is attached. The subgroups that follow are called flavones, flavanols, flavanones, flavanols, catechins, anthocyanin and chalcones. The biological properties of different flavonoids exhibit various properties in the mammalian system both in vitro and in vivo like antioxidant, radical scavenging, anti-inflammatory, antiviral, anti-cancer and anti-mutagenic properties [4], [5].

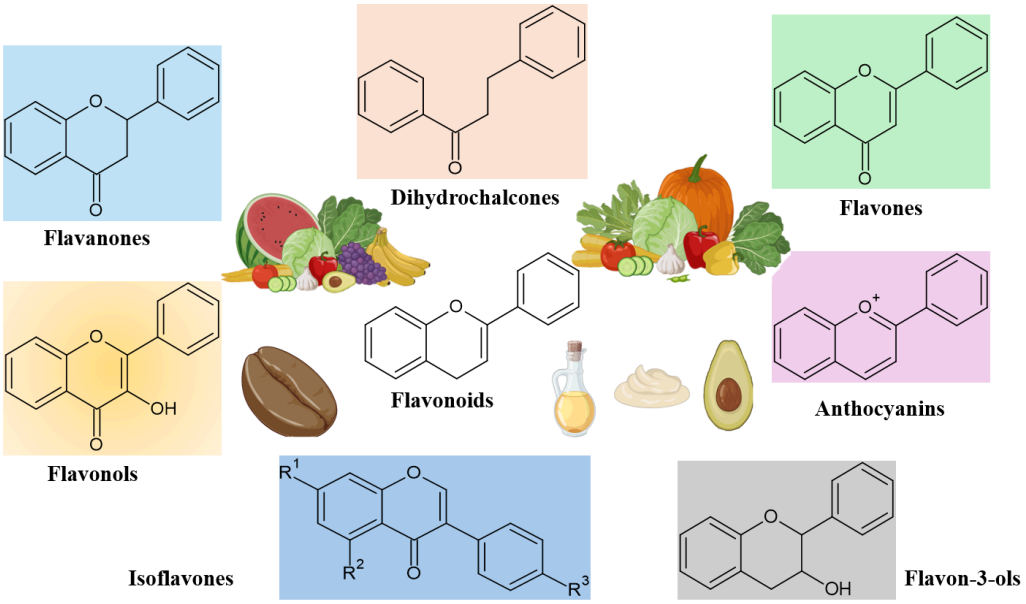


Figure 1: Sources and types of Flavonoids

1.2. Flavone:

Flavones are a subfamily of flavonoid as they possess characteristics of flavonoid and are also utilized in cancer, cardiovascular disease, neurodegenerative disorders, etc. Flavones have been an essential stepping stone in the making of other therapeutic agents. Most of the metabolic diseases are postulated to result out of oxidative stress and thus, of relevance is the fact that recent research has demonstrated to attest to the positive impact of flavones on the oxidative stress related diseases [6]. Flavones occur abundantly in the leaves, flowers and fruits in a glucoside state. The key sources of flavones are celery, parsley, red peppers, chamomile, mint, and ginkgo biloba. This subclass of flavonoids includes leuteolin, apigenin, acacetin, and tangeritin. They are doubly linked between positions 2 and 3 and a ketone at position 4 of the C ring. The hydroxyl group of most flavones of vegetables and fruits is in the 5 position of the A ring, whereas the position of other hydroxylation can be variable, chiefly position 7 of the A ring or position 3' and 4', of the B ring, depending on the taxonomic family of the vegetable or fruit [7]. Acacetin and apigenin are flavones that are significant natural polyphenolic compounds. The compounds are in the general group of flavonoids that are known to possess diverse biological activities and applied in the treatment of different diseases properties [8]. These natural polyphenolic secondary metabolites can be isolated in plants although acacetin can be majorly extracted in morning leaves, henna (Lawsonia inermis Linn.), Eupatorium odoeatum. Numerous natural, semisynthetic, and synthetic analogs of flavones have been produced and tested concerning several therapeutic properties [8].

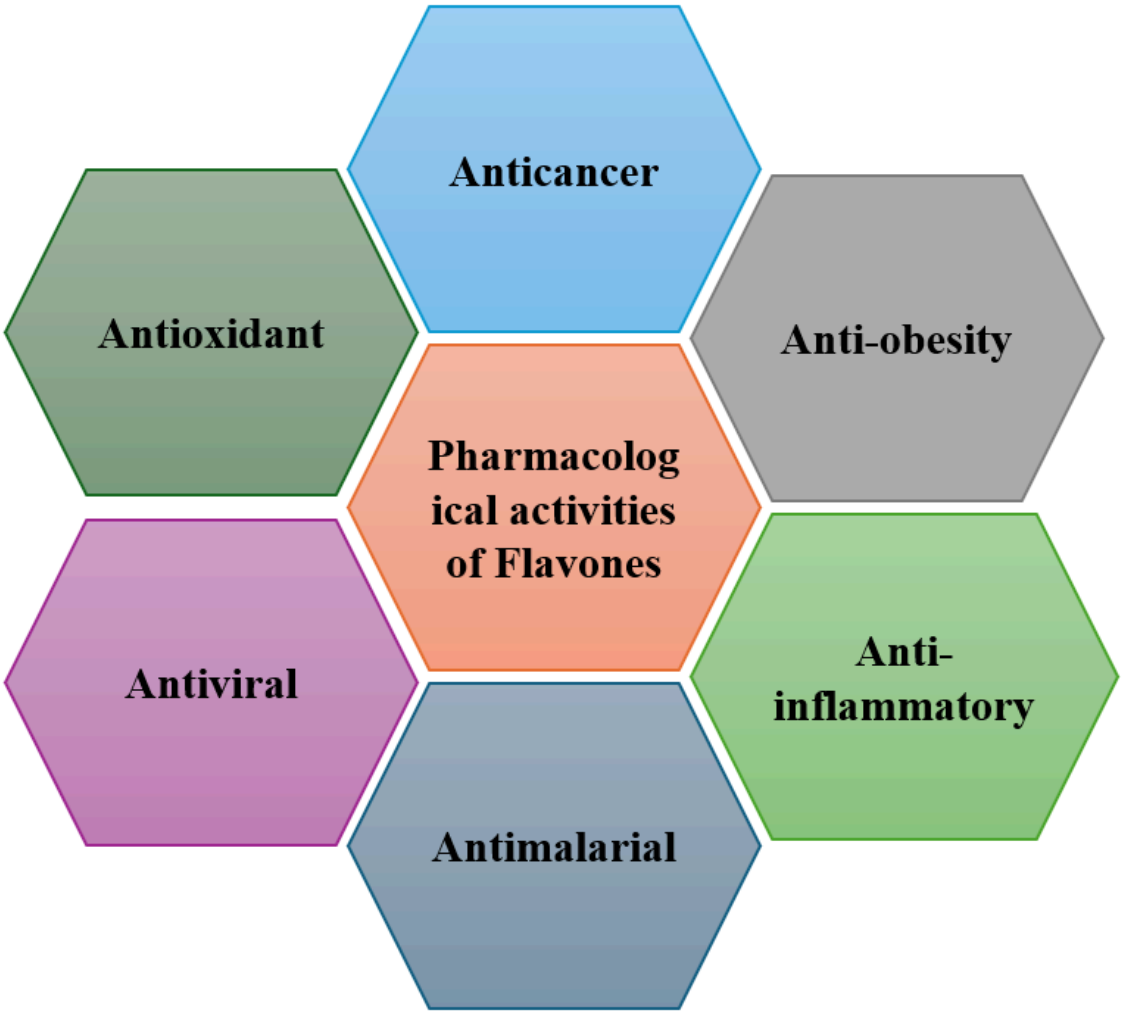


Figure 2: Versatile Potential of Flavone Nucleus [9], [10], [11]

Chemistry of Flavone:

Flavone is a group of flavonoids that are derived based on 2-phenylchromen-4-one(2-phenyl-1-benzopyran-4-one). The molecular formula of the flavone molecule is C 15 H 10 O 2. It possesses skeletons that are three-ringed C6-C3-C6 and they are termed A-, C-, and B-rings respectively. Flavones contain three functional groups: hydroxy, carbonyl and conjugated double bond; therefore, they respond normally based on all the three functional groups. Flavones are of the planar structure having C-O-C bond angle of 120.9 degrees. Its bond length between C-O is 1.376 A0 and its dihedral angle is around 179.2 degrees. There are different synthetic schemes to produce flavones such as Claisen-Schmidt condensation, Baker-Venkataraman rearrangement and Ionic Liquid Promoted synthesis [12], [13].

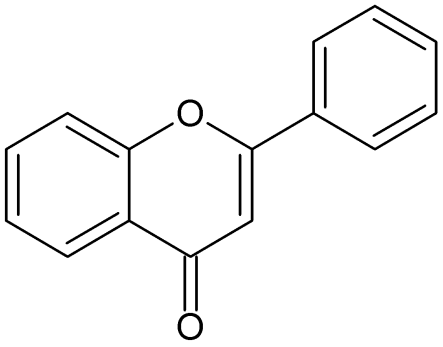


Figure 3: Basic structure of flavone

1.3. Acacetin:

The chemical name of acacetin is 5, 7-dihydroxy-4'-methoxyflavone, and chemically it is a flavonoid (chemical subgroup of polyphenols) which is a flavone compound occurring in nature. It is classified by its unique structural role with two hydroxyl groups at the 5 and the 7 position of the A-ring and a methoxy group at the 4 position of the B-ring which are 4' [12]. This unique arrangement contributes significantly to its physicochemical properties and biological activity. There are many plant species which contain acacetin, most notably Turnera, Rabinia, Saussurea, and Acacia; and acacetin is basically present in Turner diffusa(Damiana), Saussurea involucrate, and Robinia pseudoacacia [14], [15].

As other flavonoids, acacetin acts in plants as a guard against environmental stresses like UV rays, pathogens and herbivores. This is because over the last several decades, acacetin has received significant biomedical interest because of its extensive range of pharmacological activity, consisting of antioxidant, anti-inflammatory, anti-cancer, cardioprotective, neuroprotective and antimicrobial activities [6], [16].The anti-cancer potential of acacetin is one of the most important properties of this chemical [16].

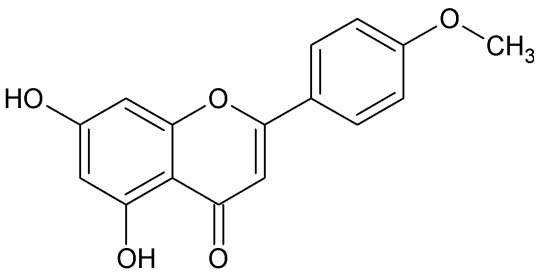


Figure 4: Structure of Acacetin

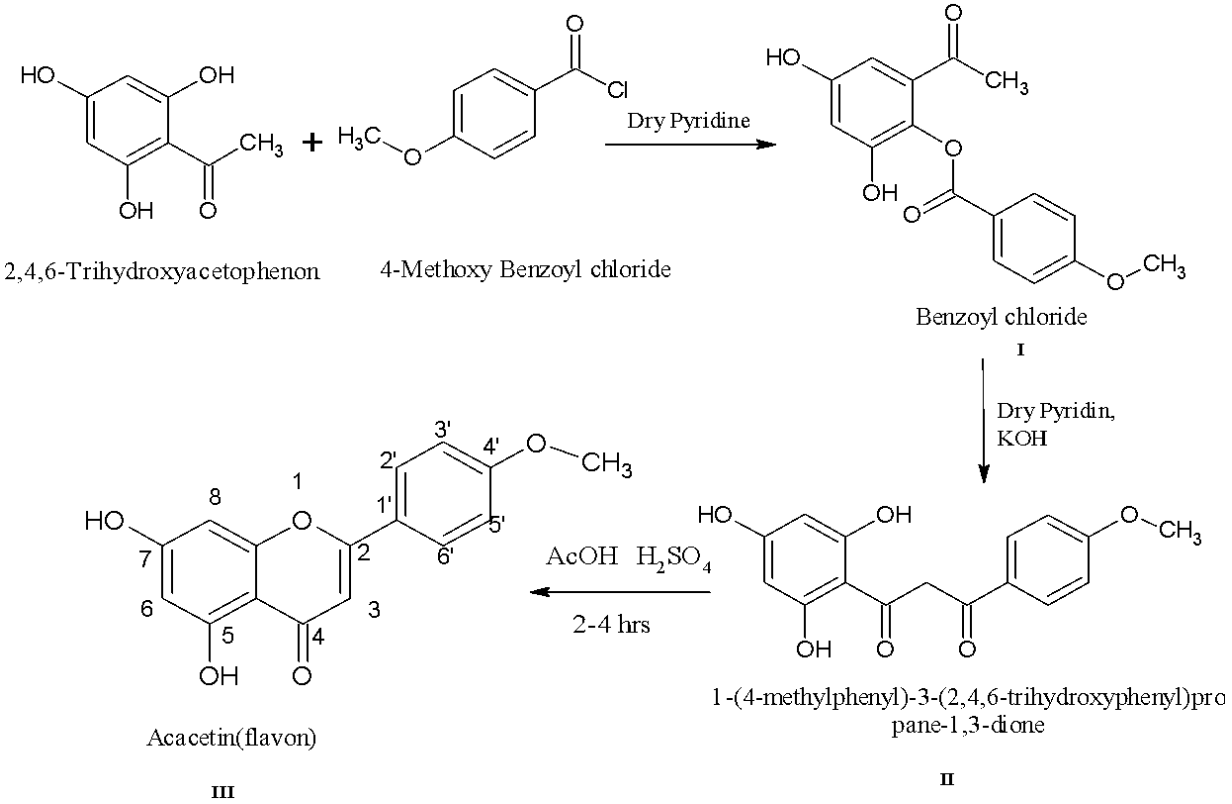
Table 1: Physicochemical properties of Acacetin

IUPAC NAME	5,7-dihydroxy-4'-methoxyflavone
Chemical class	Flavone
Molecular formula	$C_{16}H_{12}O_5$
Molar mass	284.26 g/mol
Solubility	Soluble in DMSO, ethanol, methanol, and acetone
Density	1.5 g/cm^3

Melting point	265-267 ℃
Appearance	Pale yellow crystalline powder
Log P	2.27

As has been proven, acacetin is able to suppress the growth of cancer cells and cause them to undergo the process of apoptosis in a range of human cancer cell lines as well as those of the breast, lung, prostate, liver, colon, and leukaemia origins [17]. The pathways of action of these effects include the control of cell cycle progression, mitochondrial membrane potential, and intrinsic and extrinsic apoptotic pathways. Acacetin is reported to stabilize the cell cycle at G2/M with the use of cyclins and cyclin-dependent kinase (CDKs). It also causes cytochrome c to be released by mitochondria and caspases especially caspase-3 and -9 which play a key role in facilitating apoptosis. In hormone sensitive cancer like breast and prostate cancer, acacetin disrupts the hormone signalling pathways, and thus lowers tumor growth and progression [18].

2. SYNTHESIS OF ACACETIN:



Scheme 1: Synthesis of Acacetin

Steps involved in the synthesis of Acacetin:

Step I:

Approximately 2.15 g of 1-(2, 4, 6-trihydroxy phenyl) ethanone was placed in flask (beaker) and 3g of 4-methoxy benzoyl chloride and 3ml of dry redistilled pyridine were added to mix the products which warmed. The reaction mixture was then added after 30 minutes with stirring to 100mL of 1M hydrochloric acid mixed with 30.71g of crushed ice. Filter using suction and wash using 3.13 ml of ice-cold methanol and 3.13 ml of water. It was recrystallised again using methanol [12].

Step II:

The 1-{2-[(4-methoxyphenoxy) methoxy]-4, 6-dihydroxyphenyl ethenone (0.2 mol.) was added to 27.64 mL of dry pyridine in a flask. The solution is brought to 50 °C. Add Potassium hydroxide (0.3 mol.) and stir mechanically which powder quickly in a mortar warmed in an oven at 100 °C. The mixture was stirred 2h-3h until the yellow potassium salt of the product was separated. The mixture was allowed to cool down to room temperature followed by acidification of the reaction mixture using 10% aqueous acetic acid. The mixture of the reaction was left to stand 24h to separate the precipitate. The product was recrystallized using methanol [12].

Step III:

In a round-bottomed flask, 4-(4-methoxyphenyl)-1,3-dihydroxybutane-1,3-dione (0.15 mol.) was dissolved in the glacial acetic acid (1.53) and 0.15 mL of concentrated sulphuric acid was added and stirred. The mixture was refluxed at a water bath with occasional shaking for 90 minutes. The mixture of the reaction was poured over crushed ice. The product was filtered and washed with water till the solution was not acidic. Drying of the product was done in an oven at 50 °C [12].

3. STRUCTURE ACTIVITY RELATIONSHIP (SAR) OF ACACETIN:

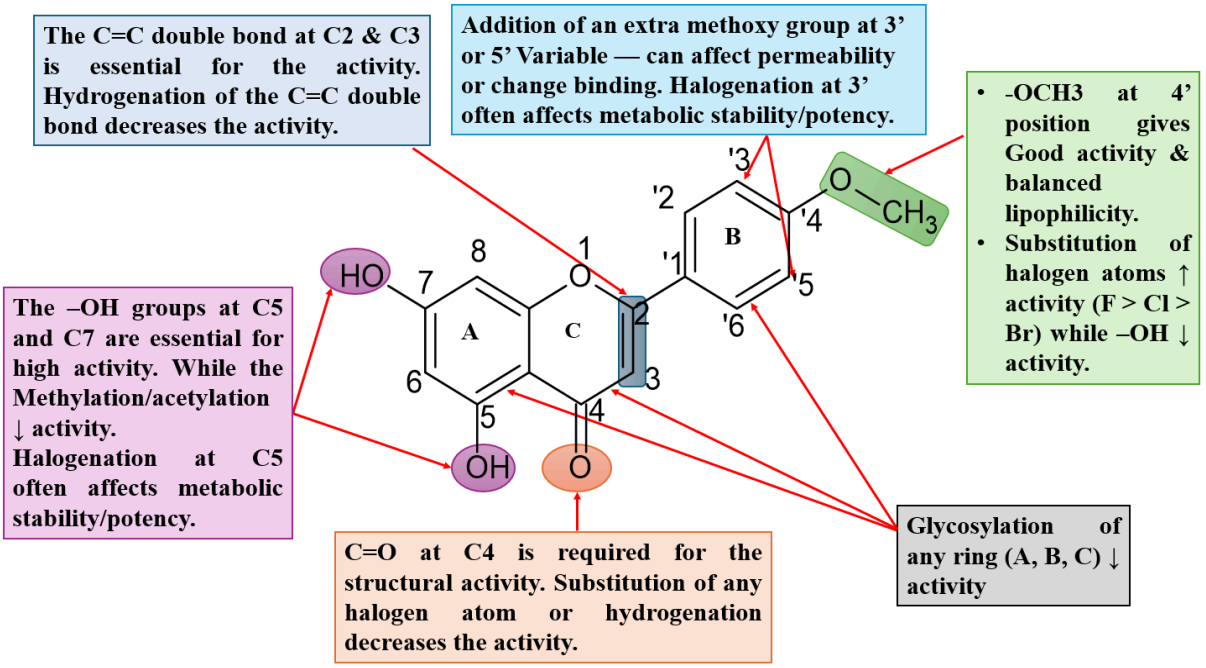


Figure 5: SAR of Acacetin

he substitution pattern of acacetin (5,7-dihydroxy-4'-methoxyflavone) largely affects its anticancer activity. These free hydroxyl groups on the A-ring are essential to potency: activities of cytotoxic activity are greatly impaired by methylation or acetylation of these functional groups, presumably due to the likely role in hydrogen-bonding to target proteins including kinases and apoptotic regulators [19]. The 4′-methoxy group on the B-ring enhances lipophilicity and improves cellular uptake; replacing it with a hydroxyl diminishes activity, while halogenation (e.g., fluorine) can further improve potency and metabolic stability [20], [21]. Moreover, the C2=C3 dual bond and the C4 carbonyl (the unchanged flavone skeleton) preserving the planarity and enabling the interaction of the molecules is critical; the saturation of the double bond into flavanone usually suppresses the activity [19]. Glycosylation of the 5 or 7-OH (e.g., in linarin) also reduces anticancer activity, which validates the use of the aglycone form is more effective [22].

4. MECHANISM OF ACTION:

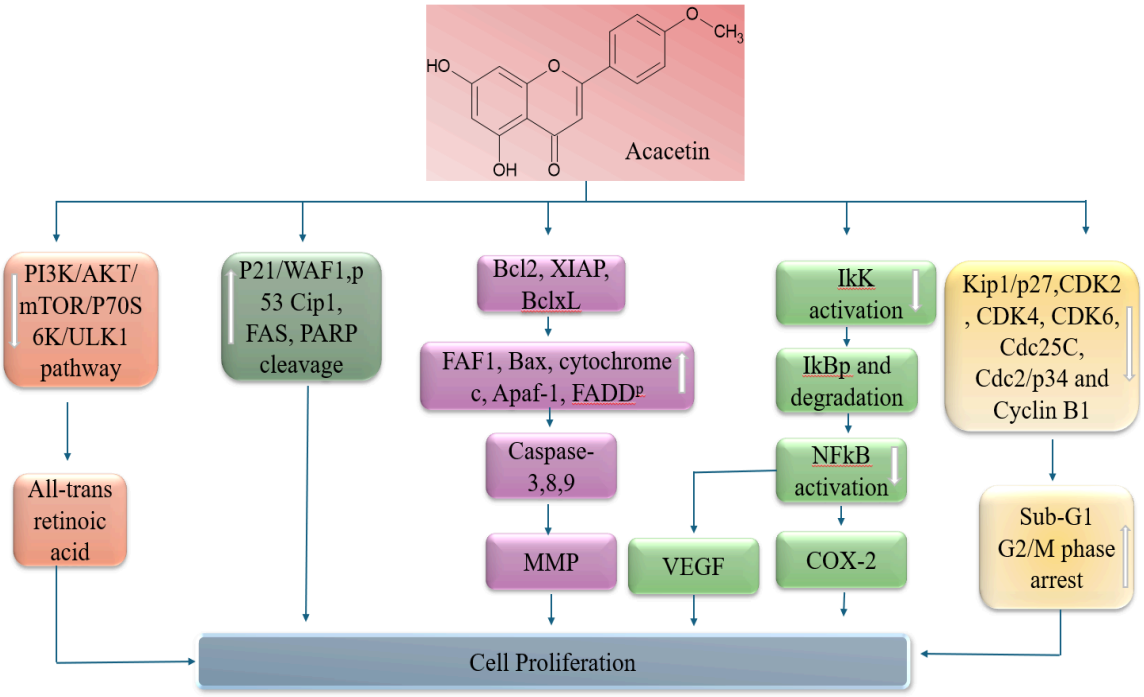


Figure 6: Intrinsic (Mitochondrial) Apoptosis Pathway

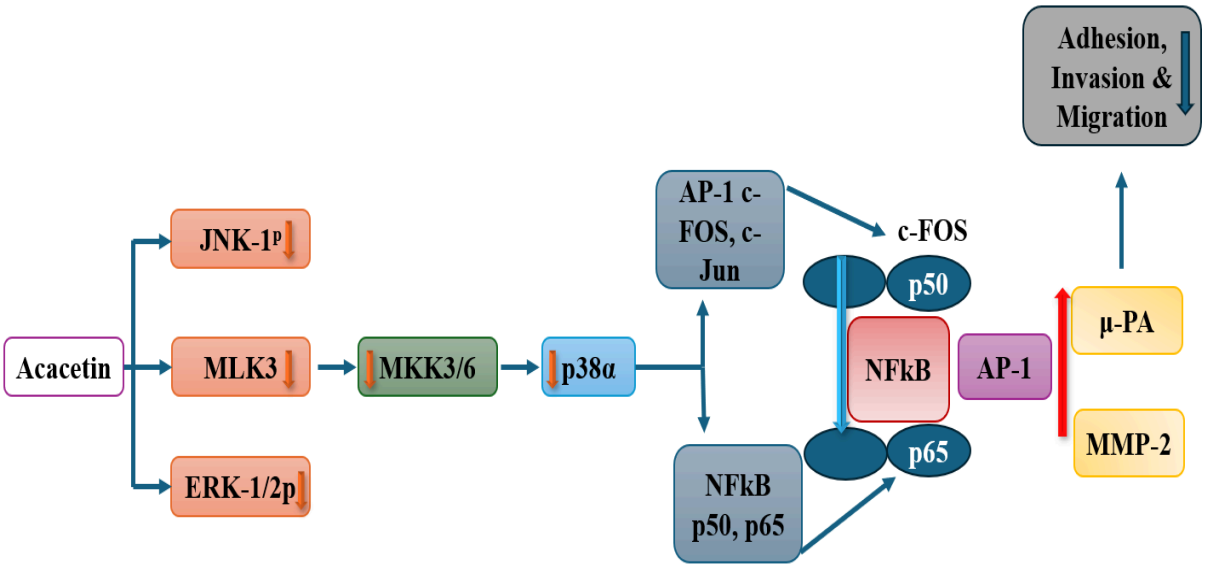


Figure 7: Extrinsic (Death-Receptor) Apoptosis Pathway

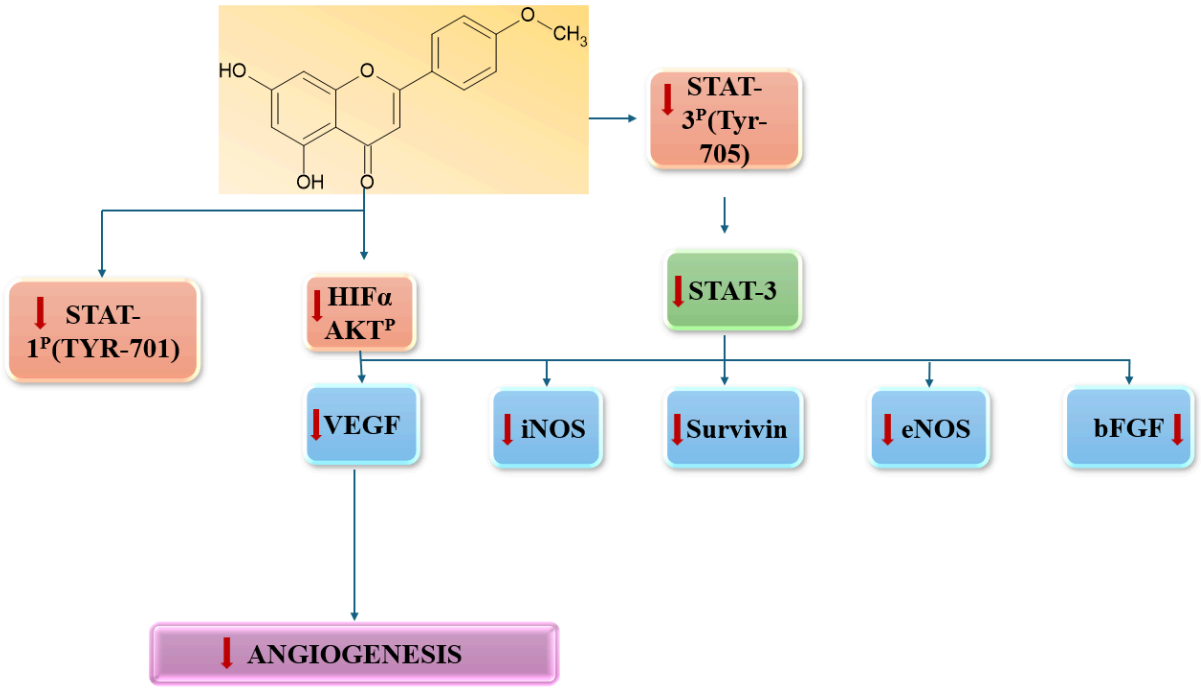


Figure 8: p53-Mediated Apoptosis / Cell-Cycle Arrest

1. **Intrinsic (Mitochondrial) Apoptosis Pathway:**
   The Figure 6 above demonstrates the Anticancer mechanism of acacetin. Down-side arrows indicate the downregulation whereas the upregulation is indicated by inbox up-side arrows on the targets/transcription factors. The outbox arrows depict the order of the event.
   This is an internal stress-induced pathway:
   DNA damage, oxidative stress, oncogenes activation, etc.
   A large number of cancers are strongly dependent on the inhibition of intrinsic apoptosis (through the overexpression of Bcl-2 and Mcl-1) [23], [24], [25].

2. **Extrinsic (Death-Receptor) Apoptosis Pathway:**

Figure 7 demonstrates that in the pathways, the inbox up-side arrows depict the up-regulation, and the down one depicts the down-regulation of the targets/transcription factors. The outbox arrows depict the order of the event.

The activation of the pathway is triggered by cell-surface receptors (Fas, TRAIL-R1/R2, TNF-R).

The evasion of this pathway by many cancers occurs by overexpression of decoy receptors. Mechanism of acacetin to suppress the invasion and migration of cancer cells [23], [24], [25], [26].

3. **p53-Mediated Apoptosis / Cell-Cycle Arrest:**

Down-side arrows indicate the downregulation whereas the upregulation is indicated by inbox up-side arrows on the targets/transcription factors. The outbox arrows depict the order of the event.

p53 is altered in approximately half of cancer in humans. Angiogenesis inhibitor angiogenesis [23], [24], [25].

Table 2

Feature	**Intrinsic (Mitochondrial) Apoptosis Pathway**	**Extrinsic (Death-Receptor) Apoptosis Pathway**	**p53-Mediated Apoptosis / Cell-Cycle Arrest**
Main action	Apoptosis & cell cycle arrest	Anti-migration & anti-invasion	Anti-angiogenesis
Primary target pathway	PI3K/AKT/mTOR, NF-κB, caspases	JNK, ERK, MLK3, AP-1, NF-κB	STAT-3, HIF-1α, AKT
Key molecules affected	Caspases, Bax/Bcl-2, p21, Cyclins	MMP-2, uPA, AP-1	VEGF, bFGF, iNOS, eNOS
Outcome of the tumor	Stops growth, induces death	Prevents metastasis	Prevents blood vessel supply
The cancer process targeted	Proliferation	Prevents metastasis	Angiogenesis
Result	↓ Cell proliferation	↓ Migration & invasion	↓ Blood vessel formation
Main Cancer Types Affected	Breast, lung, colon, leukemia, lymphoma, ovarian, prostate, pancreatic	Colon, pancreatic, breast, melanoma, glioma, leukemia, lymphoma	Breast, lung, colon, ovarian, prostate, sarcoma, glioblastoma

Limitation:

The supporting evidence on the anticancer effects of acacetin is highly founded on in vitro studies, and a small number of animal studies; therefore, its success and safety in humans have not yet been ascertained. It is also not well characterized with respect to its bioavailability, pharmacokinetics and metabolic stability. Current studies only cover a restricted spectrum of cancers and molecular pathways, and its impact in multifaceted tumor microenvironment, and long-term toxicity profiles are poorly comprehended. Moreover, the structure-activity relationship data has been limited to a limited number of derivatives meaning that the chemical space of acacetin is under-explored. These weaknesses of the current review are because of the limitations of the journal format. Without these restrictions, there are many derivatives of acacetin that are more anticancer active that would be discussed rather than just the parent compound.

Conclusion:

To sum up, acacetin is a naturally occurring flavonoid that has a wide range of pharmacological effects such as, antioxidant, anti-inflammatory, antibacterial, anti-obesity, and organ-protective properties, as well as potential to protect against cancer that is promising. Existing data have revealed that acacetin has been shown to regulate numerous oncogenic signaling events, cause apoptosis, block proliferation and angiogenesis and inhibit tumor growth in most experimental cancer systems, which demonstrates its usefulness as a preclinical lead agent in anticancer drug development. However, Future work needs to be further systematic studies of its systematic in vivo and preclinical studies, systematic PK/PD and formulation optimization, further development of SAR-controlled analogues, combination therapy, and increased understanding of its effects on the tumor microenvironment, cancer stem cells, and metastasis.

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